TOWARDS SUSTAINABLE ENTROPY

Investigations into the influence of confinement on the behaviour of chemical systems

VERS UNE ENTROPIE DURABLE

Recherches sur l'influence de l'environnement confiné sur le comportement des systèmes chimiques

A Thesis Submitted to the Division of Graduate Studies
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by

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This is how the world is known: incompletely, and in pieces.

Svetlana Alpers

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Yo soy yo y mi circunstancia.

Jose Ortega y Gasset

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Abstract

The chemical reactions that make life possible occur under confinement within structures whose interior dimensions complement the size and shape of the reactants they contain. The molecular machinery of life operates under a thermodynamic regime that is far from equilibrium and so not well described by the theory taught to chemists. Because evolution favours energy conservation, the existence of enzymatic nanoreactors to control and support biochemical processes points to an advantage universally employed by living organisms – so why has this not yet translated into the chemical sciences?

This thesis explores the question in two parts: the physical science of entropy-driven reactions within nanostructures and the social methods of knowledge translation. Theoretical and experimental research tracks how entropy impacts reactivity and how low-dimensional reaction spaces can affect the entropic costs of a chemical reaction. After surveying the development of entropy from its roots to its current applications in chemical research, chapters explore its expression in molecular bonds, in chemical synthesis, and in the assembly of nanoscale building blocks to macroscopic structures. The second section examines the challenges and opportunities that arise from translation between independent systems of knowledge, first the overlap of chemical and military knowledge in a teaching context and then the overlap of academic and political knowledge in a research context. I include an example of nanomaterials for multi-drug resistant cancer treatment to illustrate how both technical and social systems must align to successfully progress against complex challenges.

I argue that molecular structures that confine reactants within a potential gradient grant access to the entropy – and so the direction and rate – of the reaction. By attending to the values shared across the relevant scientific and social knowledge systems, the ability to design nanoarchitectures that govern the entropy of reactions has the potential to make a substantial contribution to sustainability practices.

Résumé

Les réactions chimiques qui rendent la vie possible se produisent dans des structures confinées dont les dimensions intérieures correspondent à la taille et à la forme des réactifs qu'elles contiennent. Le mécanisme moléculaire de la vie fonctionne selon un régime thermodynamique loin de l'équilibre et donc mal décrit par la théorie enseignée aux chimistes. L'évolution favorisant la conservation de l'énergie, l'existence de nanoréacteurs enzymatiques permettant de contrôler et de soutenir les processus biochimiques indique un avantage universellement utilisé par les organismes vivants. Pourquoi cela ne s'est-il pas encore traduit dans les sciences chimiques ?

Cette thèse explore la question en deux parties : la science physique des réactions entraînées par l'entropie au sein des nanostructures et les méthodes sociales de transfert des connaissances. La recherche théorique et expérimentale suit l'impact de l'entropie sur la réactivité et la manière dont les espaces de réaction peuvent affecter les coûts entropiques d'une réaction chimique. Après avoir examiné le développement de l'entropie depuis ses origines jusqu'à ses applications actuelles dans la recherche chimique, les chapitres explorent son expression dans les liaisons moléculaires, dans la synthèse chimique et dans l'assemblage de blocs de construction à l'échelle nanométrique. La deuxième partie examine les défis et les opportunités qui découlent de la transposition entre des systèmes de connaissances indépendants, d'abord le chevauchement des connaissances chimiques et militaires dans un contexte pédagogique, puis le chevauchement des connaissances académiques et politiques dans un contexte de recherche. J'inclus un exemple de nanomatériaux pour le traitement du cancer afin d'illustrer comment les systèmes techniques et sociaux doivent s'aligner pour progresser avec succès face à des défis complexes.

Je soutiens que les structures moléculaires qui confinent les réactifs dans un gradient de potentiel donnent accès à l'entropie – et donc à la direction et à la vitesse – de la réaction. En tenant compte des valeurs communes aux systèmes de connaissances scientifiques et sociaux pertinents, la capacité à concevoir des nanoarchitectures qui régissent l'entropie des réactions peut contribuer de manière substantielle aux pratiques de durabilité.

Co-Authorship Statement

Chapter three grew from work first undertaken by OCdt Jun Young Ko as part of his undergraduate honours thesis work for myself and Dr. Cécile Malardier-Jugroot; the work presented here is my own. I conceived of the work, produced the models and perfomed the analysis, and wrote the paper; CMJ provided resourcing, revision, and supervision. This chapter was previously published as:
McTaggart, Matt, and Cécile Malardier-Jugroot. "The role of helicity in PFAS resistance to degradation: DFT simulation of electron capture and defluorination." *Physical Chemistry Chemical Physics* 26.5 (2024): 4692-4701.

The experimental data in chapter four were collected in two periods. First came the QENS experiment, designed by CMJ and MG, performed by me, MG and XL and analyzed by CMJ and myself. Later, I conceived, performed, and analyzed the kinetics work, developed the ‘dimensionality’ theme, and wrote the paper. Resources and supervision were provided by CMJ. Chapter three was previously published as:
McTaggart, Matt, Xia Li, Michael Groves, Vishva Shah, Manish Jugroot, and Cecile Malardier-Jugroot. "Impact of dimensionality and confinement on reaction dynamics and thermodynamics within 1D and 2D nanostructures." *The Journal of Chemical Physics* 154. 17 (2021): 174903.

Chapter five centres its discussion on experimental data and discussion generated in collaboration with Mr. Nathan Zeeb, Dr. Jennifer Snelgrove, and Dr. Cecile Malardier-Jugroot, with experimental assistance provided by Mr. Bob Whitehead. I performed the experiments with NZ and JS and wrote the paper. CMJ provided resources and supervision. The work has been published as:
McTaggart, Matt, Nathan Zeeb, Jennifer Snelgrove, and Cécile Malardier-Jugroot. "Bioinspired hierarchical additive construction of gold ‘snowflakes’." *MRS Advances* (2025): 1-8. https://doi.org/10.1557/s43580-025-01184-0.

The intersection of chemical science and its educational and political context discussed in chapter seven was previously published as a chapter in: McTaggart, Matt, and Cecile Malardier-Jugroot. "Nanomedicine and Drug Delivery Systems in Overcoming Resistance to Targeted Therapy." *Current Applications for Overcoming Resistance to Targeted Therapies*. Springer, Cham, 2019. 291-312. I performed the literature review and wrote the chapter with revision from CMJ.

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Chapter nine describes Science meets Parliament, a program I initiated in 2017 and has been presented in partnership with the Canadian Science Policy Centre and the office of Canada's Chief Science Advisor since 2018. I have been the program Chair for the entirety of the program. The organizing committee is highly collaborative but I have had significant influence over its direction. Elements of chapter eight have been previously published as:
Zhao, Jiaying, Meghan B Azad, Erin M Bertrand, Cole Burton, Valorie A Crooks, Jackie Dawson, Adam T Ford, Angela Kaida, Arjun Krishnaswamy, Chikin Kuok, Catherine L Mah, Matt McTaggart, Amanda J Moehring, Dominique Robert, Albrecht Schulte-Hostedde, Heather Sparling, Mary A De Vera, Stephanie Waterman, and Trushar R Patel. "Canadian Science Meets Parliament: Building relationships between

scientists and policymakers." *Science and Public Policy* 48.4 (2021): 447-450.
and in an edited blog article as:
Robert, Dominique., et al. “De l'importance des relations entre politiciens et scientifiques.” The Conversation, 14 Apr. 2020, http://theconversation.com/politicians-and-scientists-need-strong-connections-during-the-coronavirus-crisis-and-beyond-136482.
Discussion of the five-year impact and outcomes is currently in preparation with the same set of co-authors, excepting Dr. Kuok. I was the primary author of the program aims, development, and interpretation of survey data; my co-authors contributed their perspectives as participants. Formulation of the program impact was necessarily co-created during discussions and article construction.

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List of Acronyms

ANCOVA	Analysis of covariance
BOMD	Born-Oppenheimer Molecular Dynamics
CSPC	Canadian Science Policy Centre
DCS	Disc-chopper time-of-flight spectrometer
DFT	Density functional theory
DI water	Deionized water
DLS	Dynamic light scattering
ECM	Extracellular matrix
EDX	Energy-dispersive X-ray scanning
EPR	Enhanced permeability and retention
FDA	Food and Drug Administration (USA)
FWHM	Full width half maximum
IUPAC	International Union of Pure and Applied Chemistry
MDR	Multiple drug resistant
MOF	Metal organic framework
MP	Member of Parliament
MRR	Molecular rotational resonance
NIST	National Institute of Standards and Technology (USA)
NP	Nanoparticle
NSERC	Natural Science and Engineering Research Council
PEG	Polyethylene glycol
PES	Potential energy surface
PFAS	Poly- and per-fluorinated alkyl substances
PFOA	Perfluorooctanoate (-oic acid)
PFOS	Perfluorooctane sulfonate (-ic acid)
PSMA or SMA	Poly-styrene-alt-maleic acid
QENS	Quasi-elastic neutron scattering
ROTP	Regular Officer Training Program
SEM	Scanning electron microscopy
SMP	Science meets Parliament
TEM	Transmission electron microscopy
TME	Tumor microenvironment
XRD	X-ray diffraction

List of Symbols

d	Instantaneous change
h	Planck's constant
k or k_B	Boltzmann's constant
k	Rate constant
k_i	Incident wave vector (QENS)
k_s	Scattered wave vector (QENS)
n	Amount in moles
p or P	Pressure
v or V	Volume
A	Arrhenius constant
D_{trans}	Translational diffusion coefficient (QENS)
E_a	Activation energy
ΔE	Energy exchange (QENS)
H	Enthalpy
$\Delta H^{\ddagger}$	Transition state enthalpy
N	Number of nuclei (QENS)
Q	Heat
Q	Wave vector (QENS)
R	Ideal Gas Constant
S	Entropy
$S_{inc}(Q,\omega)$	Incoherent dynamic structure function (QENS)
$\Delta S^{\ddagger}$	Transition state entropy
T	Temperature
$\langle u^2 \rangle$	Mean-square displacement (QENS)
σ_{in}	Incoherent scattering cross-section (QENS)
ω	Energy (QENS)
$\Gamma_{trans}(Q)$	Half-width half-maximum of Lorentzian (QENS)
Δ	Average change
κ	Transmission factor
$\Delta\Omega$	Scattering arc (QENS)

1. Introduction: Chemistry as a social practice

In the first lesson of our first-year introductory chemistry class, I define chemistry for my students as "a set of practices that humans do to develop knowledge about the matter that makes up our universe: the properties of different types of matter, how they function, how they interact with each other, and how they combine and recombine." Embedded within 'practices that humans do' is an acknowledgement that scientific knowledge is necessarily acquired, adjudicated, interpreted, and applied by a specific group of people situated within specific social circumstances.

As scientists we commit ourselves to accept the verdict of nature: scientific knowledge is that which allows us to act in ways that are least resisted by reality[1]. We must also accept that no one is able to receive the verdict of nature except through the distorting lens of our circumstantial experience. Given the limits of individual perspective, open communication between a responsive, diverse set observers with equal share in intellectual authority – peer review – is necessary to transform the subjective experiences of a few into objective knowledge for all[2]. Since peer review occurs according to shared values, standards, and methods established on the basis of co-created norms, the community itself grants or withholds recognition of what counts as an *expérience* and whose experiences count[3]. Recognition is therefore an important act by the scientific community in our determination of scientific legitimacy.

Accordingly, "chemistry" is demarcated by social rather than empirical boundaries. It comprises all activities over which the community of chemists would reasonably claim the right to grant or deny recognition of legitimacy. That said, I do not think that chemists require exclusive jurisdiction over a given task for it to be included within chemical practice. Chemists and physicists share quantum mechanics; chemists and biologists share metabolic processes; chemists and political science share regulatory practices. Non-exclusivity ought not delegitimize a topic for scholarship by chemists when the subject is approached in a way that respects chemical knowledge, the community of chemistry practitioners, and the communities of knowledge and practice with which the subject intersects.

The overarching topic of my research is that certain nanoscale structures create a mechanism to efficiently concentrate usable energy from the ambient environment into a chemical reaction, manipulating the system's entropy to reduce or eliminate the need for an external, top-down source of energy. I've styled this as 'sustainable entropy' to harmonize with 'sustainable energy', the central technical issue for realizing sustainable development. By doing so, I hope to invoke the idea that the diffusion of energy (i.e. entropy) is as worthy of investigation as its production to "meet the needs and aspirations of the present without compromising the ability to meet those of the future.[4]"

The studies collected in the early chapters of this thesis demonstrate that the entropy of a reaction, and therefore the rate and direction of a reaction, can be influenced via the direction of movement down a potential energy gradient within confining structures. Entropy is a physical property, but sustainability is social. The determination of which "needs and aspirations" are deserving of sustainment, and at what level is not a scientific fact but a political choice, so framing 'sustainable entropy' in combination requires the integration of knowledges from subatomic materials to global society. In the final chapters I examine cases of intersection between chemistry and military, political, and regulatory knowledge systems. While not progressing sustainable entropy as such (we do not yet live in that world, alas), these studies offer lessons on interactions between neighbouring knowledge systems in the contexts of innovation, education, and political engagement that can be translated into sustainable entropy once the research has developed to that level.

In this thesis, outlined below, I seek to demonstrate that sensitivity to the conditions in which an activity is embedded improves the performance of all aspects of chemical practice, from theoretical methods, experimental physical chemistry, and the production and characterization of materials, to chemical pedagogy, public policy, and governance.

Chapter outlines

Chapter two: Entropy and its circumstances

In this opening chapter I survey the historical development of the concept of entropy from its inception in the mechanical theory of motive force in Revolutionary France to its twentieth-century application to chemistry. I argue that the circumstances under which the theory of entropy was created strongly limits how it is taught, thought of, and employed by today's chemical community. Experiments and theories that assume a large number of independent objects acting on long time scales do not necessarily capture the real behaviour of chemical systems acting on a small number of interacting objects on short time scales. As a counterexample, I offer the evolution of life as a community of chemical practice whose four-billion-year exploration of physico-chemical space is recorded in the molecules that compose living bodies. Unlike human chemistry, nearly all biochemical functions occur within built to purpose nanoscale structures. If evolution favours efficient use of available energy and converged to the use of confining structures to support the chemistry of life, then we ought to investigate what advantages we can gain from construction and use of similar structures to improve the efficiency and open the range of possibility for our chemical processes.

Chapter three: The role of entropy in PFAS degradation

Theoretical chemistry generates models upon which simulations can be run whose quality are judged by how well their predictions correspond to experimental data. In the creation of the computational model of the system, the choice of model chemistry is turned into an explicit step in the software. Model pluralism is a necessary framework for theoretical chemistry that can and should be considered in other chemical practices: by accepting that multiple theory choices are possible and attending to each theory's conditions for applicability opens areas for scientific exploration that are otherwise inaccessible.

In this chapter, I describe a theoretical study in which I model various perfluorinated alkyl substances and simulate their behaviours after electron capture. The simulations reveal that the enthalpy and entropy are at odds

and that the helicity of the molecular geometry plays an important role in the destabilization and defluorination of the compound.

Chapter four: The role of entropy in reactivity under confinement
In prior work we have noticed that reaction rates and spontaneity depend on the size of the space containing the reactants. In Dr. Xia Li's Master's work she made a strong case for a distinct 'confinement effect' that occurs when the lengths of the interior dimensions of a reaction vessel are on the same order as the molecules that they contain. In a particularly demonstrative experiment, she showed that the polymerization of pyrrole occurred within a 2-3 nm reaction space but the reaction does not occur when the space is enlarged to 50 nm.

In this chapter I develop this idea further to examine how the number of confined dimensions influences the effect of confinement. During the research leading to my master's degree, I discovered that self-assembled styrene-alt-maleic acid (SMA) polymers could take on different architectures when dissolved in water at neutral pH according to the average length of the constituent polymer chains: moderate length chains (under ~100 kDa) assemble into nanotubes as described by Dr. Malardier-Jugroot while longer chains (greater than 100 kDa) assemble into bilayer sheets. In both cases, the surface of the interior spaces are predominantly hydrophobic styrene groups and the minimum diameter of the internal space is under 3 nm. The polymer structure therefore affords two confined reaction vessels whose only critical difference is the number of unconfined dimensions: one in the case of nanotubes or two free directions of travel when sandwiched between bilayer nanosheets.

Chapter five: Bioinspired hierarchical additive construction
Polymeric and hybrid nanostructures that contain well-defined low dimensional spaces mimic the conditions of biomineralization processes, thereby offering a powerful set of levers to control the synthesis and movement of crystalline nanomaterials. In this chapter, I demonstrate that polystyrene-alt-maleic acid molecular architectures can be made to direct the storage or movement of 2-3 nm gold nanoclusters formed within them. The system is found to be stable through freeze-drying and rehydration and

to direct release when differential dehydration motivates water flow through the polymer nanotubes. The combination of stability or dynamism depending on bulk conditions creates the possibility for development of nanoscale additive manufacturing. This work offers an accessible example of how structuring of the reaction space can begin to model biological synthetic processes, building from the bottom up.

Chapter six: Molecular sensors for nanostructure characterization
To conclude the physical sciences section, I propose methods to probe the effects of reactant-scale structures on the molecules confined within them. Characterizing the exact influence of the confined chemical environment on reactants remains an open challenge. Inspired by Dr. Sebastián Ovalle's recent work, I present experimental findings that suggest promising paths forward.

Chapter seven: Nanomaterials for Targeted Drug Delivery
To exemplify how the physical and social sciences intersect in practice, I show how a research program can be frustrated by failing to consider the training and regulatory environments impacted by its material and methodological advances. I examine how the conceptual framing of nanomaterials as targeted drug delivery systems has impacted their progress towards their application in the treatment of multi-drug resistant cancers. I will begin with a description of efforts to develop common nanosystems for this application, the physiological and pharmacokinetic challenges impeding drug delivery vehicles, and the few products that have found a path to success. I will argue that the chemist's 'materials first' solution fails in a 'disease first' problem space, in part because chemical education prepares students to assume a degree of system independence that is not well aligned to the complex and dynamic physiological surroundings through which the material is meant to navigate and deploy. Further complications arise at the regulatory stage when researchers focused on the material properties of a delivery vehicle clash with policy systems developed to validate the medicinal properties of a drug.

Chapter eight: Chemical education for military students

The Introductory Chemistry course at the Royal Military College of Canada is our students' first (and in most cases last) exposure to chemistry at the university level. The undergraduate student population is entirely composed of military members, yet the first-year general chemistry course was designed with no specific reference to the students' identities or the military environment within which it's being taught. After all, the facts of chemistry as printed in the textbook do not change based on where or by whom the book is read. However, by ignoring the course's context we deny ourselves a potent mechanism for increasing its relevance to students and therefore student motivation and learning. In this chapter I describe the ways in which we have worked to motivate military students to study chemistry through demonstrating to them that expertise in chemical knowledge systems provides a credible and advantageous path into social identities that they find most valuable and personally meaningful.

Chapter nine: Science Meets Parliament

The collection of communities of practice that perform the thing we call "chemistry" are themselves situated within a social, political, and economic context that bear on which questions, methods, observations, and conclusions are recognized as legitimate - and which are largely ignored. I do not think it is controversial to reject the model of the "Pure" science independent and unsullied by mortal concerns, since like all human endeavours it is necessarily mediated through human minds, hands, and senses. Nor do I think anyone could seriously argue that government, private capital, or any other external organizing force exercises complete control over the content or direction of science. Therefore, the relationship between science and its surroundings must lie somewhere in between: scientific communities of practice and their surrounding societies influence each other. How can researchers engage with government or politics while avoiding the Scylla of political alienation and the Charybdis of capture by partisan interests?

In 2017, I initiated Science Meets Parliament in Canada to provide a training program to prepare researchers to build relationships with Canada's Parliamentarians and to create spaces for those relationships to grow. Since

then, Science Meets Parliament has grown to become an established and nationally recognized leader in this space.

Chapter ten: The kind of problem entropy *is*

To conclude, I summarize the key results and their implications for pressing entropy into service for sustainable chemical practices. Our introduction of nanoscale reaction structures fundamentally challenges the relationships between elements of a system and between the system and its environment and in such a way that the assumptions underwriting our general derivations of entropy functions are challenged. Rather than a simple analytical function of equilibrium properties, or statistical description of disorganized complexity, structured reactivity spaces represent a type of organized complexity with an irreducibly large number of interacting dependent variables.

2. Entropy and its circumstances

Introduction

Entropy is our best explanation for why physical processes progress in the direction they do and not the other way around. It is implicated in the beginning and end of the universe and the flow of time between these cataclysms. Entropy stands alongside energy and temperature in the trinity of properties underwriting the three classic laws of thermodynamics, together describing a system's ability to effect or resist a change of state. The concept has guided theory development in the physical, formal, and social sciences. As others have noted, "the interest in entropy is not surprising since it provides many advantages for interdisciplinary, multilevel investigations. Its unifying potential can hardly be overemphasized. It applies both to the processing of matter-energy and of information in systems."[5] Because the names of fundamental thermodynamic properties arise in so many and various applications that it will be useful to begin by explaining what I mean before entering into further discussion. These descriptions are only intended as introductions; more precise definitions will be provided throughout the text as the context requires.

The Universe

The universe comprises all space and everything in it. The way matter and energy are distributed within space is the 'state' of the universe. The probability that the universe exists in its current state is 100%. Accordingly, the probability of each past state having occurred is 100%. The probability that a given state will occur in the future lies somewhere between 0 and 100%, with the sum total probability of all future states remaining constant at 100%. We can subdivide the universe in any way we choose to ease our efforts to understand why certain states become more probable as the critical moment (now) approaches in time and why the probability of alternative futures recedes. The section we select as the principal object of study is labelled the 'system' while the rest of the universe comprises its 'surroundings'.

Energy

The property of energy is that which accounts for the possibility for change over time. Introductory chemistry texts typically define thermodynamic energy as the total amount of work and heat (orderly or random motion) that a system could possibly release. This is a useful definition within its range of application, limited by its ignorance of electromagnetic and particulate radiation. To access a broader focus on what energy *does* rather than the *mechanism* through which it is expressed, we will say that energy is the total amount of potential for a system to produce a change in the relative probabilities of the future states of the surroundings with which it interacts.

Temperature

Temperature is a measure of the proportion of a system's total energy that is held as heat in the random motion of its component parts. For a system to be said to have a temperature then that temperature must be consistent throughout, so any sample portion of the system must have the same temperature as every other sample. Differences in temperature between parts of a system or between a system and its surroundings are expected to become equal over time as heat energy flows from areas or objects with the higher temperature to the lower.

Entropy

Entropy is a measure of the actual distribution of energy held by a system as compared to all the ways in which it could be distributed at a given temperature. The change of entropy is a critical determinant for predicting or explaining spontaneous changes in a system: all directions being equal, a process that enables the transfer of energy into a wider, more uniform distribution across more available states (such as the transfer of heat from objects of higher to lower temperature) is the most probable change of state and so can occur without further intervention. Meanwhile, a process by which energy is concentrated into fewer states deviates from the most probable outcome and so requires an injection of energy.

When we recall that transferring energy changes the relative likelihood of a future state but the sum total probability of all future states remains constant (conservation of energy), that concentrated energy is more likely to become

transferred into a greater number of ways to hold it than it is for diffuse sources of energy to focus it into fewer (entropy tends to increase over time) and that no system can have less than none of its energy held as random motion (the existence of absolute zero), then we recover the three great laws of classical thermodynamics.

Whichever way we choose to construct the thermodynamic laws we can feel secure in the solidity of their foundation. Indeed, the multiplicity of forms in which they operate supplies its own assurance of their security. As Einstein says in his autobiographical notes, "A theory is the more impressive the greater the simplicity of its premises is, the more different kinds of things it relates, and the more extended is its area of applicability. Therefore the deep impression which classical thermodynamics made upon me. It is the only physical theory of universal content concerning which I am convinced that, within the framework of the applicability of its basic concepts, it will never be overthrown."[6] Einstein offers the kinetic theory of gases as a principal example of "the achievements of mechanics in areas which apparently had nothing to do with mechanics." Indeed, we still use the Ideal Gas Law as a gateway into thermodynamic theory for our introductory chemistry classes, blending it as seamlessly as possible into discussions of enthalpy, entropy, and spontaneity which are later applied to reaction dynamics in solution and electrochemistry. Practical labs accompanying the lessons are designed to show that relationships between the abstract thermodynamic variables they wrote down in class can accurately describe their real physical experience.

Einstein goes on to describe how classical mechanics was made to concede its place as the presumptive foundational theory for all natural sciences. Maxwell's electromagnetic fields first resisted expression according to thermodynamic principles, the search for which led to the investigation of black-body radiation. Max Planck's resolute search for a model to fit experimentally observed spectra that culminated in the discretization of energy as $E = h\nu$ and the advent of quantum mechanics. Planck's story seems to demonstrate that science can work that way under ideal circumstances. However, Planck himself believed that "A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die and a new generation

grows up that is familiar with it", a sentiment he demonstrated by remaining loyal to classical determinism in spite of the quantum probabilistic world his work had inspired[7,8]. We might want to believe that recalcitrant problems of the type presented to Planck always attracts scientific curiosity, only awaiting genius to reveal itself through their resolution and move scientific progress forward. In practice, however, a researcher's preferences or ability to recognize, take seriously, investigate, or discuss certain ideas over others is as much a function of their technical, economic, cultural, and political circumstances as by their academic interests.

Entropy is no exception. Despite its apparent universality, entropy (along with every other scientific theory) carries at least some historical contingency regarding its development, interpretation, acceptance, and application. To better understand thermodynamic entropy's place within contemporary chemistry, we will begin with an historical review of how it was first developed and later adopted into the chemical sciences.

A conceptual history of entropy

Before and after the chemical revolution

Today we take it for granted that one of the fundamental uses of chemistry is to explain why chemical reactions occur the in the direction they do (and not the other way around) but this has not always been the case. Discovering the limits of material transformations was indeed a motivating question for the pre-modern natural philosophers and alchemists. We can easily follow Robert Boyle's reasoning in 1661's *The Skeptical Chymist* to think that materials are composed of simpler elements that donate their characteristic properties to the objects they compose[9]. Our common experience tells us that fire is able to deconstruct green wood into liquid flowing water, airy rising smoke, and dry, non-flammable ash. But where among these non-combustible components did the wood gain its ability to burn? Georg Stahl provided the answer that was to inform chemical theory until the late 18th century: phlogiston, a weightless, fluid substance whose presence imparts flammability to materials and lustrous shine to metals. To help the reader in resisting the knee-jerk disgust of phlogiston that is almost a shibboleth for modern chemists, I will insert a quote from Richard Watson, Chair of Chemistry for the University of Cambridge in 1764[10]:

"You do not surely expect that chemistry should be able to present you with a handful of phlogiston, separated from an inflammable body; you may just as reasonably demand a handful of magnetism, gravity, or electricity to be extracted from a magnetic, weighty, or electric body."

To the best of our modern theories, magnetism is not carried by a magneton particle; gravitons are predicted by some theories but have not (yet) been observed; and electrical charge is carried by at least two particles: electrons and protons. If after 250 years we have yet to prove the existence or non-existence of Professor Watson's short list of property-carrying particles, perhaps we should not find it so unbelievable that phlogiston-borne chemical reactivity was once taken seriously.

The common understanding is that the weightless phlogiston particle was rendered unnecessary by Antoine Lavoisier's experimental confirmation of the conservation of mass and so had no place in the theory of chemistry that emerged. Although that explanation seems inconsistent with the acceptance of caloric - Lavoisier's own weightless, fluid substance of "heat". One may also wonder why proponents would feel it necessary to fashion themselves as "anti-phlogistonists" if it was indeed a passive, strictly empirical transition[11]. The real battle may not have been about phlogiston *per se* but rather about shifting the main focus of chemical investigation from "properties" to "composition". The principle of conservation of mass, as established and spread through Lavoisier's *Traité élémentaire de chimie* published in 1789 and confirmed through careful weighing of all products and reactants, offered access to a consistent picture of the microscopic composition of materials that encouraged chemists to adopt the idea that the properties of a compound do not necessarily reflect those of the elements that compose it[12]. As Fourcroy stated: "Two or more bodies, united by the attraction of composition, form a substance whose properties are very different from those of any one of the bodies before their combination."[13] By 1816, property-based chemistry was so discredited that Humphrey Davy could claim that: "This [assigning properties to elements that they donate into compounds] is an attempt to introduce into chemistry a doctrine of occult qualities, and to refer to some mysterious and inexplicable energy

that must depend upon a peculiar corpuscular arrangement."[13] We now know, of course, that the mysterious energy of a chemical system actually is explicable and does indeed depend on the peculiar arrangement of corpuscles, but Davy's sentiment remained the standard in chemistry until van't Hoff's work on the special arrangement of atoms in molecules became widely accepted 60 years later.

The advances in chemical knowledge that followed widespread adoption of Lavoisier's theory are undeniable, but it is also the case that the anti-phlogistonists inhibited development of the field by delegitimizing questions that their methods could not answer. Chemical composition alone was insufficient to explain reaction rate or direction and so those topics were depreciated in chemistry research. For example, even if chemists of the day could measure the amount and identity of each element and quantify the transfer of heat in the combustion reaction,

$$C_8H_{18} + 12\ O_2 \longrightarrow 9\ H_2O + 8\ CO_2$$

that knowledge would not explain why C_8H_{18} and 12 O_2 readily recombines into 9 H_2O and 8 CO_2 but will never reforms back into C_8H_{18} or 12 O_2. The chemists in the 18th and 19th centuries required something more to explain the direction of the process than its composition or the movement of heat through caloric. Hasok Chang cites this requirement to make a convincing case that phlogiston theory should not have been abandoned when it was (if at all). Not because the idea of phlogiston the particle was worthwhile *per se*, but because it provided an avenue to continue investigation into reaction dynamics and intrinsic material properties. The questions for which entropy is needed to find an answer were important to the phlogistonists but not to the anti-phlogistonists. Would parallel development of chemistry in the property-based tradition have led to an earlier chemical theory of entropy? We will never know because the ideas that would ultimately become entropy were not developed in chemistry, but in mechanics.

Mechanical developments

Lazare Carnot was born in 1753 into a bourgeois Bourguignon family. His academic excellence earned him a commission in the Army corps of

engineers at a time when officer positions were reserved for the nobility. His military interest lay primarily in the construction and defence of fortifications, building on the theoretical and literal foundations laid by Vauban. Carnot's studies in mathematics and mechanics while a Captain focused on power transfer in machinery, work that he published as *Principes fondamentaux de l'équilibre et du movement* in 1783. Dissatisfied with the limited options for social advancement afforded him in the ancien régime, Carnot entered politics and rose to prominence during the Revolutionary era[14]. Carnot the legislator initially focused on public education but shifted his attention to national defence after the fall of the French monarchy. He was even on the battlefield during his two-week turn as the nominal French head of state from 5-20 May 1794, overseeing the Army of the North in their campaign to claim the Austrian Netherlands. (Coincidentally, and almost certainly unbeknownst to him, Antoine Lavoisier was executed by the revolutionary government on 8 May 1794, during Carnot's presidency). Carnot was a firmly centrist republican and among the few members of the Convention nationale and Comité de salut public who remained in government during the massacre of the terreur and the counter-massacre of the Thermidorian reaction, becoming one of the five original members of the ruling Directorate in 1795. As a principal political leader of the French revolutionary wars, Carnot had a long and tumultuous relationship with Napoleon Bonaparte – first supporting General Bonaparte as a protégé, then serving as First Consul Bonaparte's Minister of War, before leaving public office altogether in protest of Emperor Bonaparte's claim to hereditary monarchy in 1804[15].

During this turbulent time, Carnot released a second edition of *Principes du movement* with significant updates and new ideas[16]. This edition shows how the specific medium that applies force to a machine (e.g. water, wind, or animal motion) can be reduced to a common quantity that he called the "*moment d'activité*" and that we would call work. By using the example of a simple water wheel, he describes how the height, and only the height, determines the maximum amount of force that a mass of water can impart to a machine. Furthermore, water in motion transfers more of its motion to a wheel already in motion than if it strikes a wheel at rest. Taking this idea to its limit he reasons that the maximum amount of work can be obtained when

the force is applied through a series of infinitesimally small movements: each droplet meeting no resistance to its perfect transfer of its motion into the machine. Finally, if this water wheel were connected to a water pump and all of the work generated by each small movement of water driving the wheel was transferred into the pump to produce an equally small movement of water up a pipe, then the limit of this perfect machine would be to move the exact same amount of water to the exact same height as it began in a perfectly reversible cycle. Because no additional water could be moved, the hope of a perpetual motion machine must be abandoned. Additionally, since no real machine is without some resistance in its mechanism, some useful work will always be lost during real, irreversible processes.

Lazare Carnot's work is the first expression of the idea that transformations of one form of 'force' into another extracts an unrecoverable cost in all but the theoretical limit of reversible processes. Carnot makes no attempt to explain what happens to the lost force: since he was writing in a time before the description of energy, let alone its conservation, that question is not one that we should expect him to have raised.

While residing in the Luxembourg Palace in 1796 as a Director of France, Carnot's first wife Sophie Dupont gave birth to their son, Nicolas Léonard Sadi Carnot. The material and political conditions within which Sadi was raised were very different from those of his father, yet his early life and career were closely modelled on his father's pattern. He, too, showed a talent for mathematics at a young age and was enrolled at 16 into the École Polytechnique – a school founded by Lazare Carnot for the education of military engineers. In 1814, he graduated into the École du Génie in Metz – one year after the death of his mother and one year before his father's permanent exile to Magdeburg, Prussia. Napoleon's final defeat in 1815 ushered in the restoration of the monarchy under Louis XVIII and marked a sharp change in the trajectory of Sadi's life. Where 19-year-old Sadi Carnot could have been welcomed as the son of 'the organizer of victory', he would now be shunned as the son of a 'regicide'. Nevertheless, he continued to faithfully follow in his father's footsteps: taking his commission in the Army corps of engineers, inspecting fortifications, and studying the flow of power in machinery.

The first steam engine in Magdeburg arrived in 1818. By the time Sadi next visited his father there in 1821, the steam engine had displaced the water wheel as the archetypal mechanical prime mover, and accordingly heat displaced gravity as the original moving 'force.' As water provided a medium to transfer of the force of gravity onto the wheel, steam provided a medium to transfer the expanding action of heat onto the piston. However, unlike gravity-driven mechanical movement, heat was thought to be subject to a conservation law. Antoine Lavoisier's caloric theory, based on the indestructible, self-repelling, heat-carrying caloric particle, was the dominant theory of heat during Sadi's life. The concentration and diffusion of caloric could explain why heat would move from a hot object to a cold object until their temperatures equalized. Less well understood but sufficiently explainable was the observation of 'latent heat': the amount of caloric that a solid block could absorb without temperature change while melting into liquid. That the movement of caloric could impart motion (as in a steam engine) but did not do so in all cases (as in a pot on the stove) provided Sadi with fertile ideas to plant in the field his father had tilled.

In 1824, one year after his father's death, Sadi Carnot self-published *Réflexions sur la Puissance Motrice du Feu* – a text that is now counted among the founding documents in thermodynamics but was nearly ignored in its own time. Although it would be ungenerous to suggest that *Réflexions* is nothing more than an update of *Principes du movement* for the industrial age, it is true that Sadi, like Lazare, shows how the specific medium that applies heat to a machine (e.g. steam, oxygen, or other gas) can be reduced to a common quantity that we would call work. By using the example of a simple heat engine, he describes how the temperature difference and only the temperature difference, determines the maximum amount of force that a given amount of caloric can impart to a machine. Furthermore, caloric at high temperature transfers more of its motion to an engine already at high temperature than if it is at a cold temperature. Taking this idea to its limit he reasons that the maximum amount of work can be obtained when the force is applied through a series of infinitesimally small movements: each particle of caloric meeting no resistance to its perfect transfer of its motion into the machine. Finally, if this heat engine were connected to a cold reservoir and

all of the work generated by each small movement of caloric driving the engine was transferred into the reservoir to produce an equally small movement of caloric out of the engine, then the limit of this perfect machine would be to move the exact same amount of caloric to the exact same temperature as it began in a perfectly reversible cycle. Because no additional caloric could be moved, the hope of a perpetual motion machine must be abandoned. Additionally, since no real machine is without some heat dissipation in its mechanism, some useful work will always be lost during real, irreversible processes.

However, focusing on the resemblances ignores Sadi's original and critical insights. His invention of the ideal heat engine, known today as the Carnot cycle, created the framework necessary to discover connections between volume, temperature, heat, work, that would prove central to thermodynamics. One implication found in Sadi's work for which Lazarre has no parallel is the relationship between temperature and the maximum efficiency of extraction of work from heat. A water wheel at 100 m above sea level delivers the same amount of work per unit of water as a wheel at 1 m above sea level because there is no relationship between the absolute height of the wheel and the amount of water transferred. In contrast, Carnot notes that "it requires more caloric to maintain the temperature of a quantity of air at 100° whose volume is doubled than it does to maintain the temperature of the same air at 1° during an equal expansion." Expanding the volume of air at a higher absolute temperature requires a larger amount of heat transfer than it would to perform the same expansion at a lower absolute temperature, so the efficiency of the process is inversely proportional to temperature - higher temperatures can evolve less work per unit of heat expenditure than at lower temperatures. Modern textbooks present the maximum efficiency of a heat engine (now known as Carnot's theorem) as a result of the second law of thermodynamics and derive its expression from entropy arguments so it's interesting to find that the logical progression presented in modern classrooms reverses the historical development.

Despite his capability in mathematics, Carnot presented his ideas in a prose format with few equations outside of some estimates for specific heat

capacity of various gases employed as evidence to show that the amount of motive power (work) available from a given caloric flow (heat transfer) stood independent from the choice of transfer medium. Some have pointed to the lack of a mathematical treatment as the reason that Carnot's pamphlet failed to attract much attention at the time of publication, although we will soon see that the ideas were presented clearly enough to be translated into algebraic expression by one so inclined. Rather, it would be difficult to imagine his work meeting the same cold reception had he not been so exposed to social and political ostracization following the restoration of the French monarchy. In 1832, Sadi Carnot died of cholera in a Parisian asylum; he was 36 years old. His short life can be read as a tragedy, with his unwavering devotion to following his father's path through a fatally altered political landscape providing the hamartia. Despite the early and obscure end to his life, Carnot's work would survive to directly inspire the next seven decades of thermodynamic development.

Classical thermodynamics

It is popularly cited that Carnot's work sat dormant for close to 25 years, awaiting rediscovery by William Thompson Lord Kelvin and Rudolf Clausius in the mid-19th century. However, the mathematical analysis of Carnot's narrative reasoning was complete within two years of his death, with Émile Clapeyron's publication of *Mémoire sur la puissance motrice de la chaleur* in 1834[17]. Clapeyron's derivation begins by assembling the ideal gas law *avant la lettre* as the combination of the laws of Mariotte (or Boyle, depending on your national affiliation) relating pressure to volume and Gay-Lussac relating pressure to temperature, $pv = R(T + 267)$, -267ºC being the contemporary estimate for absolute zero. Predating the mole as a unit of measurement and so the ideal gas constant, Clapeyron's R is specific to each gas according to its particular pressure and volume for an equivalent mass at the temperature of the warmer of the bodies in the Carnot cycle (i.e. holding units of pressure-volume per mass-temperature) which he brilliantly demonstrates graphically on a volume-pressure chart. Since the experimental evidence that Carnot chose to include in his pamphlet had already established that the choice of which gas to use as heat transfer medium was arbitrary and had no influence on the validity of the theory of maximum work, Clapeyron's equation of state enabled and simplified his

analysis and definition of the quantities of heat capacity, heat, and work for an ideal gas.

Clapeyron did not intend to imply a mechanical theory of heat despite his provocative opening statement to section II, “It has long been noted that one may use heat to develop motive force and, conversely, with motive force one may develop heat,” evidenced by the expansion of his statement to say that a mechanical force can be generated from the passage of caloric from a warmer to colder body. The first derivation of an idea he credits to Carnot is for amount of heat transferred as a function of volume in an isothermal process, $\Delta Q = RClog(v/v')$ or, in modern notation, $\Delta Q = nRTln(V_1/V_2)$. We would also note is equal to the amount of work transferred from the system to its surroundings, although this relationship would need to wait for the definition of internal energy. The Clapeyron equation emerges as a result of determining the maximum work available for a given heat transfer, $dT/dP = v/R$. In modern notation it is written as $dP/dT = \Delta S/\Delta V$ and used to define the curve defining two phases at equilibrium, again we find Clapeyron gesturing toward quantities and concepts that would be identified far later. In this case, Clapeyron’s R does indeed express the same units as entropy (pressure-volume per temperature) although it would be inaccurate as well as anachronistic to stretch Clapeyron’s intention to match our current understanding.

Despite his clear mathematical analysis and original contributions to Carnot’s work, Clapeyron, too, met with little fanfare on publication. William Thompson, Lord Kelvin in England and Rudolf Clausius in Prussia would become the idea’s major proponents within their respective spheres. Kelvin’s appreciation of Clapeyron led him back to Carnot’s original work and inspired him to translate that document for English readers, connecting and bolstering the theory with Henri Regneault’s recently published experimental data. Thompson held a particular interest in temperature, of course, being best remembered for refining the value of absolute zero from -267° to -273° C. He would also come to befriend James Joule – the experimental physicist whose work eventually mounted a successful challenge to Lavoisier’s particle theory of heat and its conservation law. Joule was not the first to cast doubts, as Thompson notes in his 1849

account by quoting Carnot that "To deny it [the conservation of heat] would be to overturn the whole theory of heat, in which it is the fundamental principle. It must be admitted, however, that the chief foundations on which the theory of heat rests, would require a most attentive examination. Several experimental facts appear nearly inexplicable in the actual state of this theory." Thompson concurs and adds that "… the necessity of a most careful examination of the entire experimental basis of the theory of heat has become more and more urgent. Especially all those assumptions depending on the idea that heat is a substance, invariable in quantity;" immediately pointing to Joule's measurements of temperature rising in a closed conductor subjected to a magnetic field: "The extremely important discoveries recently made by Mr Joule of Manchester, that heat is evolved in every part of a closed electric conductor, moving in the neighbourhood of a magnet, and that heat is *generated* by the friction of fluids in motion, seem to overturn the opinion commonly held that heat cannot be *generated*, but only produced from a source, where it has previously existed either in a sensible or in a latent condition." [italics in original][18]. Despite his doubts, Thompson accepts the caloric theory as axiomatic for the purposes of recounting the works of Carnot and Clapeyron, since "It might appear, that the difficulty would be entirely avoided, by abandoning Carnot's fundamental axiom; a view which is strongly urged by Mr Joule … If we do so, however, we meet with innumerable other difficulties—insuperable without farther experimental investigation, and an entire reconstruction of the theory of heat, from its foundation."

Clausius was more willing to take up the challenge. In 1850, he showed that Regneault's and Joule's experimental results were inconsistent with a conservation theory of caloric and instead supported a mechanical theory of heat[19]. Working from the maxim that "In all cases where work is produced by heat, a quantity of heat proportional to the work done is expended; and inversely, by the expenditure of a like quantity of work, the same amount of heat may be produced," Clausius first applies Carnot's work to reproduce the major results of Clapeyron and Thompson and then extends past them to give the novel result that the ratio of the heat capacities at constant volume and constant pressure should be a constant for a gas that approximately obeys ideal behaviour, a result agreeing with experimental work that had

until then resisted explanation. As if in reply to Thompson, Clausius demonstrates that it was not necessary to 'abandon Carnot's fundamental axiom' after all, only to reject that part which claims that the quantity of heat should remain constant. The first part of the statement, that "the production of work as the equivalent of a mere transmission of heat from a warm body to a cold one," still held the key idea: the maximum amount of work that can be drawn from a transfer of heat can depend only on the amount of heat and the temperatures of the hot and cold bodies and not on the substance that transmits it, since this could permit a redistribution of heat from cold to hot without no expenditure of work. Clausius accepted this revised version of Carnot's principle as a second maxim for the development of his theories. We can recognize the first and second laws of thermodynamics in Clausius' first and second maxim, and for that reason that Josiah Gibbs when would later remark that Clausius' first memoir on thermodynamics "marks an epoch in the history of physics."[20]

Atomization

A mechanical theory of heat founded on an equivalence of productive motion expressed as work and unproductive motion expressed as heat, begs the question, the motion of what exactly? Surely, the gas that holds the heat and expends the work. Clausius continued to develop the implications of the mechanical theory and in 1854 he presented an axiomatic law for reversible cycles,

$$\int \frac{dQ}{T} = 0$$

Progress toward an analytical proof of this statement demanded a mathematical description of the material that gave rise to the behaviour: a kinetic theory of gas. Clausius' early attempts at a molecular theory met challenges from Christoph Buys Ballot and James Clerk Maxwell – the first refuted and the second corrected. In order for small, light gas particles to carry the energy necessary to fulfill their thermodynamic obligations they would need to travel at hundreds of meters per second. Buys Ballot argued that he should therefore be able to smell his dinner as immediately as he could see it. Clausius' response was the mean free path, showing that molecules as the density of air are subjected to so frequent collisions that

the inhibited diffusion of a gas would indeed conform to our mealtime experiences. Maxwell's hesitancy was more subtle and ultimately overcome by his own persistence. First, he improved Clausius' theory by replacing his assumption of a constant speed for all molecules with a more physically accurate distribution. This, however, led to the implication that the viscosity of a gas should be independent of its density, a result that conflicted with the common knowledge. His wife Katherine provided the experimental assistance to validate the result from kinetic theory and Maxwell was converted.

Others were not so easily convinced. Just as chemistry had all but abandoned investigating the properties of matter in favour of its composition, mechanical physics was only interested in the motion of masses to the exclusion of their composition. Atomic theory was firmly established among chemists but not accepted by physicists. To illustrate the distance between the two sciences on this point, in 1865 Josef Loschmidt applied the new Clausius-Maxwell kinetic theory to estimate the size of a hypothetical gas molecule; meanwhile, August Kekulé was publishing the aromatic structure of benzene as an alternating single and double bonded carbons in a six-member ring[21,22]. That same year, Clausius coined the word 'entropy,' a neologism he derived from the Greek τροπή, "to turn," adding the prefix 'en' to make it harmonize in sound and construction with energy (from the Greek έργο, "to work"), and gave the letter *S* to signify it[23]:

$$dS = \frac{dQ}{T}$$

From here, two independent versions of thermodynamics would emerge – one based on the properties of particulate matter, founded on a belief in the real existence of atoms and one based on a continuum of matter that remained agnostic on the question of atoms.

Josef Loschmidt had been trained by chemists and so was open to connecting kinetic theory the molecular structures whose behaviour it is meant to describe. He worked under Josef Stefan at the University of Vienna, whose interest in the radiation of a black body according to temperature (what would become the Stefan-Boltzmann law) ensured that his students were up to date on Maxwell's discoveries. The mentorship

Boltzmann received after arriving in Vienna in 1863 for his Ph.D. studies placed him in the ideal circumstances to develop a statistical approach to thermodynamics. After Clausius finally presented his proof connecting the kinetic theory of gas to the constant entropy of a reversible circuit in 1871, Boltzmann made a claim of priority showing his own 1866 proof was mathematically equivalent[24]. He also, of course, generalized Maxwell's distribution to account for all energies of a system, not only kinetic translation. Boltzmann's mechanics would go on to successfully establish a firm correspondence between the statistical expectations arising from the behaviour of a large number of atoms to classical properties of the objects they compose. His philosophical commitment to atomic theory meant that he was never without his detractors, but his statistical mechanics more practical challenges, too. One of the most significant came from his colleague, Loschmidt: how, he asked, could time asymmetric entropy emerge from the time symmetric laws of classical mechanics? Solving for the evolution of a system according to Boltzmann's theory demonstrates that fluctuations on the nanometer scale does allow for entropy to increase – to violate the second law – but only for microseconds at a time; larger scales quickly reduce the already low probability of violation[25]. Boltzmann's ideas influenced Max Plank's use of small resonators to model blackbody radiation and Einstien's model of fluctuations in Brownian motion. Despite this, the physics community remained skeptical of the atomic theory and Boltzmann's adherence to it. He died by suicide in 1906, just as the shift to his favour would have occurred. As a biographer said, "It is the tragedy of Boltzmann's life that he did not experience the glorious victory of his ideas."[25] Incidental to our current discussion, but "entropy" is also a cognate to the Greek word ντροπή, "shame."

Independently in the United States, Josiah Gibbs was developing his own approach to statistical thermodynamics. The details and differences lie beyond the limited aims of this introduction but are recommended reading[26]. Gibbs was interested in equilibria between heat, pressure, chemical potentials, material phases, electrical charge, osmotic pressures, and more: all sources of energy available to a system balanced according to maximizing entropy for a given temperature. This is famously expressed as the Gibbs free energy of a system:

$$\Delta G = \Delta H - T\Delta S$$

Where *H* is the enthalpy of the system, *T* is the temperature, *S* is its entropy, and *G* is an amount of energy equal to the work that the system can perform as it spontaneously changes from its current state towards equilibrium[27]. Gibbs initially applied geometric rather than kinetic methods to derive his thermodynamic expressions, and so was able to remain agnostic on the question of atoms[28]. There is some irony that Gibbs' is the more commonly taught and applied among chemists, given that Boltzmann's approach is expressly particulate and accommodating of fluctuation where Gibbs' is not. However, its simplicity is a strength, allowing for its application to the broad category of equilibrium problems and facile tabulation of the results.

The thermodynamic theory we inherited is undeniably useful, but the assumptions, priorities, and language of the mechanical knowledge tradition in which it was developed has limited its applicability to chemical problems. Most critically, it is ill-equipped to address non-equilibrium or far-from-equilibrium problems where its key properties of temperature and entropy go undefined. This issue has become more evident in recent decades as our tools to characterize, synthesize, and employ artificial or biological systems outside of equilibrium has greatly improved. Modern theoretical updates to thermodynamics, such as fluctuation theorems that account for states containing few particles, short timeframes, and energies on the order of kT, remain framed within the physics discipline and have not been adopted by chemistry curricula[29,30].

This short history helps to explain how and why the concept of entropy developed in relation to mechanics instead of chemistry, despite the potential that it could have been otherwise. By narrowing the scope of legitimate chemistry, Lavoiser's revolution nurtured the blossoming of composition-based discovery that was describing the three-dimensional structures of molecules before the physicists were prepared to accept the reality of atoms. Simultaneously, it pruned away green branches of property-based investigation that may yet have borne fruit, delaying the chemistry of spontaneous reactions. I use the word 'delaying' here intentionally. Naturally, it is impossible to make positive claims about

alternative histories; the current state of the chemical sciences in a world where the phlogistonists maintained their tradition alongside the new chemistry can never be known. We do, however, have recourse to an independently-formed community of chemical practice, one that has explored the physical chemistry of reaction space without interference from social or political culture: living organisms.

Evolution as a chemical practice

The evolution of life on Earth provides an example of developing chemical knowledge outside of human social systems of science. Life has been performing a comprehensive scan of the physico-chemical space for four billion years. Naturally, the knowledge gained has not been encoded in stories, texts, or equations. Rather, it is embodied in living organisms themselves. Embodiment as a way of knowing is more reliable than knowing in language because reality provides a more robust test than rationality: rhetoric can make a false theory convincing but cannot make it perform work. Indeed, we consider our own scientific knowledge more firmly established when it is embodied in instrumentation and equipment that extends human senses and abilities. Evolution, and the diversity of life that it generates, provides for many parallel paths of experimentation where different environmental conditions create a useful variety of pressures against which a chemical system is constantly tested. As a peer review mechanism, practical physical employment is far superior than popular social acceptance: the chemical knowledge expressed by life is definitively replicable.

This is not to suggest that living systems subject to Darwinian evolution is a perfect experimental mechanism. Evolution is also subject to certain biases such as conservatism, abundance bias, and a need to preserve homeostasis.

Implied in the word ‘evolution’ is that the physical and chemical space living systems can explore is limited to those areas that may possibly be reached from areas previously explored. Life is fundamentally conservative: it builds on what already exists rather than starting *de novo*. As far as we know, all species currently living on Earth descend from a common

ancestor. If radical, spontaneous departure from the fundamental model is possible it has not been observed. Even though evolution is continuously iterating through the accessible solution space and allowing alternative solutions to co-exist in parallel, its requirement for continuity constrains what solutions it may encounter. Human science, on the other hand, is not limited in this way because leaps of inspiration are possible. Science is therefore far more likely than evolution to discover and harness nuclear fission as an energy source, even though we have been gathering knowledge for far less time.

Second, life shows a bias towards the elements and energy sources most abundant for use in its immediate environment. Embodied knowledge is reliable, but the range of experimentation is ultimately circumscribed by the availability of the raw materials with which the organism could work. Carbon, hydrogen, nitrogen, oxygen, phosphorus, sulfur, iron, calcium, potassium, sodium are the most abundant elements in living systems because they are the more abundant elements in the environment. Forms of energy, as well as matter, are more or less abundant according to the environment: solar energy in the sunshine, geothermal vents in the deep ocean. Connecting the two constraints to imagine an organism that has evolved a type of radiophagy that enables its metabolism of nuclear fission, we would expect to find it living in or on radioactive mineral deposits and for it to be better adapted to uranium than plutonium. Technological development does not share this limitation. Science, engineering, and industry enable humans to adapt the environment to our needs. Materials and energy are collected and directed to where we require them in suitable quantities and qualities.

Finally, extreme chemical activity or physical conditions are incompatible with the most sensitive or most critical physiological activities. Evolution is less likely to successfully explore processes that put essential functions at risk for the obvious reason that they are less likely to survive long enough to be reproduced in subsequent generations. Homeostasis, the stability needed for survival and reproduction, maintains the platform through which evolution is able to explore. Here again fission energy is less likely to have evolved due to the danger that high energy photons and particles pose to the

stability of organic structural, mechanical, or information storage systems. Living systems have developed methods to synthesize and store some dangerous chemicals, such as extreme pH conditions or the toxins produced by venomous and poisonous organisms through developing specialized organs and tissues to provide protective space, shielding, and time. Human science and engineering have also developed the means to separate dangerous processes from our critical life systems. Radioactive sources would not be stored in maternity wards, for example, although humanity's mixed (if not failing) record on protecting our vulnerable populations from hazardous materials shows that survival is not as strong a driving force in our own development.

Both science and evolution are historically contingent, limited by the availability of resources, and guided by practical priorities, and each provides an effective mechanism for the discovery and refinement of chemical knowledge. Having access to a second, independent chemistry community allows us to compare practices and question differences. For example, living cells perform safe, robust, and coordinated synthesis, storage, transport, and disposal of a large variety of molecules within their microscopic borders. How do they achieve this level of precision while respecting energy and material constraints?

Biological reaction processes are almost universally enzyme mediated, and so performed within highly tailored nanoscale reaction spaces. In previous work I have claimed that by imitating these biological reactors structure in synthetic materials we might capture the advantages of evolutionary chemical knowledge in a more suitable medium for human science and industry[31]. At that time, we recognized that nanoscale confinement contributed towards reaction dynamics by paying some of the entropic costs in advance.

The work presented in this thesis significantly builds on that work by identifying and quantifying the thermodynamic effects expanding the range of their application. Nature shows us a role for entropy in molecular machines and well-ordered nanoscale spaces that is not contemplated by classical and statistical mechanics. Further development of a chemical

theory of entropy to guide the development of nanoscale reactors offers a path to achieve a new and more sustainable chemistry.

In contrast to chemistry's early expectation of uniformity in theory, chemists today can and do move seamlessly between different chemistries according to the utility of a given model to illustrate the chemical principle under discussion or to apply a chemical method in practice. This development is, in my estimation, good. It acknowledges that theories of entropy for continuous matter, for large numbers of random particles, and for systems too small for statistics all contribute to understanding while denying any requirement to choose between them for any reason other than their usefulness in context. It also invites a kind of speciation within the chemical community of practice into sub-communities of more specialized practices, evolving to maximally fill each niche of chemical knowledge.

As with the evolutionary community of living organisms, the branching complexity of subspecialties, their combinations, and extensions enables a more thorough exploration of our chemical environment and a broader application of the knowledge that we discover therein. It also allows modern chemists to move between non-congruent and non-hierarchical models of chemistry comfortably, rapidly, and routinely with sensitivity to both the physical environment of the system under study and the social environment of the chemist at the moment of application. The legitimacy of a model determined only by its suitability to address the problem to which it is applied. If we were to evaluate which of the models is "better", we must first identify the task we wish it to perform. This trait may be most clearly exemplified by computational chemistry where practitioners must make an explicit choice of chemical theory to produce their models and simulations. The next chapter uses simulation to examine a challenge in environmental science and begins to explore how entropy could be leveraged to support intramolecular reactivity.

3. The Role of Entropy in PFAS degradation

This chapter was previously published as:
McTaggart, Matt, and Cécile Malardier-Jugroot. "The role of helicity in PFAS resistance to degradation: DFT simulation of electron capture and defluorination." *Physical Chemistry Chemical Physics* 26.5 (2024): 4692-4701.

Abstract

Defluorination of perfluorinated alkyl substances (PFASs) via the direct capture of excess electrons poses a promising path to environmental decontamination. Herein we show that quantum-chemical model optimization methods can be adapted to simulate the changes to molecular geometry that result from electron capture. These reaction pathways demonstrate that the introduction of an additional electron causes a loss of the helical arrangement along linear carbon tail chains. Regaining helicity is sufficiently favourable to enable fluoride release in C7-C10 PFAS chains; shorter chains are enthalpically hindered from degradation while the additional charge is stabilized on longer chains by the greater entropy their flexibility permits. These results suggest that reductive PFAS treatment processes could be made more effective under high pressure or confined conditions.

Introduction

Perfluorinated alkyl substances (PFAS) comprise a large class of aliphatic compounds in which all carbon-hydrogen bonds in the non-fluorinated equivalent have been replaced with carbon-fluorine bonds. Fluorination results in increased hydrophobicity and resistance to chemical or physical degradation as compared to their hydrogenated alkyl counterparts[32]. It is due to their structural stability, and to their long-term unregulated industrial production and disposal, that PFAS have become pervasive and persistent environmental pollutants[33]. This in turn has motivated a rapid rise in efforts to understand PFAS toxicology, decontamination, and destruction.

Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) and their anions are especially widespread and have therefore received

relatively high scrutiny from the scientific and regulatory communities. The United States Environmental Protection Agency is empowered to develop non-enforceable, non-regulatory national Health Advisories to identify the "drinking water concentration level of a specific contaminant at or below which exposure for a specific duration is not anticipated to lead to adverse human health effects." In June 2022, published updated interim Health Advisory values for PFOA and PFOS, concluding that the lifetime interim Health Advisory for PFOA[34] is 0.004 ng/L (4 parts per quadrillion (ppq) – 0.006% of the 0.07 µg/L (70 parts per trillion (ppt)) values published in 2016) and for PFOS[35] is 0.02 ng/L (20 ppq – 0.03% of the 70 ppt 2016 value). These updated values indicate that in practice there is no safe level of these abundant, ubiquitous, highly stable substances.

Naturally, PFAS degradation and decontamination has also become a high value research domain. Effective techniques are needed, and quickly, to extract and destroy the PFAS that has already infiltrated our water supply. The literature is rich with recent reviews on the current state of the overall field[36–41], emerging technologies[42–44], advanced reduction and oxidation methods[45–47], as well as several specific techniques[48–53]. The focused community effort has generated exciting advances towards effective and efficient PFAS degradation in organic solvents[54] or low/no solvent[55] but methods that operate in aqueous solution hold the promise of in situ PFAS groundwater decontamination. One set of techniques for the degradation of dilute PFAS in water is via the capture of hydrated electrons, e^-_{aq}. The sources of electrons vary and include the use of electrodes[56], plasmas[57–60], photochemical interactions with electron donors[61–64], or radiolysis of the water[65–67].

As a recent review comprehensively covers, theoretical studies to elucidate the defluorination mechanisms complement the experimental work although identification of the elementary steps on the reaction pathway remains as recalcitrant as the molecules themselves[68]. Theoretical and experimental studies on the site and rate of electron insertion show that electron capture is independent of the length of the carbon chain or carbon-fluorine bond dissociation energy[69,70]. Bentel's comprehensive study demonstrated a correlation between carbon chain length and degradation rate that remains

unexplained by their table of carbon-fluorine bond dissociation energies[71]. Yamijala's Born-Oppenheimer Molecular Dynamics (BOMD) study found that the initial loading of the additional electron across the carbon chain made the site of defluorination nearly random on an ultrafast (<100 fs) timescale[72]. Simulation of hydrated electron dynamics by Biswas et al. showed polarization of the surrounding water shell before electron capture that affected both insertion point and subsequent C-F bond strengths, altering the relative probability of which fluorine will break its bond to carry the charge away as an anion[73]. Their subsequent dynamic work on expanded systems further confirmed the behaviours and femto- to picosecond timescale[74]. Taken together these studies suggest that the mechanism linking chain length and degradation rate occurs after electron capture. Furthermore, these theoretical studies are consistent in their treatment of bond strength as the decisive factor in the determination of whether and where defluorination will occur and understate the contribution of how those bonds are arranged within the molecular structure.

Structural representations and mental models

From the beginning, PFAS compounds were discussed in contrast to their non-fluorinated analogues[32]. Even the name "per- and poly-fluorinated alkyl substances" defines the class of compounds by comparison to their hydrogen-only counterparts. The analogy is a useful one and quickly conveys the principal characteristic of the class; however, the convention privileges the similarity in schematic bond connectivity over the differences in molecular geometry created by the H to F exchange. Because the stronger C-F bond dissociation energies are foregrounded they have been the subject of theoretical studies. Conversely, the shorter bond-bond length and the higher electronegativity, higher electron density, and larger atomic radius of the fluorine constituent produce important differences between the PFAS and its H-analogue bond lengths, angles, and dihedrals and the rotational freedom about the C-C backbone.

For a literal illustration of how bond structure becomes privileged, we must consider the structural formulae used to identify the compounds. We use structural formulae to picture the molecules under discussion, and by so doing may easily forget that they are not actually "pictures." The symbols

and connections constitute a pictogram with rules for composition and interpretation. It is a visual language: the structural formula for octanoic acid shown in Figure 3.1 is a translation of that name into pictographic form, not an image of the molecule itself. Where the carbon chains appear to be drawn in the trans configuration, we ought to understand that to be fallacious. This is the default conformation in which to display alkyl chains with the understanding that at room temperature CH_2-CH_2 bonds undergo rapid, fluid exchange between the various conformers. However, the barrier to rotational conformation exchange is significantly higher for CF_2-CF_2, so the same assumption of fluidity between conformers is not appropriate and therefore the trans-default representational standard does not apply. If we are to understand both the alkyl and PFAS structural formulas as non-conformer specific, then we can conclude that the structural formulae contain no spatial information.

Yet the illusion is compelling enough that one could easily misinterpret the identical line lengths and direction as indicative that the molecular geometries are also identical. In recognizing that it is a connection schematic only, we should also recognize that the effect of H-F exchange on bond length, direction, and rotational freedom are not represented at all. It is far more difficult to notice what is absent than what is present and so the evident similarities are given greater attention than the non-evident differences. This is a problem for two reasons. First, mental modelling is an important tool chemists use to develop and evaluate mechanism diagrams. Second, neglecting the molecular geometry gives the false impression that the molecular geometry can be neglected. In a tightly formed, stable compound the bond lengths, angles, and dihedrals are critical contributors to its chemical behaviour and available reaction pathways.

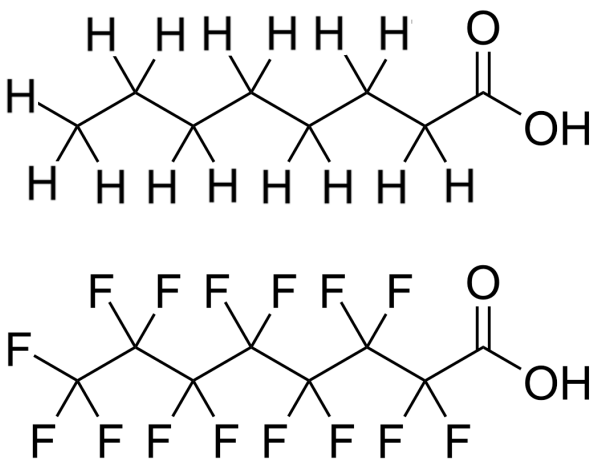


Figure 3.1: Structural formulae of octanoic acid (top) and perfluorooctanoic acid (bottom). The layout seems to convey that the two molecules share the same linear trans conformation; however, these are connectivity schematics only and contain zero geometric information.

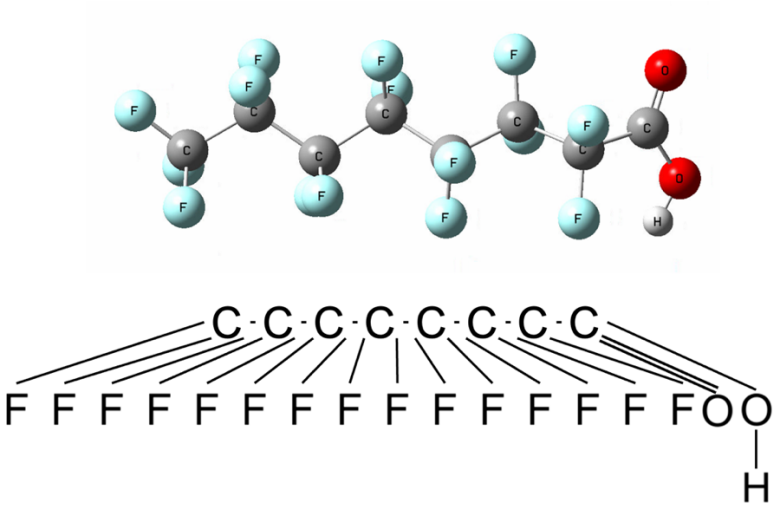


Figure 3.2: A picture of an optimized model of PFOA (top) and a second structural formula of PFOA (bottom). The picture depicts molecular connectivity and geometry and thus comparatively greater information content than the Fig. 1 structural formula, despite visual similarity. By contrast, the information content of the PFOA structural formula shown here is identical to that held by the more typical layout in Fig. 2.1.

Molecular geometries of linear PFAS chains

In the specific example of octanoate/perfluorooctanoate, the direct structural analogue takes on new and important features when their geometries are

optimized to their ground state. Most notably, PFAS carbon chains twist into a compact helix, in contrast to the straight, linearly-aligned carbon chain of the H-analogue. The more accurate and complete representation also shows the similarities in connectivity but doesn't overstate its importance, inviting different perspectives on the problem of PFAS resilience. For instance, the helical conformation makes it more obvious that the C-F bond is not only stronger but more difficult to access than the C -H bond, which could impact treatment methods. The compact structure makes the PFAS more rigid than the H-analogue and this mechanical rigidity could affect reactivity. A helical structure creates a persistent conformational chirality which could alter its susceptibility to degradation under treatment conditions. If the compact, helical conformation is the stable conformation: how can the PFAS be induced into a less-stable elongated, linear state? The point of this discussion is not to advocate for 3D ball-and-stick or electron density representations to replace all 2D line drawing as a publication standard (although it would improve our accuracy in graphic communication of our subject molecules) but instead to underline the value of increasing the number and type of (sometimes literal) perspectives on a problem.

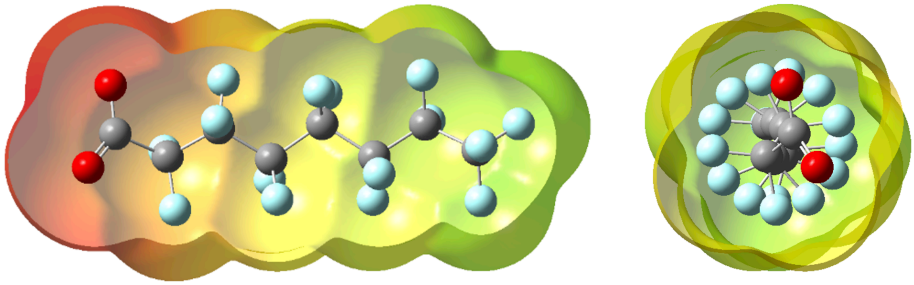


Figure 3.3: Side and end views of a perfluorooctanoate model with charge on the electron density surface shown in red (negative) at the carboxylate head group progressing toward green (neutral) at the tail. Carbon is shown in grey, fluorine in blue, oxygen in red. The helicity imposed by fluorine-fluorine repulsion is evident.

Computational Details

The level of theory employed in this work, DFT B3LYP-D3(BJ)/6-311+(2p,2d)[75–77], follows from the important experimental validation of the method conducted by Schilberg and coworkers[78]. They identified stable

structural conformers of PFOA by comparing theoretical model predictions to molecular rotational resonance (MRR) spectra, noting that fluorine-fluorine repulsion induces a helical conformation of the carbon tail. This comparison validates the theoretical model used for the systems shown here. While we focus on the conjugate base in this work to better represent the oxidation state of the compounds under environmental conditions, our models correspond with the trends demonstrated in their experimental work.

Bentel and co-workers employed the same model chemistry for their extensive study of bond dissociation energies of per- and polyfluorinated carboxylates and sulfonates at varying chain lengths[71]. That study, unlike this one, employed the SMD model to provide implicit simulation of solvation in water. We tested the model but ultimately chose not to include it in this work. Critically, the dielectric cavity generated by the implicit model stabilizes a local metastable conformational minimum preceding a critical transition state, clouding the reaction mechanism revealed by the simulation method. In fact, the developers of SMD have shown that it is not well suited for ion dissociation calculations without including a shell of explicit water molecules, an issue observed across ionic solutes expected to have a strong hydrogen bonding interaction with water[79,80]. The PFAS species under investigation here are compact and electron rich, indicating that the intramolecular forces, rather than solvent interactions, are decisive. For these reasons, the high computational expense of computationally-sound explicit aqueous solvation is neither justified nor required for the simulation sets that follow.

That being said, DFT methods using the B3LYP functional are known to overbind certain anion states, predicting a stable or metastable anion where none exists[81,82]. While existing experimental and dynamic simulation results strongly indicate that a -2 oxidation state with a lifespan of at least femtoseconds must be possible, we confirmed key optimizations using the range-separated CAM-B3LYP functional which corrects the energies of long-range exchange interactions and improves the accuracy of energy level calculations[81,82].

Simulating electron capture through optimization

Although the terms are occasionally used interchangeably, molecular modeling and molecular simulation are distinct computational processes. To create a molecular model is to produce a representation of the molecule that suits the purpose for which it was built. By contrast, to perform a simulation is to put a model into action and to study its response to stimulus. In both modeling and simulation, we apply theory to a construction in an attempt to gain or validate insights by extension of the theoretical results onto the real molecule. For models, we might study its atomic geometry, bond strengths and lengths, or electronic structure. Simulations of molecular behaviour could tell us about reaction mechanisms, transport properties, spectroscopic outputs, or intermolecular interactions.

Not all calculation processes are common to modeling and simulation. The process of optimizing the geometry of a molecule, for instance, begins with the set of nuclear charges and their approximate positions and the number of electrons in the system. One tries to make the initial locations of the nuclei a reasonable guess, but in principle the positions are arbitrary. The Born-Oppenheimer Approximation holds that electrons adapt instantaneously to nuclear movement and therefore allows the electronic orbital structure to be calculated on a static landscape[83]. The total energy of the molecular system can now be determined by application of the appropriate theory. If we were to map all the possible nuclear positions we would find a multidimensional surface whose “height” is determined by the system energy - the potential energy surface (PES). Peaks and valleys on the PES represent nuclear coordinates with particularly high energy (highly strained geometries) or low energy (stable geometries). Geometric optimization is the iterative process of moving the nuclei “downhill” along the PES until coming to rest at the local or global minimum energy, corresponding to physically meaningful metastable or stable states[84]. This set of nuclear coordinates and molecular orbitals now form a theoretical model of the molecule under study. Because optimization is a process used in model generation and not application, optimization is typically considered a modeling process and not a simulation process.

However, what if the initial geometry is not arbitrary but is itself a physically meaningful optimized model? Could optimization then simulate a spontaneous chemical process? Most inter- or intramolecular processes rule out this hypothetical by definition: the optimized model is already at its energetically stable geometry and therefore not prone to reaction. Electron capture stands out as an exception. According to the Born-Oppenheimer Approximation, electron motion is instantaneous compared to nuclear motion and so the optimized molecular geometry of the pre-capture state is a physically meaningful initial geometry of the post-capture state. Therefore, optimization of a model generated on the PES of the n oxidation state would move downslope along the PES of the n-1 oxidation state in a manner that simulates the molecule's response after reduction. Because the starting and end points are physically relevant, the pathway that the optimization follows to connect them represents a mechanism of action.

This study uses optimization methods to simulate the behaviour of PFAS molecules immediately following reduction by electron capture from the -1 to the -2 oxidation state. All carboxylate and sultanate models were optimized to the DFT CAM-B3LYP-D3(BJ)/6-311+G (2d,2p) level of theory at the -1 oxidation state using the Gaussian 16 software package[85]. The agreement between these models and the experimental geometries supports our claims that the optimized structures can be used as a physically meaningful starting point for simulation of the geometric changes that follow reduction in related compounds[78].

The oxidation state was then set to -2 to place the model on the new, post-electron capture PES. Examination of the calculated orbital energies of the molecular geometries reveal that the additional electron initially lies in at a positive energy level in all cases. The positive orbital energy (or negative electron affinity) indicates that it either does not attach at all, in which case the model is in conflict with experiment, or that the electron attaches via resonance with a metastable orbital. To determine the status of the unbound electron, we examine the parent molecule for the presence of a repulsive Coulomb barrier. If present, an additional electron may tunnel through it into an orbital level that is unbound (positive energy value) yet able to play temporary host to an electron trapped behind the Coulomb barrier[82]. The

stabilization method is performed by varying the scaling factor α of the diffuse functions on the atomic centres and then plotting the higher-lying orbital energies as a function of scaling factor. If a Coulomb barrier capable of supporting a metastable anionic state is present, it will be revealed by the presence of "avoided crossings" on the plot – points at which pairs of orbitals sharply change in their sensitivity to the scaling factor – indicating resonance between the α-sensitive exterior state and the α-insensitive attached inside-barrier state (Figure 3.4)[82]. We applied the orbital exponent stabilization method using DFT CAM-B3LYP-D3(BJ)/6-31+(p,d) on the initial geometries of carboxylate and sulfonate structures[82,86,87].

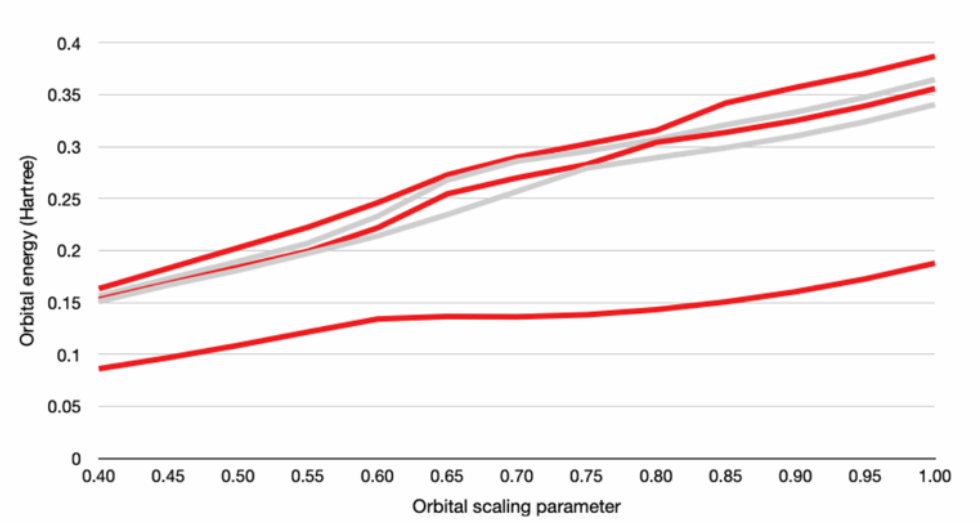


Figure 3.4: Stabilization plot of PFOA after electron capture showing the highest occupied and lowest unoccupied orbital energies as a function of the diffuse basis functions' scaling factor. The rate change in the lowest plot line around (0.60, 0.14) is created by a resonance state indicative of a metastable anion.

A smaller basis set is acceptable for the basic test provided that we accept the limitation that the results cannot be used to reproduce the true resonance energies[82,86]. All searches confirmed the presence of avoided crossings, providing evidence that the unbound electron lies in a metastable attached state consistent with existing experimental and theoretical results. Indeed, applying the stabilization method at points along the optimization pathway and at the final geometries shows that the orbital energy decreases towards the bound state as relaxation progresses.

With the metastable attachment status of the extra electron established, subsequent simulation of molecular relaxation along the geometry optimization pathway on the reduced PES could be completed using the uncorrected B3LYP functional. In this application, its usual limitation permits a wider search amongst the relevant states in which the electron is retained. These simulations are therefore of the 'extra electron' type and do not include the changes to the molecule that could be induced by the approach of an explicit hydrated electron[73]. The optimization pathway is charted to show metastable and transition states as well as the final stable state of the system after reduction. The orbital stabilization method can provide an estimate of the expected lifetime of the metastable state given energy level and tunnelling barrier information and a crude approximation places the stability timescale in the femtosecond range, consistent with Biswas' dynamic predictions; however, we can make no claim on the time or rate of reaction. Optimization does not provide time information: a greater or lesser number of steps in the simulations that follow do not in any way indicate a slower or faster process.

Results and discussion

Carboxylate simulation

Prior experimental and theoretical work on PFOA has focused on the most linear conformation since that is its lowest energy conformer. Although fluorinated alkyl chains are not as fluid in conformation change as their hydrogenated analogues, some variability in conformer is present in samples[78]. Conformer search was performed using Avogadro: an open-source molecular builder and visualization tool Version 1.2.0[71]. The systematic molecular mechanics search used the MMFF94 force field to scan the rotatable bonds and generated 243 geometric isomers[89]. We then formatted the output files for Gaussian and optimized these geometries to the PM6 semi-empirical level of theory[90]. The 100 lowest energy non-equivalent conformers were then optimized using DFT B3LYP-D3(BJ)/6-311+G. Eliminating the high strain conformers from this set left 43 non-equivalent conformers remaining, of which the 7 most stable were further serially optimized to DFT B3LYP-D3(BJ)/6-311+(2p,2d) at both the -1 and -2 charge. The results are tabulated in Table 1, below. As mentioned above, simulation of electron capture via the addition of an extra electron does not

capture the probability or location of electron insertion so the initial change in energy between the -1 and -2 charge states are reported but are qualitative at best.

The sites of defluorination on these structures give us the first indication of a trend that will continue across the changes to chain length and head group below. The five most stable conformers each terminate in a set of trans carbon-carbon bonds and in each case it is the terminal fluorine that is lost. Conformers six and seven are intersected by a cis bond on the fifth and sixth carbon, respectively. In those cases, it is a fluorine from the lowest numbered carbon on the cis bond that carries away the excess charge. In all structures the carbon-fluorine bond that breaks is the one whose loss enables the reformation of a compact helical structure. The mechanism is most clearly demonstrated by tracking the geometry of the most stable, most linear conformation as it relaxes after electron capture.

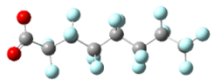
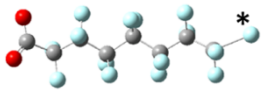
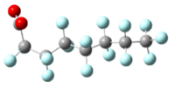
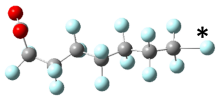
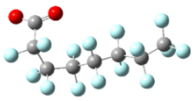
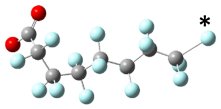
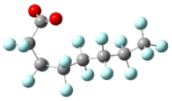
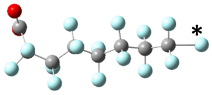
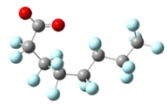
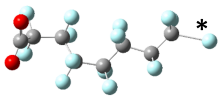
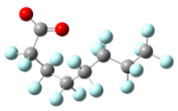
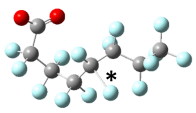
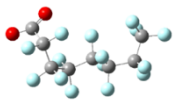
Initial conformation, charge = -1		Post-electron capture, charge = -2	
	Ee: -1953.682549 Ha Normalized: 0.00 kJ/mol e^- capture: 283.74 kJ/mol		Initial: -1953.574478 Ha Final: -1953.609328 Ha Change: -91.50 kJ/mol
	Ee: -1953.681983 Ha Normalized: +1.49 kJ/mol e^- capture: +291.62 kJ/mol		Initial: -1953.57091 Ha Final: -1953.57091 Ha Change: -91.65 kJ.mol
	Ee: -1953.681236 Ha Normalized: +3.45 kJ/mol e^- capture: +308.19 kJ/mol		Initial: -1953.563853 Ha Final: -1953.60162 Ha Change: -99.16 kJ/mol
	Ee: -1953.681089 Ha Normalized: +3.83 kJ/mol e^- capture: +316.27 kJ/mol		Initial: -1953.56063 Ha Final: -1953.605819 Ha Change: -118.64 kJ/mol
	Ee: -1953.680853 Ha Normalized: +4.45 kJ/mol e^- capture: +315.83 kJ/mol		Initial: -1953.56056 Ha Final: -1953.603718 Ha Change: -113.31 kJ/mol
	Ee: -1953.680818 Ha Normalized: +4.54 kJ/mol e^- capture: +325.68 kJ/mol		Initial: -1953.556774 Ha Final: -1953.597001 Ha Change: -105.62 kJ/mol
	Ee: -1953.680777 Ha Normalized: +4.65kJ/mol e^- capture: +309.68 kJ/mol		Initial: -1953.562828 Ha Final: -1953.605804 Ha Change: -112.83 kJ/mol

Table 3.1: The results of the search for most stable carboxylate conformers before and after the addition of an extra electron. The total electronic energy (Ee) of each structure is reported in Hartree and normalized in kilojoules per mole to the most stable conformer. The change in energy after electron insertion only reports the geometric relaxation and does not include the cost of capture. The defluorination site is marked by an asterisk.

In all the PFAS species included in this study, the lowest unoccupied molecular orbital is an anti-bonding orbital spread along the carbons in the tail, as one might expect to find at the centre of a cylinder of highly electronegative C-F bonds. The primary impact of the reduced bond order brought on by the insertion of an additional electron is a weakening and lengthening of the C-C bonds. Greater distance between the carbons also increases the distance between neighbouring fluorines, which reduces their steric repulsion and allows the carbons to relax toward their ideal tetrahedral geometry. As a result, the helix unwinds and the tail straightens—longer C-C bonds compensate for the larger fluorine radius and the molecule comes to more closely resemble its alkyl analogue.

By extending bond length and relaxing bond angles, the system realizes an overall energy benefit which creates a metastable local minimum in some chain lengths, as described in detail below. In that case, an activation step is required to activate defluorination. By scanning the reaction coordinate, we find that the process passes through a transition state that joins the metastable elongated conformation with the final, stable helical conformation. The transition state sits atop a saddle point on the PES, a point at which all geometric dimensions are at an energy minimum save one which is at a local maximum. In this case, the dimension at its local maximum is the length of the terminal carbon-fluorine bond as reflected by animating the imaginary frequency. The reaction's activation energy is the energy required to stretch the C-F bond to this transition state. At the transition state the reaction could regress back to the local minimum, but once the transition state is crossed the molecule spontaneously and irreversibly relaxes into its helical configuration as the additional electron is carried away by disassociation of the terminal fluoride ion.
Initial conformation therefore impacts which fluorine is most likely to leave because it determines which compact structure is most accessible and least impacted by the unsaturated carbon. The advantage is multiplied over the chain of trans carbons returning to their helical conformation and so it is at the terminal points of those segments that defluorination occurs.

Our observation that the site of defluorination is more strongly dependent on the geometric conformation of the molecule than on the strength of a

particular C-F bond is new, although it is consistent with other results suggesting that the addition of the electron incites but does not directly cause defluorination[70].

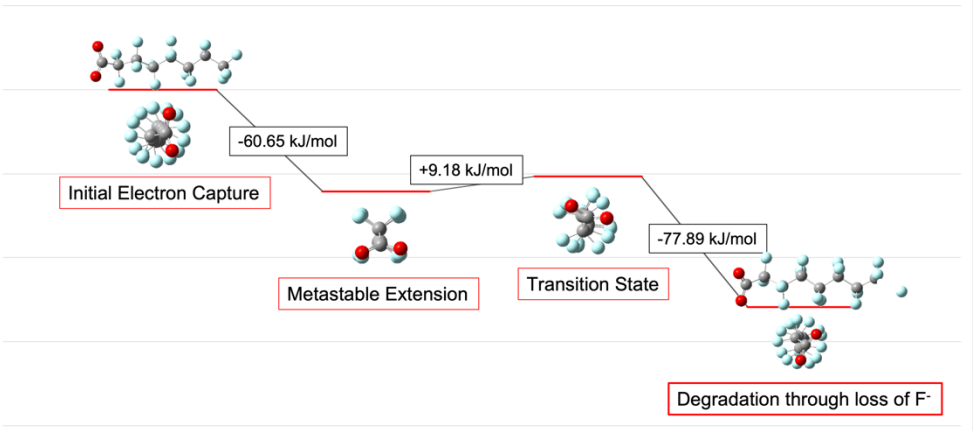


Figure 3.5: The relaxation pathway of PFOA after the capture of an additional electron. Initially, lengthening C-C bonds cause the molecule to lose helicity and relax into a straight and extended conformation wherein C-F bonds remain intact. Only regaining the compact, helical compact form delivers enough of an advantage to afford the cost of C-F dissociation.

The effect of chain length

Because the length of the helical chain segment seems to govern defluorination and because previous studies have shown a correlation between overall chain length and degradation rate, we performed the electron capture simulation on PFAS chains from C4 to C12. The graphs below chart the progression of two characteristic behaviours of the PFAS chain during the relaxation process: the left-hand vertical axis measures the dihedral angle of the first and third most distal fluorine atoms as representative of the overall helicity; the right-hand vertical axis measures the bond length of the terminal C-F bond. The same method was applied to a set of carboxylates and sulfonates to assess the impact of the head group on the observed trends.

Carboxylates

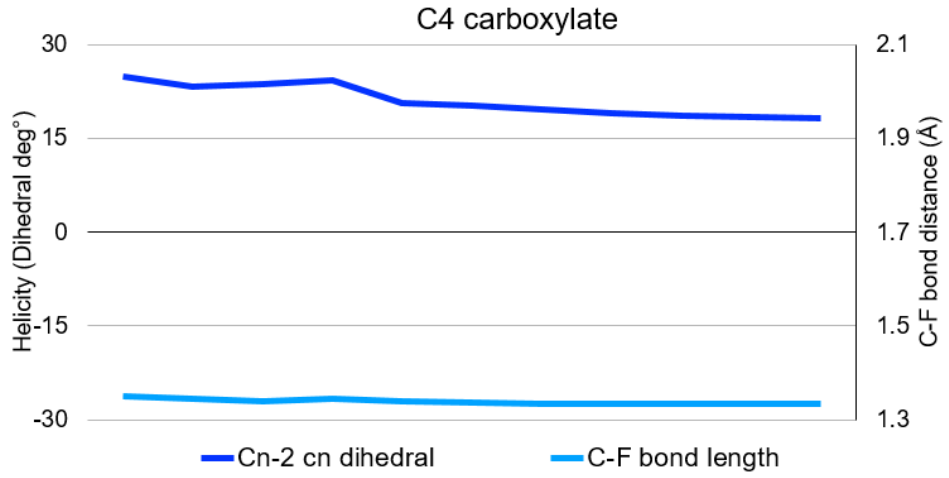
In the short (C4 – C6) chain carboxylates, the repulsion created by the additional electronic charge in the anti-bonding orbital on the carbon

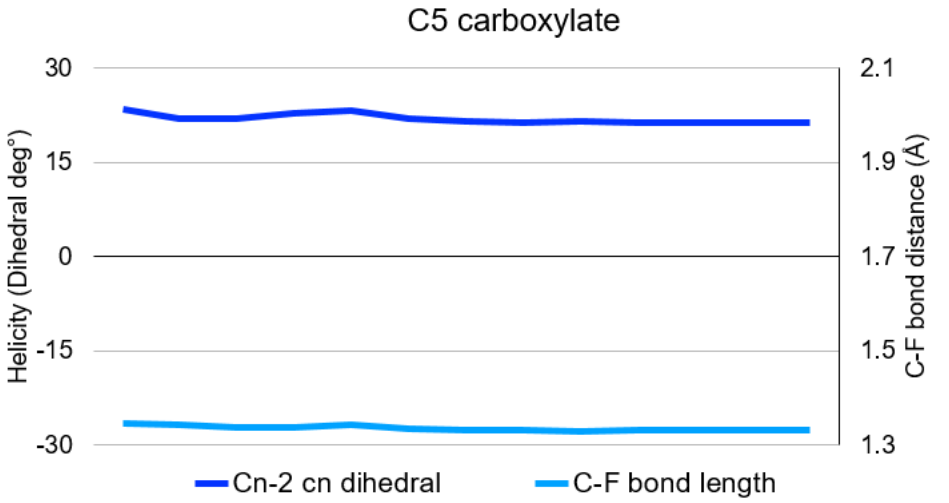
backbone produces little change in helicity; the combination of enthalpic C-C bond stretching and entropic freedom is insufficient to overcome helicity and cannot pay the energetic cost of fluoride dissociation (Figure 3.6). Scanning the energies associated with lengthening the terminal C-F bond reveals that the fluoride/zwitterionic PFAS system is still energetically favoured; however, the reaction pathway contains an activation step to reach an unfavourable transition state before it can achieve fluoride dissociation. Molecular geometry remains kinetically frustrated in the elongated, -2 oxidation state without additional energy input.

The activation energy was calculated as the energy difference between the optimized meta-stable state and the transition state determined by QST3 and Berny TS optimization. The amount of energy required decreases as the length of the carbon chain increases, with C4 requiring the most and C6 the least. At 33.2 kJ/mol and 17.3 kJ/mol respectively, the C4 and C5 chains are unlikely to overcome the activation energy at standard temperatures; C6 should obtain 4.2 kJ/mol from its environment with sufficient probability that the reaction mechanism should be achievable under standard conditions, although at a reduced rate of reaction compared to the lengths that follow.

Carbon atoms	Activation energy (kJ/mol)	Terminal C-F bond length (Å)
C4	33.18	1.52642
C5	17.34	1.45511
C6	4.19	1.38710

Table 3.2: Energy required to move from the meta-stable point to the transition state along the reaction pathway.


C4 carboxylate
30
15
0
-15
-30
Helicity (Dihedral deg°)
2.1
1.9
1.7
1.5
1.3
C-F bond distance (Å)
Cn-2 cn dihedral
C-F bond length


C5 carboxylate
30
15
0
-15
-30
Helicity (Dihedral deg°)
2.1
1.9
1.7
1.5
1.3
C-F bond distance (Å)
Cn-2 cn dihedral
C-F bond length

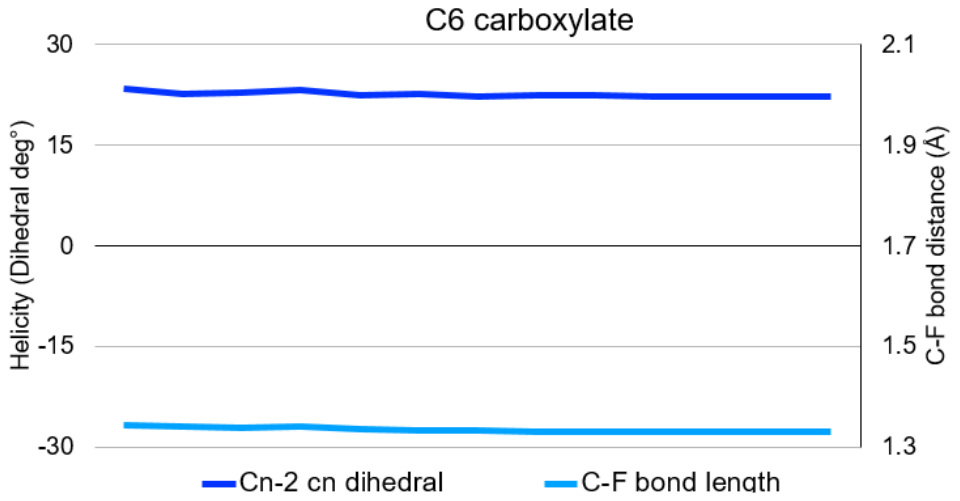
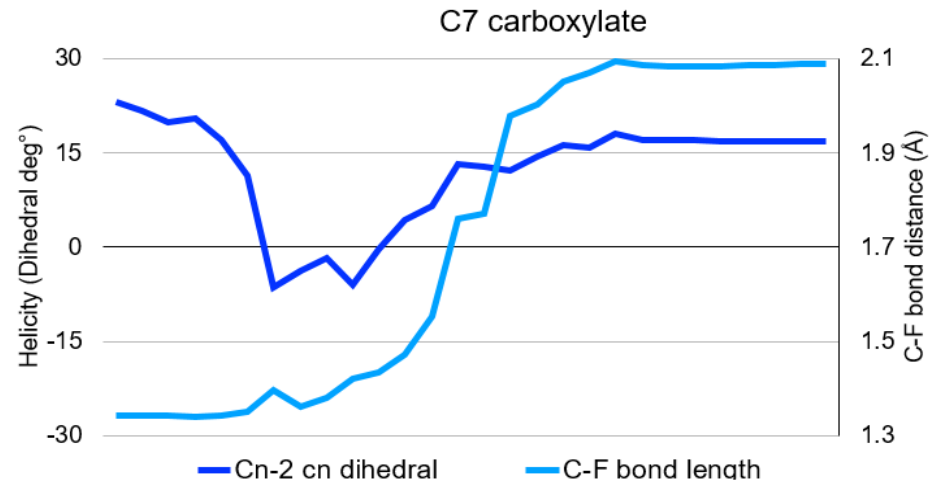
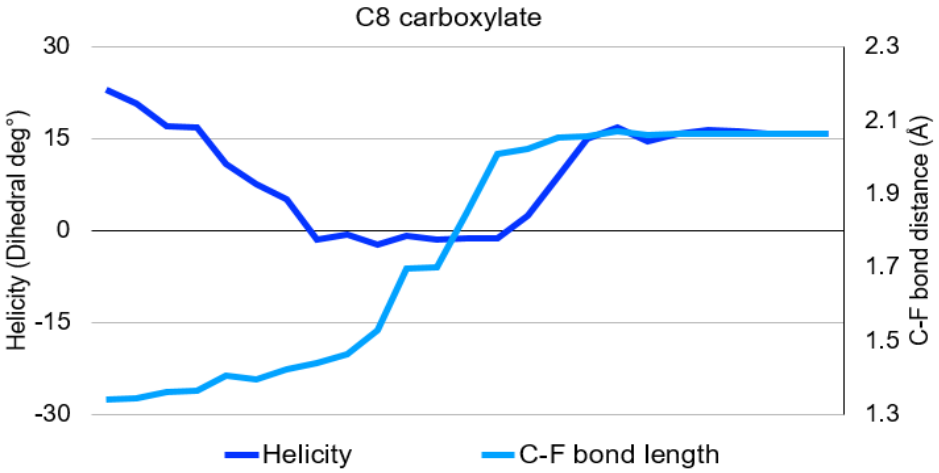


Figure 3.6: The results of simulated electron capture on C4 – C6 perfluorinated carboxylates on the helicity and terminal C-F bond length. Each of these short-chain molecules stabilize the -2 state without fluorine dissociation.

From C7 to C9, no significant activation energy is required: relieving the bond elongation caused by electron capture provides a sufficient energetic benefit to pay the enthalpic cost of fluoride release. The mechanism occurs as described above: the chain lengthens and straightens before regaining helicity in concert with terminal fluoride dissociation. The C8 molecule PFOA lies in the centre of this band and its progression through the reaction mechanism provides the clearest example (Figure 3.7).

The first effect of electron capture is the elongation and straightening of the carbon backbone, shown in the figures that follow as the movement toward zero of the dihedral angle between fluorines on the *n*th and *(n-2)*th carbons. Lengthening of the terminal C-F bond signals the transfer of the extra electron from the carbon backbone onto the dissociating fluorine, thus removing charge from the antibonding orbital and allowing the structure to relax back into its compact, helical geometry. The end state for these three structures is a near- return to the initial fluorine dihedral angles and loss of the terminal fluorine as a fluoride ion.


C7 carboxylate
30
15
0
-15
-30
Helicity (Dihedral deg°)
2.1
1.9
1.7
1.5
1.3
C-F bond distance (Å)
Cn-2 cn dihedral
C-F bond length


C8 carboxylate
30
15
0
-15
-30
Helicity (Dihedral deg°)
2.3
2.1
1.9
1.7
1.5
1.3
C-F bond distance (Å)
Helicity
C-F bond length

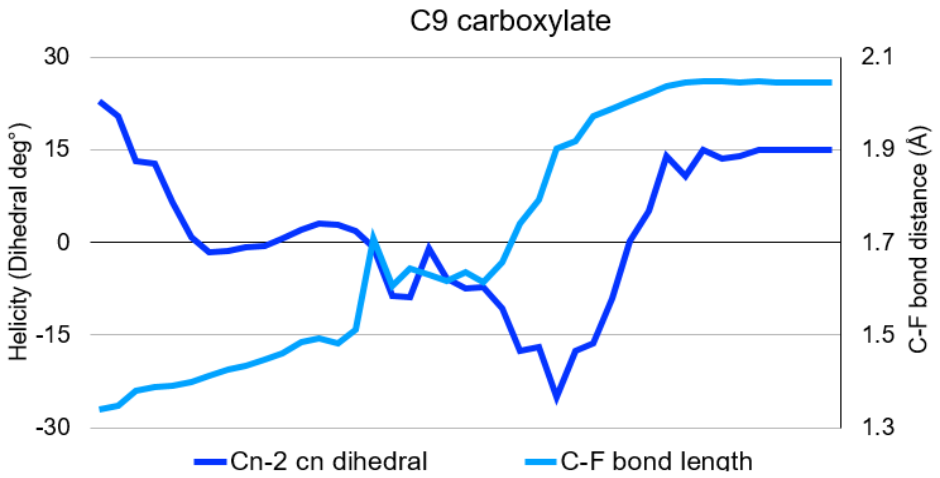


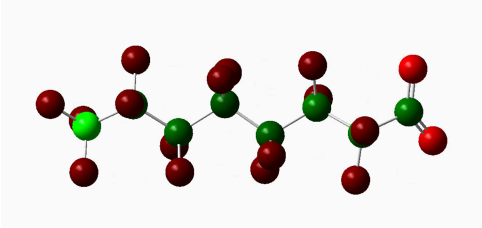
Figure 3.7: The results of simulated electron capture on C7 – C9 perfluorinated carboxylates on the helicity and terminal C-F bond length. Each of these medium-chain molecules elongate and straighten before regaining their compact helical geometry through defluorination.

Calculation of the Mullikan partial charges at each step of the PFOA fluoride dissociation simulation illustrates how electronic charge distribution changes through the fluoride release process.

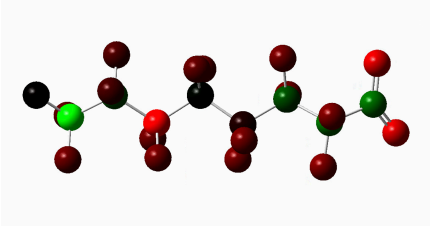
The first panel shows the partial charge distribution before and after addition of the extra electron. Before the molecular geometry adapts to the additional electron the charge is concentrated along the carbon backbone. The charge concentration here is centred about C6. As mentioned above, explicit modeling of the interaction between PFOA and a hydrated electron indicates an insertion point near the carboxylate head group. Nevertheless, the central region of the carbon backbone provides the most energetically favourable molecular orbital and so we can invoke the assumption of instantaneous intramolecular electron motion to find it there before atomic motion has had a chance to react to a specific point of capture.

As the carbon bonds lengthen, charge becomes more evenly distributed along the chain. This point is equivalent to the local minimum at which the relaxation of the shorter chain molecules halts. Next, we see the movement across the transition state and the beginning of dissociation. When the simulation ends at the optimized stable state, the charge distribution is

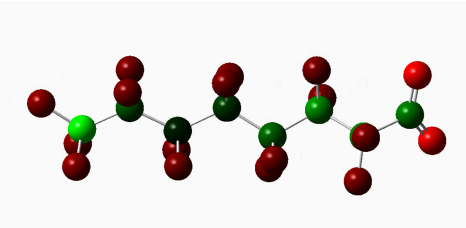
moderate along the carbon chain, now including the terminal carbon. By withdrawing the additional charge onto a fluoride ion the process reduces the positive charge concentrated on the carbon atom.



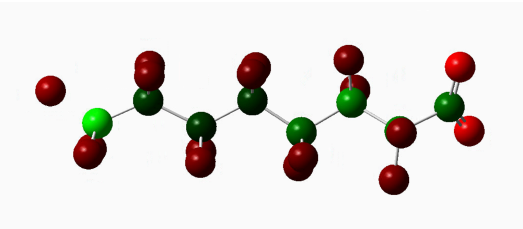
a) PFOA charge distribution before electron capture



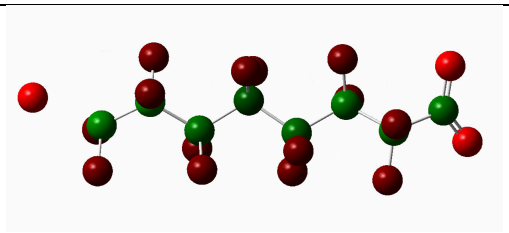
b) PFOA charge distribution immediately following electron capture



c) Charge distribution at the metastable elongated linear state



d) Charge distribution at the transition towards regaining helicity



e) Charge distribution at the end point

Table 3.3: PFOA partial charge distribution during the changes to molecular geometry induced by electron capture, assuming instantaneous movement of the electron from its insertion point to the lowest unoccupied molecular orbital before any changes to molecular geometry have had time to react. Charge distribution runs from -0.75 (bright red) to +1.25 (bright green).

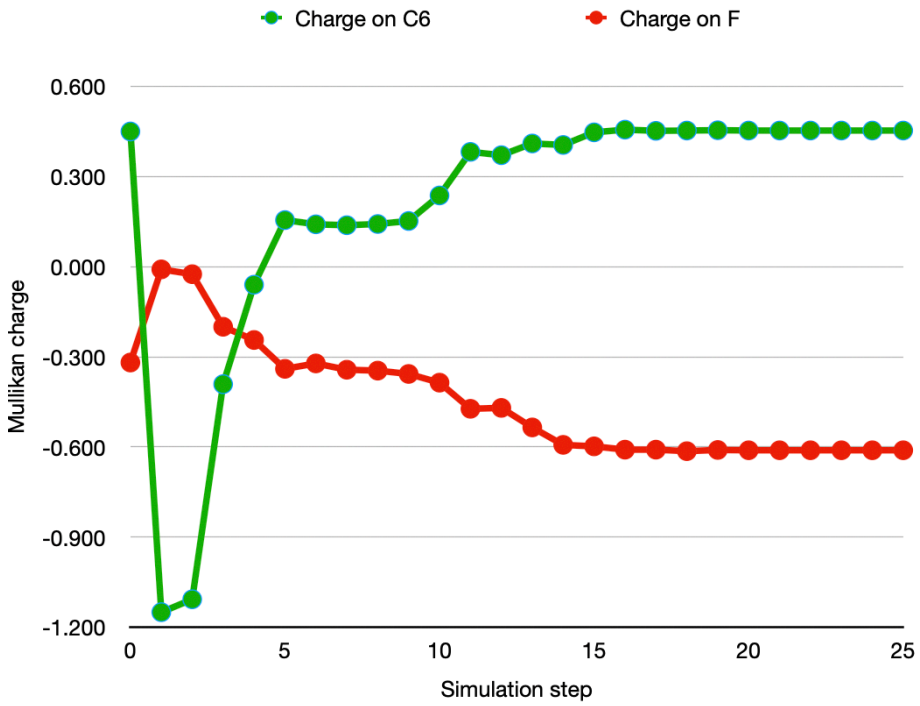
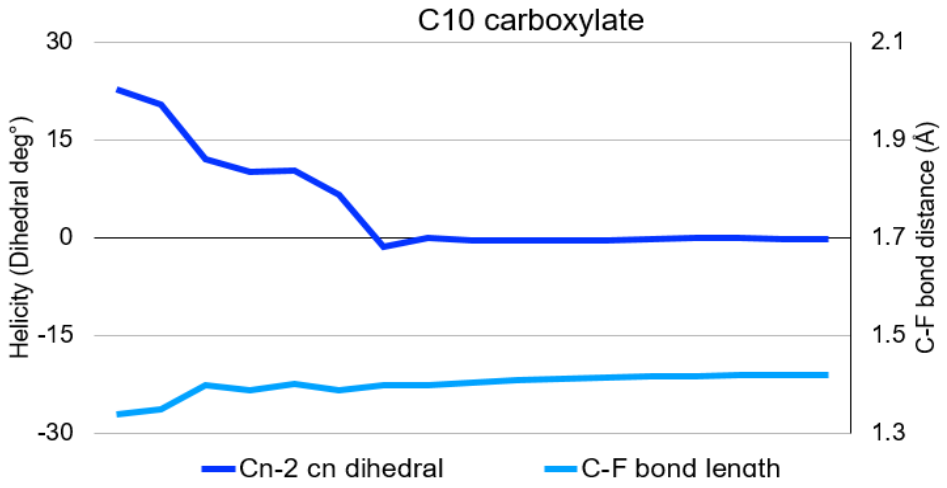


Figure 3.8: Change in charges centred on C6 and terminal fluorine during PFOA relaxation.

These middle-length chains represent the thermodynamic 'Goldilocks zone': there are enough carbon atoms that the additional charge in the anti-bonding orbital is sufficient to overcome the C-F bond enthalpy but not so many carbons that delocalization and flexibility offset the effect.

However, in C10, C11, and C12 the number of carbons lengthens the chain enough to permit stabilization of the additional electron by two complementary mechanisms: decreasing the charge concentration and by increasing mechanical flexibility. First, the anti-bonding orbital is distributed across a greater number of carbon centres. One additional charge no longer offers enough repulsion to extend and straighten the entire chain. The loss of helicity is limited and only significant toward the terminal end; the carbon chain near the functional head group retains its helical conformation. The additional charge is less concentrated and accordingly has less impact on bond breaking. Second, like all rigid rods its stiffness is inversely proportional to its length. While the additional charge may not be sufficient to fully elongate the chain, it still loosens the carbon-carbon bonding further increases the chain's flexibility (Figure 3.9).

The greater range of motion opens a greater number of accessible vibrational modes, increasing the system's entropy. This entropic benefit decreases the marginal entropy that the system could obtain from fluoride release. The delocalization and flexibility factors would act in a similar fashion for chain lengths of C13 and greater so for this reason we would expect similar results.



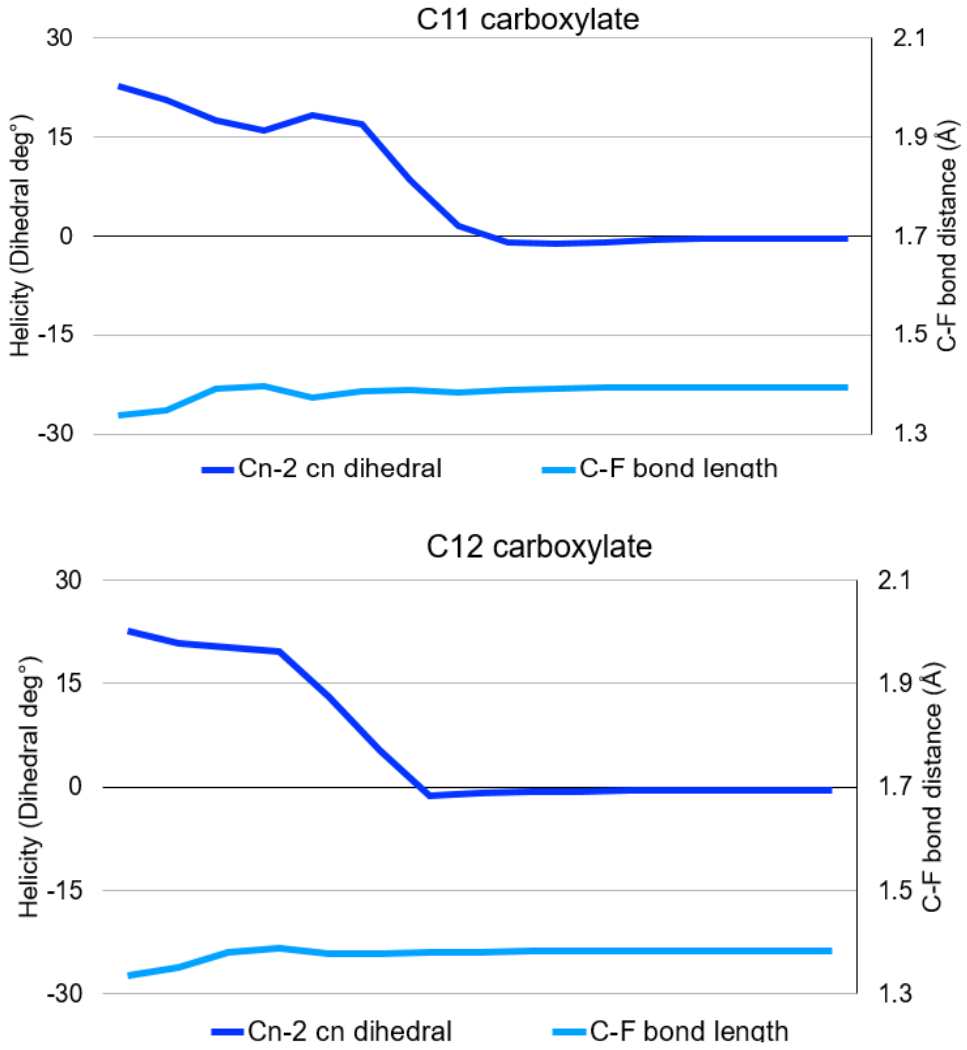


Figure 3.9: The results of simulated electron capture on C10 – C12 perfluorinated carboxylates on the helicity and terminal C-F bond length. Each of these longer-chain molecules are able to stabilize in the elongated and straightened conformation without defluorination due to the larger number of carbons supporting the additional charge and the entropy gained by the flexibility.

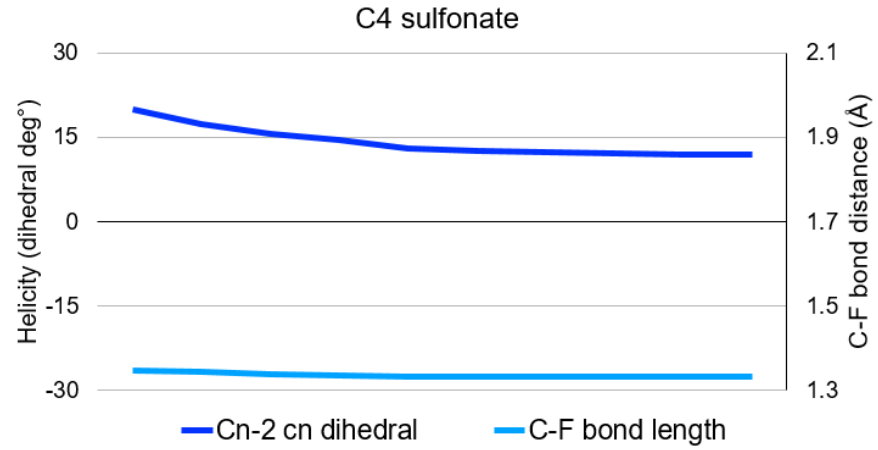
Sulfonates

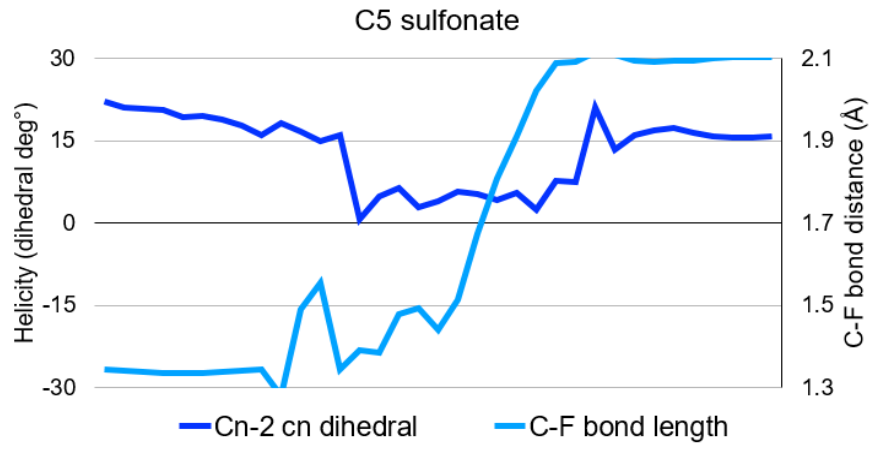
Others have described differences in degradation mechanism and kinetics between carboxylate and sulfonate species with the same number of carbons in their perfluorinated tail[91].

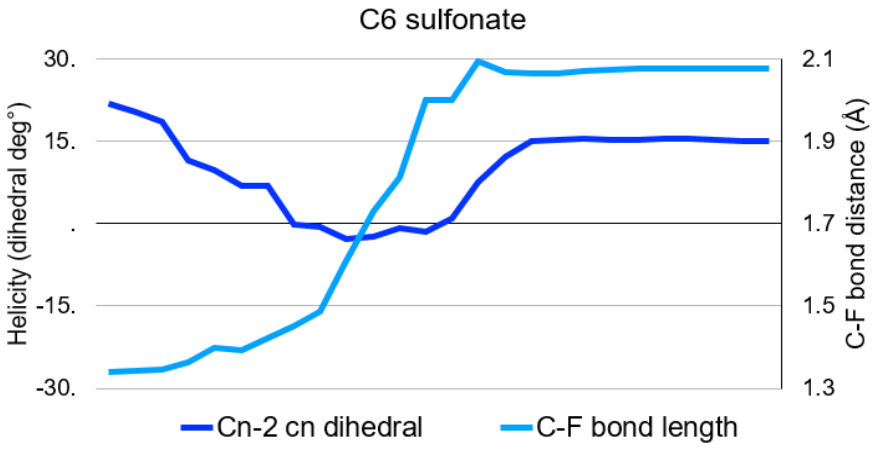
Certain predictions of which fluorine is the most likely leaving group are based solely on calculations of bond dissociation energy which, as described and demonstrated above, ignores geometric and entropic effects to their detriment. The simulations of relaxation post-electron capture presented here show that sulfonate species generally follow the same trends as the carboxylate although the change in head group affects the chain lengths at which the 'Goldilocks zone' begins and ends. The differences are due to both electronic and mechanical properties.
Only the C4 sulfonate was able to stabilize the additional electron without significant geometry change (Figure 3.10).

Spontaneous defluorination to recover helicity begins at C5 and continues through C8. These simulations results suggest that the sulfonate may be more susceptible to degradation after the capture of the additional electron at shorter change lengths due to the sulfur's effect of the molecular electronic structure. Although the head group also has a strong influence on electron insertion location and rate which these simulations do not capture, so the trend is not sufficient to draw conclusions about the overall comparative defluorination rate in bulk aqueous solution[69,73] (Figure 3.10).

Sulfonate chain lengths of C9 or greater are able to stabilize the additional electron in the extended conformation. Since the C9 sulfonate is physically as long as the C10 carboxylate it is reasonable that their mechanical flexibility and therefore the entropic advantage gained through that flexibility would be comparable (Figure 3.10).


C4 sulfonate
30
15
0
-15
-30
Helicity (dihedral deg°)
2.1
1.9
1.7
1.5
1.3
C-F bond distance (Å)
Cn-2 cn dihedral
C-F bond length


C5 sulfonate
30
15
0
-15
-30
Helicity (dihedral deg°)
2.1
1.9
1.7
1.5
1.3
C-F bond distance (Å)
Cn-2 cn dihedral
C-F bond length


C6 sulfonate
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15.
.
-15.
-30.
Helicity (dihedral deg°)
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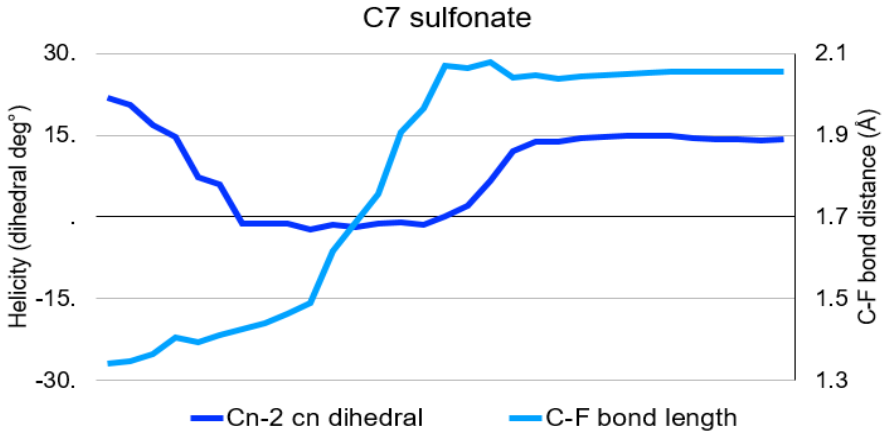
1.7
1.5
1.3
C-F bond distance (Å)
Cn-2 cn dihedral
C-F bond length


C7 sulfonate
30.
15.
.
-15.
-30.
Helicity (dihedral deg°)
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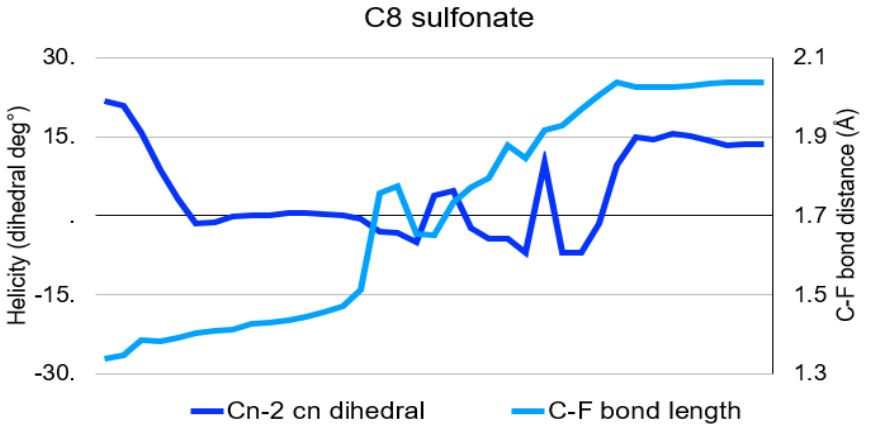
1.5
1.3
C-F bond distance (Å)
Cn-2 cn dihedral
C-F bond length


C8 sulfonate
30.
15.
.
-15.
-30.
Helicity (dihedral deg°)
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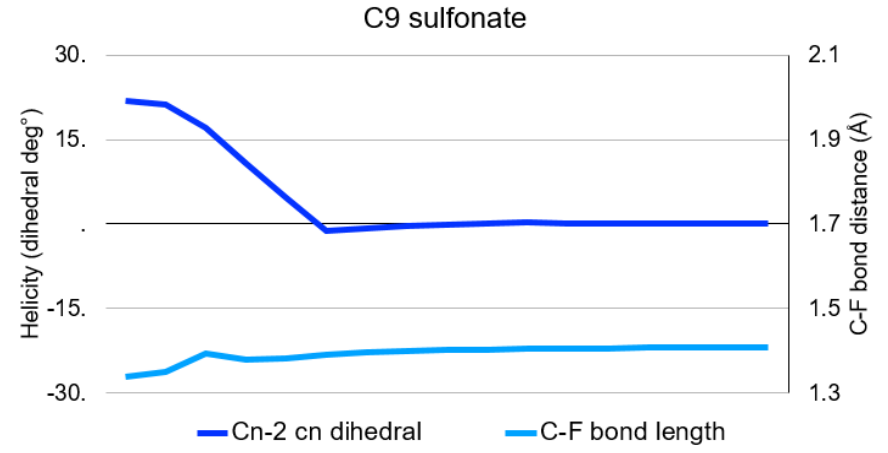
1.9
1.7
1.5
1.3
C-F bond distance (Å)
Cn-2 cn dihedral
C-F bond length


C9 sulfonate
30.
15.
.
-15.
-30.
Helicity (dihedral deg°)
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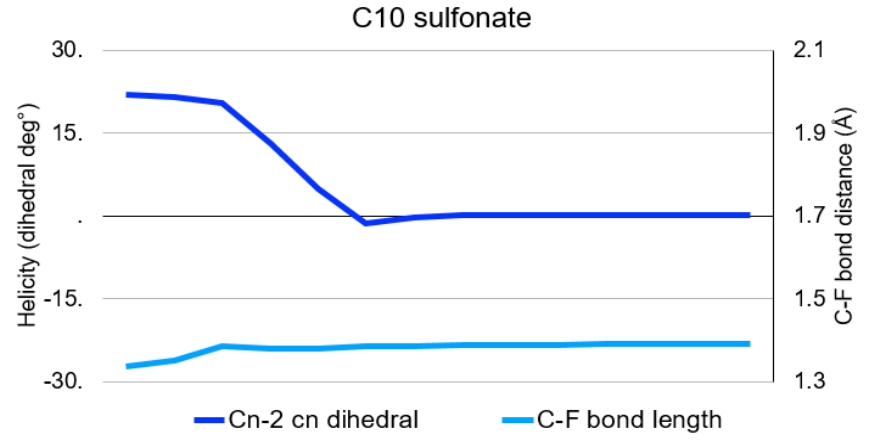
1.7
1.5
1.3
C-F bond distance (Å)
Cn-2 cn dihedral
C-F bond length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15.
.
-15.
-30.
Helicity (dihedral deg°)
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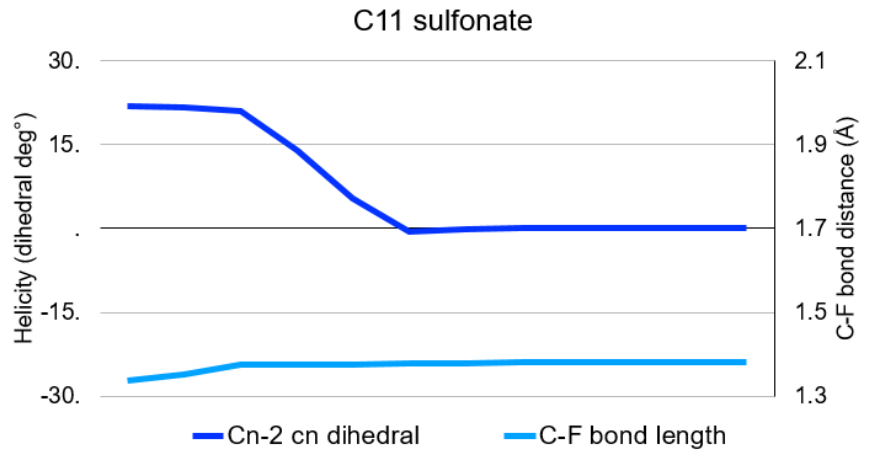
1.9
1.7
1.5
1.3
C-F bond distance (Å)
Cn-2 cn dihedral
C-F bond length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.
-15.
-30.
Helicity (dihedral deg°)
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1.9
1.7
1.5
1.3
C-F bond distance (Å)
Cn-2 cn dihedral
C-F bond length

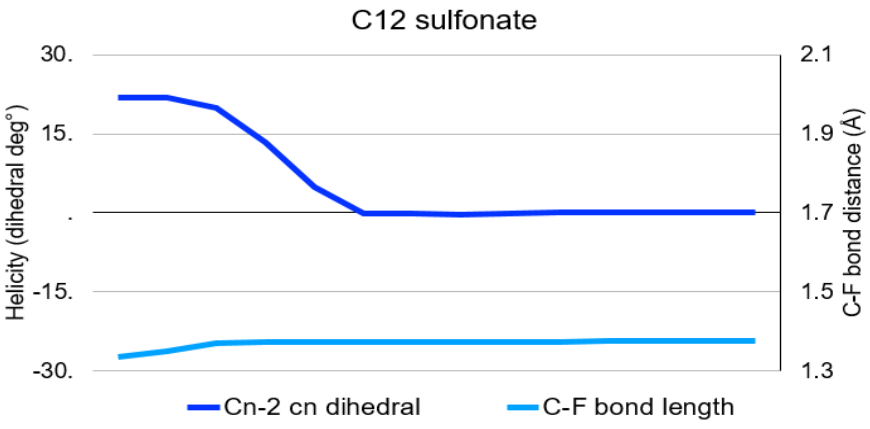
C12 sulfonate
30.
15.
.
-15.
-30.
Helicity (dihedral deg°)
2.1
1.9
1.7
1.5
1.3
C-F bond distance (Å)
Cn-2 cn dihedral
C-F bond length

Figure 3.10: The results of simulated electron capture on C14 – C12 perfluorinated sulfonates on the helicity and terminal C-F bond length. Trends run parallel to the carboxylates but shifted to a smaller number of carbon atoms on the backbone.

Implications and conclusions

Simulation

Simulating the changes in molecular geometry that follow reduction by instantaneous electron capture by employing established optimization techniques offers important advantages over the static model analysis that has been done in previous work. Primarily, the calculation of bond energies, absent any dynamic geometric changes, neglects the possible contribution of entropy on the dissociation reaction. Interpreting the optimization pathway as a physically- meaningful relaxation pathway enables greater sensitivity to how the interactions of electronic and molecular structure promote or resist defluorination.

Dynamic approaches are also beginning to show the larger role that kinetics and molecular geometry contributes to electron capture reactions. Provided that the limitations of the different methods are respected and the appropriate tests to ensure concordance with experiment are successful, complementary application of modelling and simulation invites a holistic investigation of the changes that occur following electronic restructuring. While this study presents the aftereffects of reduction, this method could be applied equally well to any process for which the Born-Oppenheimer approximation could be reasonably justified including oxidation or a prolonged excited state.

Helicity and PFAS degradation

The changes in entropy produced through changes in molecular geometry has been an overlooked tool for enabling defluorination and PFAS degradation. Differences noted by others in the difficulty of breaking down branched PFAS or mixed hydrogenated and polyfluorinated species could be re-examined through an entropy lens to search for trends that are less obvious when considered through a ‘bond dissociation energy first’ approach.

Because entropy may play an important role in a degradation technique's chain length dependence, environmental conditions also become relevant consideration. The impact of entropic interventions is temperature and pressure dependent. Temperature may play several roles, including changes to the number and ratios of accessible cis/trans conformations, the accessibility and intensity of vibrational modes affecting C-F bond dissociation, and the degree to which the change in entropy can affect spontaneous defluorination.

The elongation of the carbon chain that the simulation results indicate is prerequisite to fluoride release indicates that the pressure exerted on the molecule will also impact reaction rates. An environment in which more energy must be expended to reach or maintain the extended conformation, and in which bending degrees of freedom are limited by external forces, is one in which the defluorination 'goldilocks zone' should reach into higher chain lengths because what are mechanical advantages in free space now become disadvantages. Pressurization of the aqueous PFAS solution may be impractical for field decontamination work but, as our previous work has shown, confinement within nanoscale reactors can perform the same function while the bulk solution remains at atmospheric pressure[92]. Altering reaction conditions, solvation, catalysis, and nanoscale confinement alters the molecular freedom, which may in turn alter PFAS susceptibility to decontamination mechanisms which rely on changes in geometry to proceed. As with representational and theoretical treatments of the problem, we expect that experimental treatments will benefit from a greater number and variety of perspectives.

In this chapter, we saw that the balance between enthalpy and entropy helps to explain why electron capture destabilizes some PFAS species and not others. Earlier work suggests that performing a reaction within structures with one or more interior dimensions on the same scale as the reactants can substantially shift the balance. In the next chapter, we analyze the kinetics of a reaction performed within molecular architectures to see how limiting the movement of a reactant to one or two dimensions grants direct access to reaction entropy.

4. Entropy-driven reactivity when confined to one or two dimensions

This chapter was previously published as:
McTaggart, Matt, Xia Li, Michael Groves, Vishva Shah, Manish Jugroot, and Cecile Malardier-Jugroot. "Impact of dimensionality and confinement on reaction dynamics and thermodynamics within 1D and 2D nanostructures." *The Journal of Chemical Physics* 154. 17 (2021): 174903.

Abstract

Confinement has been shown to contribute to the dynamics of small molecules within nanoscale hydrophobic or hydrophilic cavities. Enclosure within a confined space can also influence energy transfer pathways, such as the enhancement of fluorescence over thermal relaxation. In this paper, the effect of confinement on the thermodynamic properties and reaction kinetics of small hydrophobic molecules confined in a soft polymeric template is detailed. A quasi-elastic neutron scattering experiment identified a substantial decrease in translational diffusion of pyrrole after solubilization within a hydrophobic cavity. This decrease in mobility is due to pyrrole's closer packing and increased density under confinement vs the bulk liquid. The decreased mobility and increased density explain the spontaneous polymerization reaction of pyrrole observed within the cavity. The precise characterization of the polymerization kinetics under confinement found that the reaction is independent of pyrrole concentration, consistent with the close packing density. Kinetic data also show that confinement dimensionality finds a thermodynamic expression in the transition state entropy. The dynamics and kinetics experiments reported here offer rare empirical insight into the important influence that cavity geometry places on the reactions they host.

Introduction

The relationships between the thermodynamic states of a system and reaction rates have been recognized since the 19th century, but modern tools and methods permit us to examine the nanoscale chemical environments within which reactions occur with ever-increasing precision. Similarly, the

choice of solvent has long been understood to affect reaction spontaneity and rate, but the precise determination and understanding of the shape and functional contribution of the solvation shells immediately adjacent to the reactants of interest are much more recent[93–96]. Reaction mechanisms that rely on the specificity and stability of the chemical environments found within natural and synthetic nanostructured materials such as enzymes, zeolites, metal-oxide nanopores, metal–organic frame- works, self-organizing polymer structures, or host–guest complexes exemplify the value of expanding the approach. Whether the nano- structure is suspended in aqueous or organic solution, solgel, aerogel, or soft or rigid porous crystals, there now exist many examples of materials containing well-ordered nanoscale interior spaces whose surface chemistries present a significantly different chemical environment for guest molecules than the exterior bulk medium[97–102].

So too are there well-established examples where reaction dynamics are significantly altered by a substrate molecule's confinement within those structures[103–105]. In our previous work, we have shown that the reaction rate for pyrrole auto-polymerization is increased by its solvation into the interior spaces of self-assembled poly(styrene-*alt*-maleic acid), here referred to as SMA. Early on, we identified that the scale of the confined environment was the critical contributing factor[106,107]. Likewise, others have shown the importance of matching the cavity size to the size of the confined molecule[108].

As a recent review shows, the scholarship of polymerization reactions under confinement is a particularly rich sub-field[109]. Confinement media are quite often silicate glasses, metal-oxide membranes such as anodized aluminum oxide[110–113], or MOFs/porous coordinating polymers[114–116], and for a good reason, the dry, well-defined solids are sufficiently stable to draw monomer reactants or polymer melts into the nanopores by capillary action, to maintain rigid dimensions throughout the polymerization process, and to facilitate extraction or *in situ* characterization of the resultant polymer structures. Theoretical and experimental results from these studies confirm that confinement impacts the observed reaction rates, most often producing a faster reaction rate. For diffusion-controlled processes, confinement

increases the reaction rate if the net result is to place a greater number of reactive groups within close enough range for a reaction to occur; confinement decreases the rate if the pore walls impede the reactive ends of long polymer chains from an effective search for another reactive end[117,118]. These competing factors may show a deceleration in rate over the course of the reaction as the availability and mobility of reactive species decrease[117,119].

Our work with SMA broadened the field of experimentally realized nanoconfinement structures primarily because it is suspended in aqueous solution and its self-assembly depends on weak forces. For instance, the nanoporous structure here is not submerged in the monomer, a polymer melt, nor a dilute polymer solution in which we would expect the monomer/polymer to equilibrate between the confining geometry and the bulk[120]. The spaces into which the substrate molecules equilibrate are not the confined and bulk geometries of the same chemical environment but between SMA's hydrophobic interior and the bulk water exterior. Our initial choice to use pyrrole as a substrate was made precisely because of its solubility in SMA and insolubility in water. After reaction, the polypyrrole product remains intercalated within the SMA, neither precipitating nor causing precipitation of the superstructure. Notably, the 2–3 nm channel size in the SMA assembly is large enough that it must contain some water before any hydrophobic molecule is introduced to displace it. The weakly bonded, hierarchical structure of SMA also allows for continuous, dynamic interactions with water in what we anticipate will more closely mimic biological than mineral or strictly chemical pro- cesses. While these differences create new and generative avenues for the exploration of substrate behaviors under nanoconfinement, it also creates new challenges for *in situ* characterization of product polymer length, polydispersity, tacticity, or total conversion—all of which have been found to be affected by nanoconfinement[109]. We can nevertheless use reaction processes to fruitfully investigate the physics and functions of the soft nanoconfinement nanoreactors themselves.

The effect of confinement dimension, for instance, is not as well understood. Intuitively, if single nanometer restrictions on a molecule's

movement in at least one dimension can be a determining factor in its reaction dynamics, then whether the confining structure limits the molecule to motion on a two-dimensional plane, a one-dimensional line, or a zero-dimensional point must have some influence. To determine the extent that dimensionality contributes to the overall confinement effect, we would need to isolate it from other contributing factors such as the cavity size and surface chemistry. SMA provides a rare if not unique platform to explore this question experimentally because it self-assembles into two different structures, one-dimensional nanotubes and two-dimensional laminar nanosheets, each containing a 2–3 nm confined internal space[121]. No alteration to the chemical structure of the polymer is necessary to control which nanostructure the SMA takes in aqueous solution: self-assembly is determined solely by the mean polymer chain length, and so the structures feature near-identical interior surfaces. Both nanostructures have been thoroughly characterized by small-angle neutron scattering, transmission electron spectroscopy, and dynamic light scattering at temperatures from 4 to 80º C. The shape, size, and assembled structure of SMA at 20 kDa and 350 kDa are summarized in Figure 4.1.

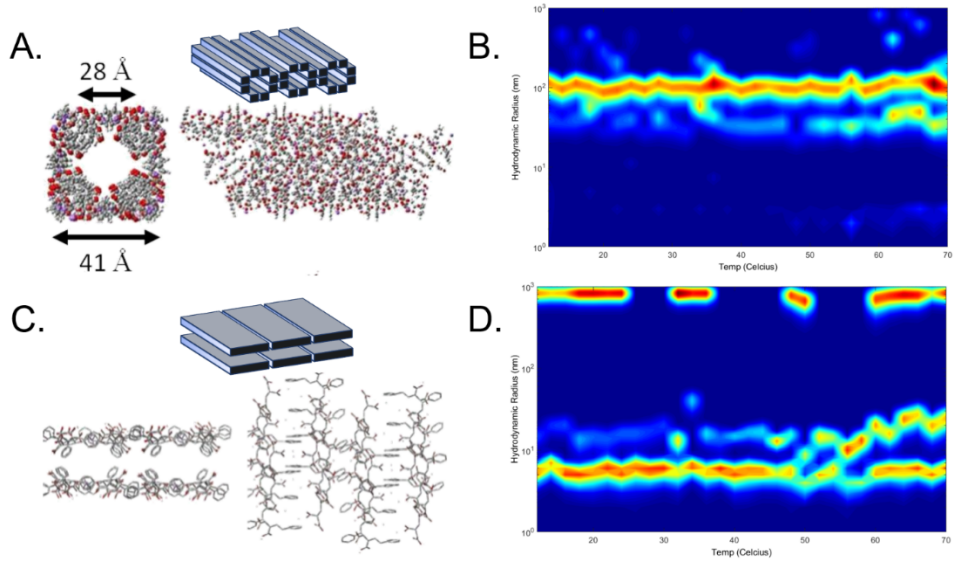

Figure 4.1: SMA in the nanotube and nanosheet configuration. (A) Schematic and molecular modeling representations of 20 kDa SMA self-assembly in neutral water. (B) Dynamic light scattering (DLS) spectrum of 20 kDa SMA in neutral water from 10 to 80º C, showing the stability of the structure with ~100 nm hydrodynamic radius. (C). Schematic and molecular modeling

representations of 350 kDa SMA self-assembly in neutral water. (D) DLS spectrum of 350 kDa SMA in neutral water from 10 to 80º C, showing the stability of the structure with ~1000 nm hydrodynamic radius and unassociated SMA chains at ~10–20 nm.

Traditional catalytic surfaces or complexes reduce energetic barriers to reaction by stabilizing or favoring the transition state through the shape and size of points of affinity and their relative bonding strengths to reactants or to products. The catalyst's impact on transition state enthalpy provides the chief mechanistic justification for observed changes in reaction rates, selectivity, or yield. Enzymatic catalysts often contain their active sites within confined interior spaces and feature surface chemistries that provide substrate molecules with favorable solvation energies, but even in this case the effect on reactant and transition state entropy is not yet resolved[122–125]. Yet there is clearly a significant change in entropy when a reactant moves from liquid solvent, which places no restrictions on its degrees of freedom, into nanostructures that remove all but one or a few selected degrees of freedom. Part of the experimental difficulty lies in the complexity inherent to natural biomacromolecules. We are motivated by the expectation that a simple model system like SMA that shares some of the critical properties of confinement shape, size, and surface chemistry may yield more decisive evidence.

Here, we report the results of complimentary investigations probing the changes to pyrrole dynamics and polymerization kinetics under confinement within SMA nanostructures. First, we examine the self-diffusion of pyrrole as a pure liquid, when it is confined to translation in one spatial dimension by its solvation within SMA nanotubes, and post-polymerization. Second, the polymerization reaction order, Arrhenius constants, and Eyring–Polanyi transition state enthalpy and entropy are determined through the measurement of the polymerization rate at a series of temperatures when pyrrole is confined to one (nanotubes) or two (nanosheets) spatial dimensions. Together, these results demonstrate that confinement and the dimension of confinement produce a significant change in the transition state entropy.

The regular, stable, and uncomplicated structure of the pyrrole:SMA system provides a model system that reveals the relationships between structure and function that are likely present but more difficult to observe in more complex confinement structures such as proteins and enzymes. We anticipate that the findings presented here will provide new insight into the mechanistic influence of macromolecule structure in order to create more accurate models of biochemical functions.

Methods

QENS experimental details

Hydrogen has a much larger neutron scattering cross section than deuterium, so the energy and wave vector of a neutron passing through a system will correlate more strongly to the movement of hydrogen-bearing molecules than they will to deuterated molecules. In this experiment, we add hydrogen-bearing pyrrole to a deuterated polymer and D_2O solution so that we may study the motion of pyrrole in isolation from the motion of other molecules in the system.

For each experimental set, a solution of 1% mass/mass of deuterated SMA (purchased from Polymer Source, Inc., Mw = 9 kDa) was prepared in D_2O and adjusted to pH 7 with NaOD. At this molecular mass and under these conditions, SMA self-assembles into cylindrical nanotubes with a hydrophobic, internal space 2–3 nm in diameter. One sample set was then treated with $PtCl_2$ to reinforce the SMA structure and grow platinum nanoparticles *in situ*; the other received no treatment[126,127]. Pyrrole (NC_4H_5) was added to each sample to reach an initial concentration of 0.66% volume/volume. Sample solutions were produced according to a schedule that permitted QENS measurement 1, 2, 3, 4, 7, 14, and 45 days after introduction of pyrrole into the system. As a further test of light sensitivity, duplicates of both sets were prepared in the dark and analyzed on the same schedule as the samples prepared under standard laboratory lighting conditions. QENS experiments were performed on the cold neutron disk-chopper time-of-flight spectrometer (DCS) at the NIST Center for Neutron Research in Gaithersburg, MD. The incident wavelength was 7.5 Å with an incident energy of 1.45 meV, resulting in a wave vector range of 0.146 $Å^{-1}$ <

$Q < 1.574$ Å^{-1} and an energy resolution of 35 μeV. For exposure to the beam, the sample was loaded into the 0.1 mm concentric gap of nested 10 cm tall cylinders. The small sample path length minimized multiple scattering and permitted >90% neutron transmission. Shortening the path length also reduces the rate of neutron–hydrogen interaction, so data collection spanned 8–10 h per sample to ensure sound statistical analysis. For all experiments, the detector efficiency, energy resolution, and normalization were measured using vanadium. To account for any H_2O ingress or incidental proton exchange with the pyrrole, a sample of deuterated polymer in D_2O was analyzed and removed from the sample data during the reduction process.

QENS analysis

Quasi-elastic neutron scattering analysis associates the diffusion properties of atoms in a sample material to the scattering angle of those neutrons that experience only minimal energy exchange during the scattering interaction. The double differential scattering cross section is proportional to the probability of a neutron scattering from its incident wave vector into the arc $\Delta\Omega$ and with an energy exchange ΔE,

$$\left(\frac{d^2\sigma}{d\Omega\, dE}\right)_{inc} = \frac{N}{4\pi}\frac{k_s}{k_i}\sigma_{inc}S_{inc}(Q,\omega) \quad (1)$$

Such that N is the number of nuclei, σ_{inc} is the incoherent scattering cross section of the sample nuclei, k_s and k_i are the scattered and incident wave vectors, respectively, and $S_{inc}(Q,\omega)$ is the incoherent dynamic structure that, as a function of the changes in wave vector Q and energy ω, depends only on the sample. The analysis involves fit- ting the incoherent dynamic structure factor to a sum of Lorentzian contributions convoluted with the instrumental resolution.

To separate the vibrational, rotational, and translational components of the pyrrole dynamics, we assume that $S_{inc}(Q)$ can be expressed as a convolution of three different kinds of proton motion[128,129] so that the incoherent dynamic structure factor can then be expressed as

(2) $$S_{inc}(Q,\omega) = e^{-\frac{1}{3}Q^2\langle u^2\rangle} S_{inc}^{trans}(Q,\omega) \otimes S_{inc}^{rot}(Q,\omega)$$

where the exponential term, known as the Debye–Waller factor, accounts for attenuation due to the isotropic thermal motion of hydrogen through its mean square displacement, $\langle u^2 \rangle$. The following two terms represent the translational and rotational dynamic structure factors. An assumption of decoupled vibration, rotation, and translation motions is found to approximate the interdependent values to within ~5%, which we accept for this analysis. Only the translational component of the pyrrole dynamics is resolved given the time and length scale captured by this experimental setup.

Based on the Lorentzian fit to the scattering function, we first interpret the data using analytical models traditionally applied to liquids[128,129]. The translational dynamic structure factor of diffusive motion has been successfully described by

(3) $$S_{inc}^{trans}(Q,\omega) = \frac{1}{\pi} \frac{\Gamma_{trans}(Q)}{\omega^2 + (\Gamma_{trans}(Q))^2}$$

where $\Gamma_{trans}(Q)$ is the half width at half maximum (HWHM) of a Lorentzian function. When using a simple diffusion model, $\Gamma_{trans}(Q)$ can be interpreted as[130]

(4) $$\Gamma_{trans}(Q) = D_{trans} Q^2$$

where D_{trans} is the translational diffusion coefficient of the pyrrole-bonded hydrogen, a proxy measure for the pyrrole and polypyrrole. The analysis presented in this work employs one Lorentzian and a constant background function, a typical fit for which is shown in Figure 4.2.

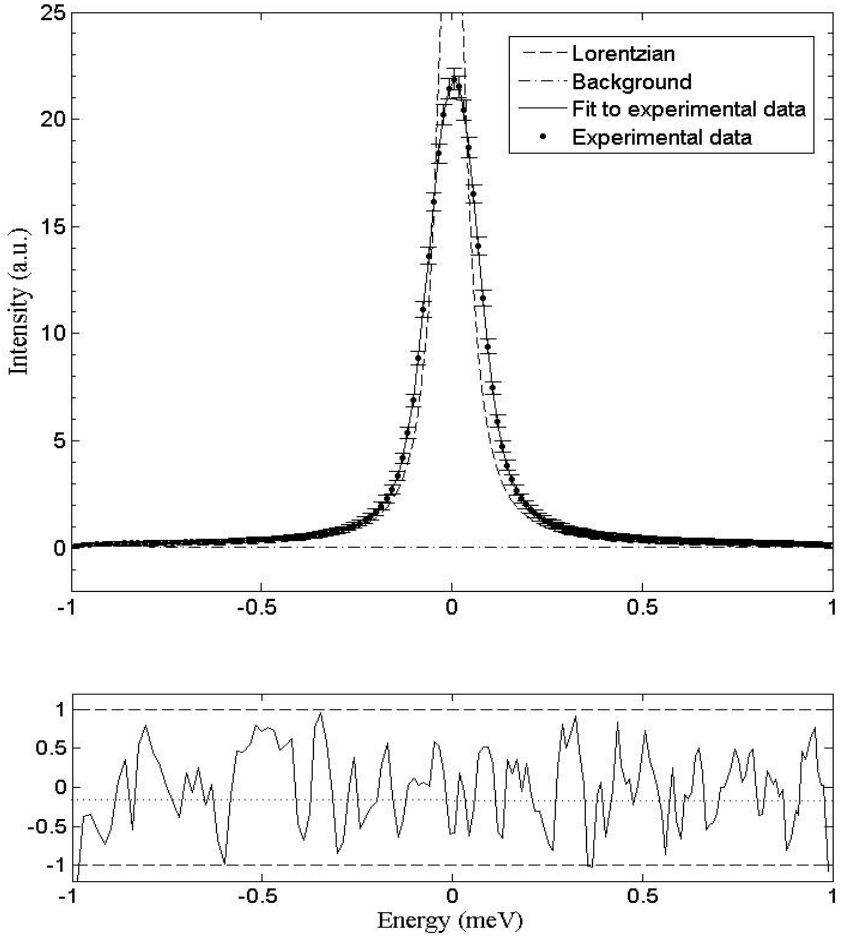

Figure 4.2: Incoherent structure factor spectrum of H-pyrrole in 1 wt.% D-SMA in D2O solution with pH 7, seven days after pyrrole addition with Pt catalyst with light exposure. 35 meV at Q = 0.50 Å−1. The upper curve shows the experimental curve as circles, the total fit component as a continuous line, and the Lorentzian component and the background as dashed lines. The lower curve shows the typical residual obtained from the fit.

UV/ Visible light spectrometry

For the reaction kinetics study, poly(styrene-*alt*-maleic acid) polymers were used with mean molecular masses of 20 kDa, which self-assemble in neutral water into nanotubes, and 350 kDa, which self-assemble into laminar nanosheets[121]. To simplify the analysis and ensure optimal isolation of structural dimension as a rate determining factor, no samples used in the kinetic studies contained platinum nanoparticles nor any other catalytic inclusion.

Aqueous 1% mass/mass SMA solutions were prepared using ultrapure water measured at 18.2 MΩ cm (Milli-Q water filtration systems). Solution pH was neutralized with a stoichiometric amount of NaOH and verified. Solutions were mixed by low power sonication at 40º C until polymer was completely dissolved. Evidence of SMA nanostructure formation was confirmed by dynamic light scattering. Pyrrole (Sigma-Aldrich, 131709) was distilled at 129º C and refrigerated in the dark until use. 20 µl of pyrrole was added to each 3 ml cuvette after the light absorbance baseline to attain an initial concentration of 0.66% volume/volume, in accordance with the QENS samples.

UV/visible light spectroscopy was performed on an Agilent Cary 7000 UMS using the 6×6 Peltier-thermostatted multicell holder and external temperature controller to maintain sample temperature as set, ±0.3º C. Data were collected through the WinUV Scanning Kinetics module v6.2.0.1588 software in absorbance mode, collecting 0.1 s of spectral data for every 0.2 nm increment between 500 and 400 nm, every 10 min for a minimum of 48.2 h and an average of 71.0 h for the pyrrole polymerization reaction within SMA nanotubes and a minimum of 51.2 h and an average of 119.6 h for the reaction within the slower acting SMA nanosheets.

Results and discussion

Pyrrole diffusion

The 2–3 nm inside diameter of a SMA nanotube is small enough to consider the translational motion of pyrrole negligible in the radial dimensions but also large enough that several pyrrole molecules—a planar molecule measuring 0.42 nm at its widest—could travel relatively unimpeded in either direction of the longitudinal dimension. From previous experience, we know that pyrrole will polymerize to polypyrrole within the SMA structure and that the reaction can be catalyzed by platinum nanoparticles embedded in the space[107,126,127]. Quasi-elastic neutron scattering experiments were performed to quantify the change that occurs to pyrrole's freedom of movement between its bulk liquid state, when confined to one translational dimension by the SMA nanotube, and when bonded into polypyrrole.

Because motion becomes restricted as the pyrrole monomers diffuse into the SMA nanotube and more restricted again once bonded to a polymer chain, we expected pyrrole's average motion to map the ratio of unreacted, free pyrrole to the bonded polypyrrole. If the reactant diffusion rate is a function of molecular mass, then the average diffusion rate would decrease as a smooth function of time as the monomers are converted into polymer chains. What we observed instead is shown in Figures. 4.3 and 4.4: a sharp discontinuity appears between the diffusion of bulk pyrrole and confined pyrrole but then remains constant throughout the period in which the polymerization reaction occurs. This indicates that pyrrole's freedom of movement is so strongly restricted by confinement within the SMA that the average rate of diffusion is independent of polymer length or molecular mass.

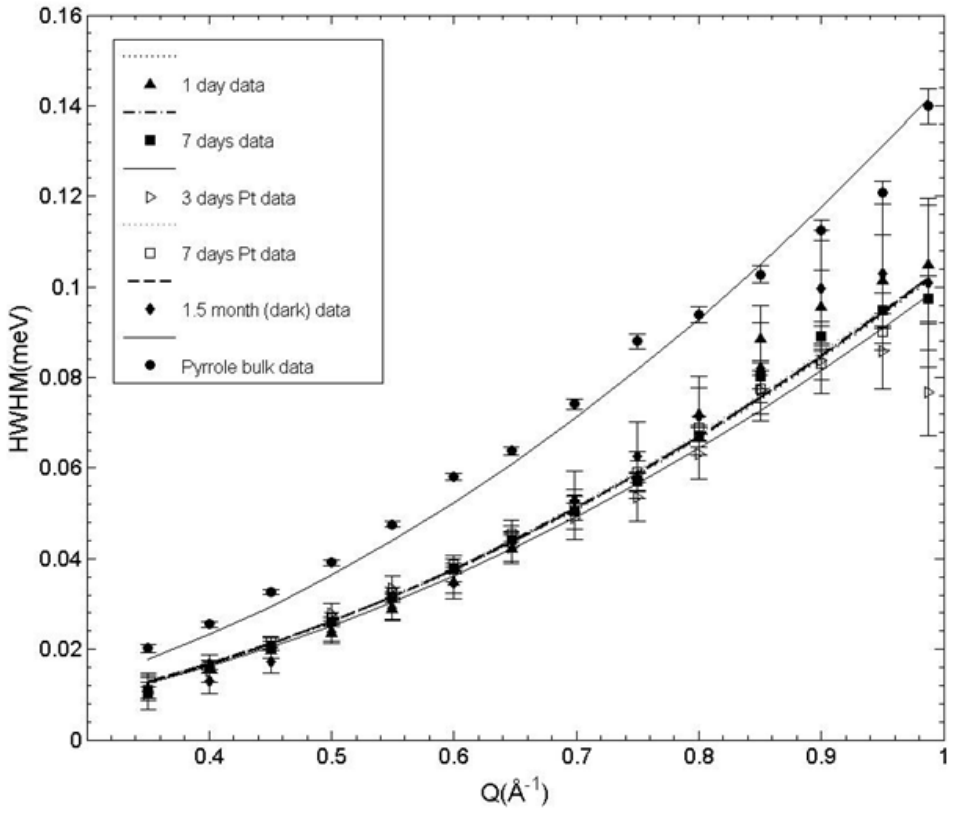

Figure 4.3: Half width at half maximum of Lorentzian functions fit to the QENS data vs the scattering angle for bulk pyrrole (top line) and pyrrole under confinement.

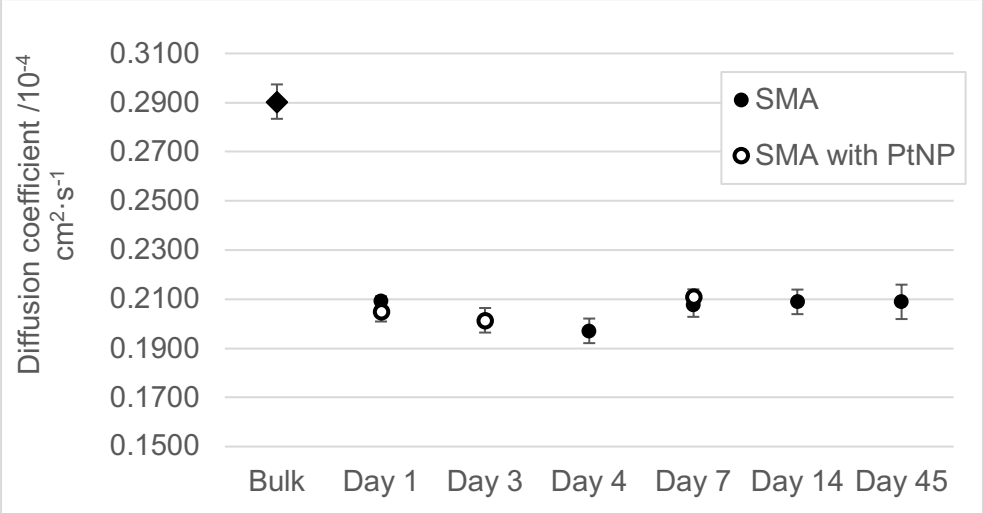

Figure 4.4: Diffusion coefficient of bulk pyrrole and pyrrole under confinement. Pyrrole is confined within the SMA nanotube after one day, but no significant polymerization will have occurred, yet the reduced diffusion coefficient that appears on day one remains unchanged throughout the polymerization reaction.

This remarkable result demonstrates that the translational motion of free pyrrole confined within the SMA nanotube is indistinguishable from polypyrrole.

One possible explanation is the van der Waals attraction between pyrrole and the styrene groups that line the SMA interior, which are sufficiently strong that the pyrrole is effectively frozen in place. First, it would be surprising for weak intermolecular forces to restrict movement to the same extent as the covalent bonds of polymerization. Second, assuming that the surface bonding could produce a comparably low diffusion rate, the relatively low number of styrene binding sites should mean that the surface pyrrole would be greatly outnumbered by the unbonded interior pyrrole that would therefore contribute more to the average diffusion rate measured by QENS. The third point undermining this line of argument is the fact that the integrity of the self-assembled structure depends on styrene–styrene interactions. If pyrrole were to interact so strongly with the styrene that its loss of mobility was equivalent to covalent bonding, then the competing forces would be enough to overcome the styrene stacking and destabilize the assembly.

As an alternative, we suggest that the observed reduction in molecular motion is due to higher density packing of pyrrole within the confined space than in the bulk liquid. The assumption that the diffusion of confined pyrrole is equally likely in both directions rests on the assumption that the nanotube walls are the only relevant restriction for most of the confined pyrrole and its movement is not affected by outside forces in either direction of travel. If we abandon this assumption and instead accept that a potential energy gradient exists such that movement toward the interior is preferred over movement toward the exterior, one created by surface tension at the water–pyrrole interface, for example, then random thermal motion would spontaneously increase packing efficiency and increase density while reducing diffusion down the potential energy gradient. This process will reach an equilibrium when the intermolecular repulsion pushes back against the gradient pressure with equal force. Should the energy differential be such that the intermolecular distance is more energetically costly than bond formation, then we will have discovered a physical mechanism for pyrrole autopolymerization under confinement. Rather than electrochemically induced or chemically catalyzed, the structural restrictions imposed by nanoconfinement funnel interfacial forces into a physical process are comparable to a high-pressure reactor.

This mechanistic model is consistent with the QENS data reported here and with previously published results. For instance, if confinement scale is responsible for the polymerization mechanism, then we would expect that enlarging the hydrophobic space past some critical point would erase the effect. Second, if the pyrrole–water interface is the source of the potential energy gradient, then replacement of the interior styrene with another hydrophobic group should not erase the effect. Both have been demonstrated in previous work: 50 nm micelles with an interior surface chemically similar to SMA failed to produce pyrrole polymerization, but the same polymerization reaction did occur when the pyrrole was confined within the chemically dissimilar poly(isobutyl-*alt*-maleic acid) 2D laminar sheets[107].

If the mechanism relies on thermal motion down a potential energy gradient from the exterior toward the interior of the confinement space, then confinement dimension should also play a distinguishable role. Brownian packing would be more efficient in one dimension than in two, so a 1D nanotube should demonstrate improved kinetics over 2D nanosheets. SMA provides an experimental platform that may be uniquely suited to investigate this question. In previous work, we have demonstrated that SMA self-assembles into well-defined 1D nanotubes at lower chain lengths and 2D laminar nanosheets at greater chain lengths. Furthermore, neutron scattering and molecular modeling show that the interior hydrophobic spaces produced through self-assembly are essentially identical in terms of confinement dimension and chemical environment.

Kinetics and dimensional effects

Polypyrrole in SMA has a characteristic absorbance peak at 466.6 nm in the UV/visible light spectrum[106,127]. To determine what effect the dimension may have on reaction dynamics under confinement, we monitored the polymerization rate of pyrrole confined within 1D nanotubes and 2D nanosheets at five temperatures, each ranging from 10 to 45º C for up to 200 h. Measurements of these same samples taken 16 months after the original kinetic data were acquired show that the absorbance of this system at its endpoint is 19.5 ± 0.3 a.u. It is unknown whether the system reaches 100% conversion at its endpoint, so we may conclude that no sample attained more than 10% conversion during the observation period.

Measured absorbance per time generates a linear plot for the reaction in both nanotubes and nanosheets, as shown in Figure 4.5. Because absorbance is linearly correlated with concentration, these plots indicate that the propagation of polymerization is independent of product or reactant concentration and remains in a pseudo-zeroth order kinetic regime throughout the observation period. The rate constant k is equal to the slope of the line typified in Figure 4.6.

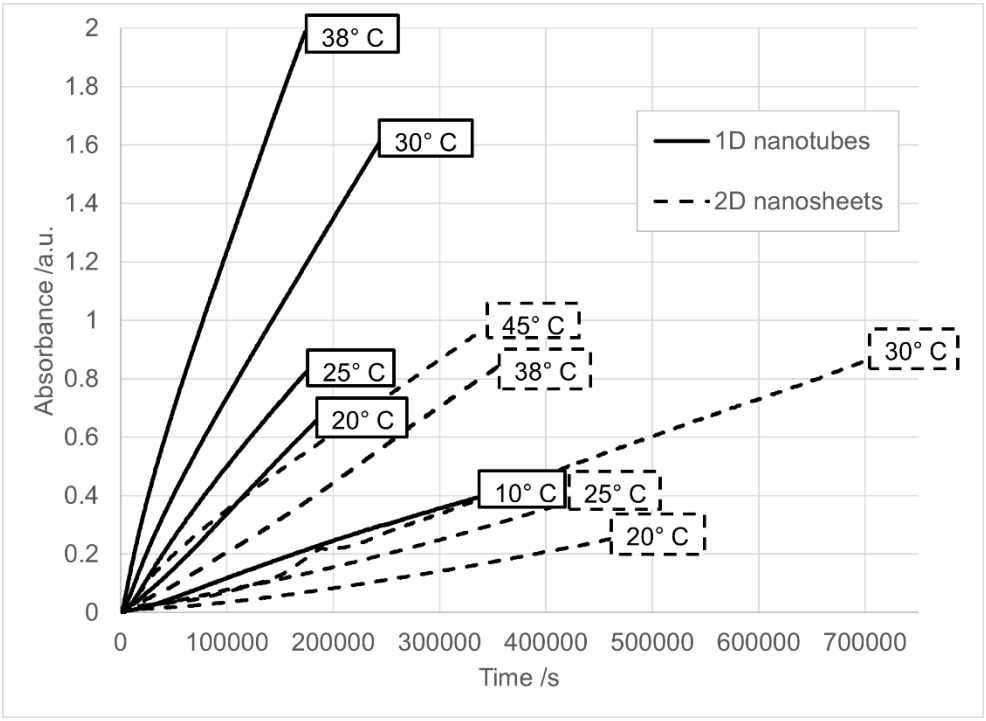

Figure 4.5: Absorbance of 466.6 nm light as a function of time to measure the polymerization rate of pyrrole under SMA confinement in 1D nanotubes (20 kDa SMA) or 2D nanosheets (350 kDa) at various temperatures. The linearity of the plots shows that the change in polypyrrole concentration over time is independent of concentration: a zeroth order reaction.

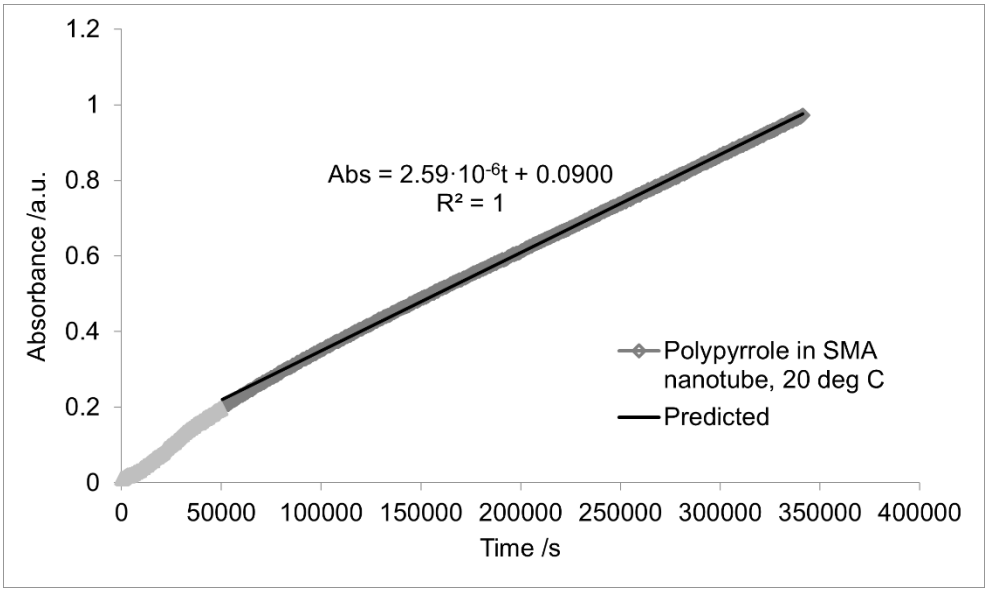

Figure 4.6: Typical linear fit to the absorbance data plotted against time. Shown is the absorbance of light at 466.6 nm by the pyrrole-SMA nanotube system between 14 and 95 h, indicating the progress

of the polymerization reaction. First 14 h, shown in light gray, indicates growth prior to reaching the steady propagation state.

Because the initial reaction kinetics under confinement are independent of polypyrrole concentration, and by extension independent of pyrrole concentration, it reaffirms that the monomer availability is not the rate limiting factor—that pyrrole is replenished at the growing ends of the polymer faster than random thermal motion triggers a reaction. This is consistent with the QENS results that support the possibility that pyrrole packing inside the SMA structures is comparable to the polymer density before the reaction occurs. The ability to determine the order of the overall reaction depends on the conversion. These results do not draw near enough to 100% conversion for us to determine how the decreased accessibility of the reactant affects the relationship of the reaction rate to reactant concentration, as it eventually must[131]. The restrictions placed on the polymer's movement by 1D or 2D confinement will impact its ability to scavenge the space for unreacted pyrrole: chains able to explore a 2D plane will have access to a more efficient search strategy than those restricted to travel in a 1D line. This difference may generate significant effects on the reaction rate during later phases, confounding thermodynamic and kinetic effects. By restricting ourselves to the concentration-independent, pseudo-zeroth order regime, we therefore simplify the task of isolating the thermodynamic effects of dimensionality.

The plots also diverge from linearity near the origin, likely due to the ongoing diffusion of the pyrrole monomer into the confined space and packing process. These early data points were excluded from the calculation of slope to improve correlation with the long- term trend. The results are tabulated in Table 3.1. The temperature dependence of the rate constant allows us to analyze the potential energy pathway according to the methods of Arrhenius and Eyring and Polanyi. The results of these calculations are given in Table 3.2.

Temperature (°C)	Rate constant ± Standard error (conc./sec)			
	1D nanotubes		2D nanosheets	
10	$1.1970 \cdot 10^{-6}$	$\pm 2.6 \cdot 10^{-9}$	Not measured	
20	$2.5944 \cdot 10^{-6}$	$\pm 3.2 \cdot 10^{-9}$	$0.5807 \cdot 10^{-6}$	$\pm 1.9 \cdot 10^{-9}$
25	$4.5152 \cdot 10^{-6}$	$\pm 1.2 \cdot 10^{-8}$	$0.9107 \cdot 10^{-6}$	$\pm 2.5 \cdot 10^{-9}$
30	$6.1741 \cdot 10^{-6}$	$\pm 5.2 \cdot 10^{-9}$	$1.3027 \cdot 10^{-6}$	$\pm 1.0 \cdot 10^{-9}$
38	$10.427 \cdot 10^{-6}$	$\pm 1.0 \cdot 10^{-8}$	$2.4916 \cdot 10^{-6}$	$\pm 3.2 \cdot 10^{-9}$
45	Not measured		$3.8156 \cdot 10^{-6}$	$\pm 2.2 \cdot 10^{-9}$

Table 4.1: Zeroth order rate constants of the polymerization reaction within the SMA nanostructures at temperatures between 10 and 45º C.

Value	1D nanotubes	2D nanosheets
Arrhenius		
Activation energy ($J \cdot mol^{-1}$)	57594	58635
Arrhenius factor (s^{-1})	50675	16666
Eyring-Polanyi		
Enthalpy of transition ($J \cdot mol^{-1}$)	55129	56096
Entropy of transition ($J \cdot K^{-1}$)	-163	-173

Table 4.2: Arrhenius and Eyring–Polanyi constants as calculated from the kinetic data in Table 3.1.

First, we should find a linear relationship between ln(**k**) and the inverse temperature according to the Arrhenius equation, which allows us to determine the reaction activation energy E_a from the slope and the Arrhenius pre-exponential factor A from the intercept,

$$\ln(k) = -\frac{E_a}{R}\frac{1}{T} + \ln(A) \quad (5)$$

It is apparent from the nearly parallel slopes of the lines in Figure 4.7 and confirmed in the calculation that the difference in activation energy between the reaction dimensions is small, on the order of 1 kJ mol^{-1}. The energy barrier is characteristic of a particular reaction pathway, so this is confirmation that the reaction mechanism and chemical environment are not

significantly different between the two nanosystems. The necessary conditions for reaction to occur via confinement are created by both the 1D nanotubes and the 2D nanosheets. This is consistent with the proposed mechanism for confinement-driven reaction; indeed, an unchanged reaction mechanism simplifies our effort to isolate spatial dimension from other considerations.

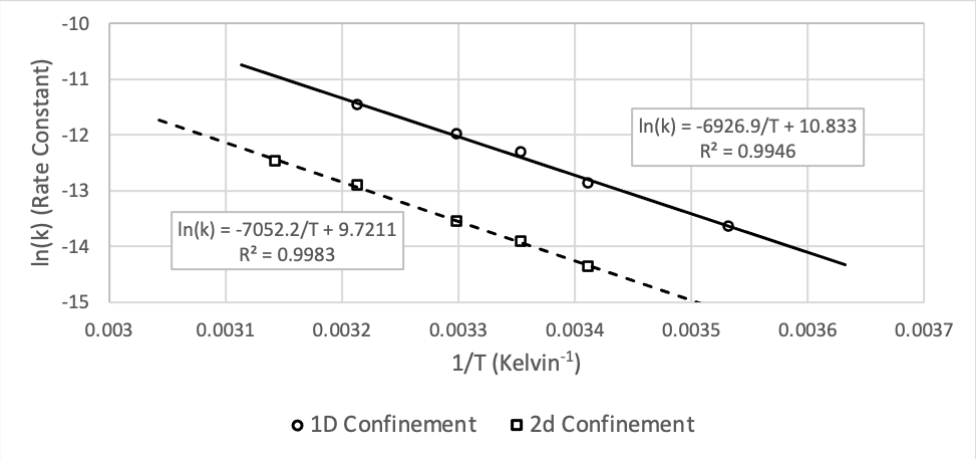

Figure 4.7: Arrhenius plot of the natural logarithm of the rate constant vs inverse temperature. The reaction's activation energy within 1D and 2D confinement structures is nearly equal, as indicated by the nearly parallel slopes of the lines of best fit; the separation on the Y axis indicates a consistent difference in pre-exponential frequency factor—an empirical factor related to the spatial orientations of the reactants.

We would, however, expect to observe a dimensional effect on the Arrhenius factor, an empirical value encapsulating the probability that the reactant molecules will meet in the correct orientation for a reaction to occur. One fewer spatial dimension reduces the orientations that a reactant molecule can take without incurring significant energetic costs, so it is reasonable that the effect of confinement could be localized to the Arrhenius factor. Analysis shows that the Arrhenius factor is three times greater for 1D nanotubes than for 2D nanosheets and accounts for the greater part of the difference in the observed reaction rates.

The decoupling of the energy barrier to reaction and reactant orientation and movement invites analysis of the transition state enthalpy $\Delta H^{\ddagger}$ and entropy $\Delta S^{\ddagger}$ according to the Eyring–Polanyi method. From the linearized equation, we see that the slope is related to the enthalpy needed to reach the transition state and the intercept to the transition entropy as

(6) $$\ln\frac{k}{T} = -\frac{\Delta H^{\ddagger}}{R}\frac{1}{T} + \frac{\Delta S^{\ddagger}}{R} + \ln\frac{\kappa k_B}{h}$$

where k_B is Boltzmann's constant, h is Planck's constant, R is the ideal gas constant, and κ is a transmission factor: the fraction of reactants that remain in the product state after passing through the transition state, which we take as unity in this situation because the proposed mechanism specifically and systematically opposes movement away from the polymerized state.

Discussion

As shown in Figure 4.8 and the tabulated data, the calculated enthalpies of transition are now within 1 kJ mol^{-1}. ANCOVA statistical testing confirms that the two linear regressions are effectively parallel: the slopes of the two lines are not significantly different ($P = 0.75$), but their intercepts are ($P < 0.0001$). This demonstrates that the effect of the spatial dimension on the rate of reaction under confinement is a translation of the line in ln(**k**/T), a function of entropy alone.

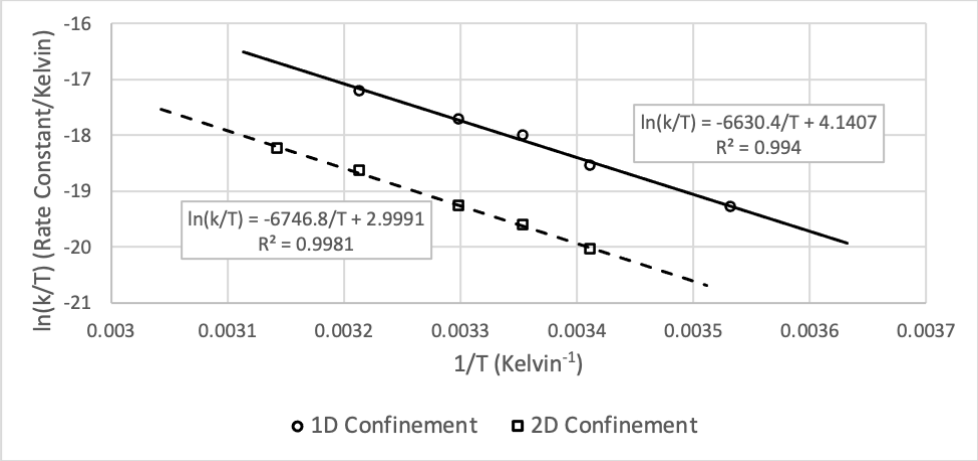

Figure 4.8: Eyring plot of the natural logarithm of the rate constant per temperature vs inverse temperature. The reaction's transition state enthalpy in both 1D and 2D nanostructures is effectively equal as indicated by the nearly parallel lines of best fit; the separation on the Y axis indicates a difference in transition state entropy.

The large negative values of ΔS, −163 J K nanotubes and −173 J K^{-1} for the 2D nanosheets, indicate a substantial reduction in mobility as the reactant monomers move from their ground state to transition state. This aligns with the proposed explanation for the QENS results: pyrrole monomers are driven to higher density through a Brownian packing process down the potential energy gradient created by the confinement structure. Furthermore, the 10 J K^{-1} difference between the two systems is a direct measurement of the additional entropy enabled by the second spatial dimension; it accounts for the additional freedom of movement that the packing process must overcome before reaching the transition state toward bond formation.

Transition enthalpy is independent of the dimensionality of the confined environment but is notable for its significant reduction when compared to its value for the chemically catalyzed mechanism in free solution. The enthalpy reported here for the propagation phase under 2D confinement is 56.1 kJ mol^{-1}, 21% lower than the 70 971 ± 14 J mol^{-1} reported for the propagation phase of the unconfined, chemically catalyzed reaction[131]. Considering the close packing necessary for a compression-driven mechanism, one would expect the energy distribution among reactant molecules to homogenize quickly; differences in translational and vibrational energies would equilibrate as they are forced into closer interaction with neighboring pyrrole and polypyrrole. Collision kinetics in free solution insist that reactants enter the transition state with *no less* than the activation energy but confined kinetics drive reactants *up to* the activation energy. This suggests that the reaction pathway traces along a minimum path on the potential energy surface toward higher densities and crosses into the bonded state through the first transition state it finds: the lowest enthalpy transition state. Confinement dynamics therefore creates a slow but efficient mechanism for chemical synthesis.

Conclusion

This system provides an unambiguous example of a reaction pathway dependent on physical confinement for its progress. Under the observed conditions, pyrrole polymerization proceeds by pseudo-zeroth order kinetics at a rate determined by the dimensionality of confinement. Without

confinement, the polymerization requires an external electrical or chemical energy source. The structure is therefore not a passive observer of the chemistry that occurs within its interior spaces: its size, shape, surface chemistry, and external environment contribute significant mechanistic effects. Confinement reduces the entropic penalty of polymerization by reducing the substrate's degrees of freedom and creates an energy gradient large enough to marshal thermal motion into driving the substrate toward and across the reaction transition state. Owing to practical difficulties, we have not yet measured reaction dynamics nor confirmed the ratio of monomer to polymer at the endpoint. These data will indicate the existence and extent of unreacted pyrrole inclusions in the SMA/polypyrrole and provide important insight into system behaviors when reactive centers become scarce. This effort will be aided by the development of methods for controlled product extraction and reactant replenishment in soft nanoreactors. Further exploration of the thermodynamic effects of confinement in SMA would benefit from a wider range of test reactions including non-polymerizing and pressure- or temperature-dependent intramolecular reactions.

Natural processes occur within a tremendous variety of nanoscale reaction spaces whose contributions to the reaction processes they host may be unjustifiably neglected. As we have demonstrated, the size, shape, chemistry, and dimension of the reaction chamber can make a critically significant mechanistic contribution to the reaction process it hosts. Computational models of enzyme-driven reactions may be improved in their accuracy by incorporating the empirical knowledge gained from simplified model systems such as SMA.

The outcomes of a chemical reaction are determined by the stability of its reactants and products, which are products of the relative amounts and distributions of energy in each. In this chapter, we found that nanoscale architectures can shape the forces acting on the molecules moving within them to impact reaction rates and outcomes. In the next chapter, we focus on how synthesis under confinement structures can begin to model the bottom-up assembly strategy of living organisms.

5. Bioinspired hierarchical additive construction

This chapter has been previously published as:
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Abstract

Biomineralization processes rely on well-defined low dimensional nanostructures to control the properties of the organic, inorganic and metallic crystals that form within them. Polymeric and hybrid nanostructures may be applied to mimic the environmental conditions and gain a powerful set of levers to control the synthesis and movement of crystalline nanomaterials. Self-assembled structures of polystyrene-alt-maleic acid and single atomic layer gold nanosheets are used to direct the growth and movement of 2-3 nm gold nanoclusters. The system is found to be stable through freeze-drying and rehydration and to support the directed release of nanoclusters to form higher order structures when differential dehydration of the system motivates water flow through the polymer nanotubes. The combination of stability or dynamism depending on bulk conditions marks this as a promising system for nanoscale additive manufacturing.

Introduction

The size of living organisms stretches across at least eight orders of magnitude from the sub-micron *Mycoplasma* bacteria to blue whales and giant sequoia stretching tens of meters[132]. If we include clonal species like Pando the aspen tree, Oregon's 'humongous fungus,' or Shark Bay, Australia's sea grass, then the scale expands into the hundreds or thousands of square kilometres and millions of kilograms[133–135]. All the more remarkable then that all biological growth occurs at the nanoscale, independent of how grand an organism that growth may produce. At the foundational level of biological organization lie molecular machines reliably constructing the higher levels through the active collection, synthesis,

transport, and placement of even smaller raw materials. These biochemical structures and processes perform uncountably many and varied acts of additive manufacturing and therefore provide a generous inspiration for the development of synthetic hierarchical functional materials.

In a previous review of biomimetic materials, we emphasized how size-dependent properties of functional architectures change between 1-1000 nanometers[108]. There we include surveys of confined superstructures that enable the controlled synthesis and transport of small molecules and inorganic nanoparticles. These two functions remain high-value targets for nanoscale construction.

In situ synthesis of nanoparticles within an organized molecular structure opens the door to properties not found in bulk materials. A recent review by Wei and coworkers provides greater depth on the role hierarchy plays in biological and bioinspired systems of controlled synthesis and assembly of multi-component nanomaterials[136]. The conch shell, they note, is a highly structured lamellar composite comprising calcium carbonate platelets arranged within a flexible biomacromolecular matrix. Despite containing only 1% organic matter by volume, the controlled crystallinity and layout of the inorganic phase raises its toughness one thousand times greater than mineral calcium carbonate. Similarly, guanine is an organic crystaline component of biological composite materials, although for its optical rather than mechanical properties, occurring in arthropods, molluscs, fish, and reptiles[137,138]. Male *Copilia mirabilis* copepods can reversibly cycle their colour between transparent and brilliant blue by altering the thickness of cytoplasm separating layers of guanine nanoplates[139]. Biomineralization processes such as these enable living organisms promote the formation of specific crystal phases at the dimensions and locations to optimize desirable properties. Naturally, it has been a long-term inspiration for research seeking to develop or improve the materials used in clinical settings for bone, tooth, or, increasingly, elastic connective tissues – although applications of biomineralization-inspired nanocrystal growth extend well beyond the medical[140].

Like the mineral and organic crystals cited above, the behaviour of nanoscale and low-dimensional metals may also be manipulated through their integration into a hybrid nanostructure. For example, the mechanical, catalytic, and optical properties that make nanoscale gold a valuable technological resource are highly sensitive to the specifics of its size and surfaces. Catalysis and molecular sensing on gold nanoparticles provides a case in point: activity is not only affected by total available surface area, but also by the crystal orientation[141–143] and surface texture[144–146]. For these reasons, calls continue for fabrication approaches that permit ever-finer control over the shape, surface area, and exposed surfaces of gold nanoparticles even as methods to produce spheroids, rods, sheets, and other higher-order structures proliferate[147–153].

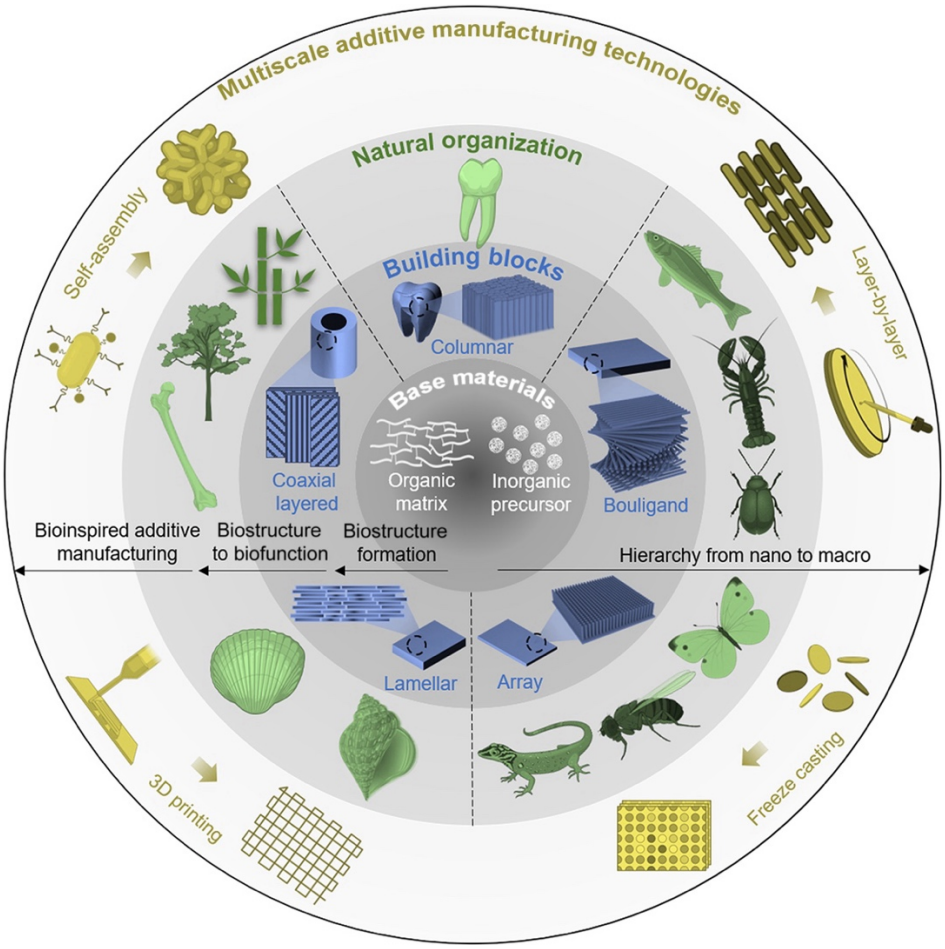

Figure 5.1: Diagram connecting the biological growth of functional materials to synthetic multiscale additive manufacturing technologies. Created by Wei et al. and published under a CC-BY 4.0 license[136].

Nanoclusters constitute a class special class of nanoparticles under two nanometers in diameter, containing few to hundreds of atoms[154,155]. At this scale the electronic structure of the cluster retains a character more like the discrete molecular orbital levels than the electronic bands of crystalline metals and so offer a set of bonding and reaction possibilities different than either single atoms or larger nanoparticles. The range of synthesis options for nanoclusters is just as wide-ranging across physical methods[156] such as photo reduction[157], microwave-assisted[158,159], radiolytic[160,161], or mass-selected gas phase selection techniques[162,163] and chemical direct synthesis[164], ligand exchange[165,166], and metal exchange methods[167–169]. Special care is taken in all methods to prevent aggregation of the clusters into larger particles, thereby protecting sites of particularly high catalytic potential for incorporation into a higher order structure.

Biomineralization-inspired methods for nanoparticle synthesis within a confined template provide an alternative to ligand-based nanoparticle stabilization techniques[170–172]. Confinement structures provide reaction spaces within natural or synthetic macromolecular constructions that induce and stabilize nanoparticle formation. Crystalline and amorphous polymers[126,173–175], dendrimers[176,177], microemulsions[178,179], and biomacromolecule-based approaches[180–184] for nanoparticle and nanocluster synthesis have been reported. Bioinspired confinement structures present an avenue for the design of nanocluster synthesis and storage systems that integrate levers of control over of particle size, shape, stabilization, and concentration as well as a means for controlled release.

Poly-styrene-*alt*-maleic anhydride (SMA), or acid when hydrolyzed in water, is a good example of a bioinspired system that provides a templating structure to precisely control the chemical environment and dimensions of its interior nanoscale spaces, and so the crystals that form within them. Indeed, depending on the mean length of the polymer chains, in neutral water SMA self-assembles into nanotubes (under ~100 kDa) or lamellar sheets (over ~100 kDa) each housing active aqueous reaction spaces of 2-3

nanometers in its smallest dimension[121]. The SMA copolymer and the structures it forms in neutral water are shown in Figure 5.2. We have previously described a method using an aqueous solution of SMA nanostructures to produce single layer 'goldene' sheets[126]. After dissolving and neutralizing a 1% SMA solution, AuCl is added on a 1:1 molar ratio with the monomer and mixed. Single atomic layer gold nanosheets rapidly form on the hydrophilic external surfaces of the polymer templates. By changing the rate at which gold chloride is introduced to the nanotube system we can coax the precursor into the confined space to preferentially produce spheroid gold nanoparticles under 3 nm in diameter (Figures 5.2 and 5.3). In combination, this biomineraliztion-like nanoparticle synthesis method creates a functional composite hybrid material with advantages for catalytic applications.

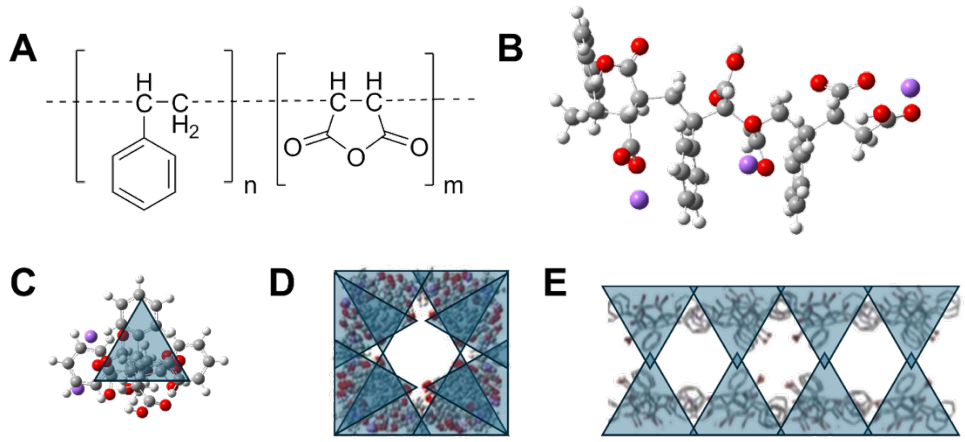

Figure 5.2: Schematic representations of styrene-*alt*-maleic anhydride and acid copolymer. A) Molecular formula of the alternating monomers B) Side view model of the styrene-*alt*-maleic acid trimer at pH 7, highlighting its linearity along the backbone C) Front view of the same SMA model, highlighting that the monomers rotate through 120° creating a triangular profile D) Front view of eight 20 kDa SMA chains self-assembled into a nanotube E) Side view of eight 350 kDa SMA chains self-assembled into a bilayer sheet.

Additive nanoparticle assembly offers a second area of application for hierarchical functional materials whose structures are able to host and transport nanoclusters or nanoparticles[185,186]. We can describe additive assembly as aggregation with intent: the same aggregating forces that nanoparticle and nanocluster synthesis so assiduously avoid are now carefully reintroduced and employed with an eye to functional engineering

and nanoscale architecture. Controlled destabilization has been achieved by affecting the protective capping ligands or the environment. Capping ligands can be released by chemical attack, external electromagnetic forces, or pressed into service for linker-assisted assembly[155,187]. Environmental changes can include solvent effects or passing a critical concentration through evaporative or selective separation into confined reaction spaces[188,189]. Few approaches offer a high degree of control over the final size, shape, or other properties of the final assembly. Confining the clusters within a micelle or other bounded nano- or micro-scale volume constrains the number of particles available for each assembly and thus the final scale of the structure. Confinement also imposes a level or spatial order onto the nanoparticles that could not be enforced on colloidal particles in solution. Construction of an assembly within a confining structure introduces the possibility for further assembly into higher-order architectures via further disruption and release into solution or, preferably, into another organizing structure at the next larger scale.

In this chapter, I demonstrate that the movement of water through SMA nanotubes loaded gold loaded generates forces can induce directed transport and release of the nanoparticles, creating the conditions for bioinspired additive manufacturing of nanostructures with textural features under ten nanometers.

Method

Gold (I) chloride powder was added to a 1% m/m solution of 20 kDa SMA in DI water at a 1:1 molar ratio and briefly sonicated for 5-20 minutes to ensure complete dispersion. The reaction mixture was left to stand until nanocluster growth was complete, as assessed by monitoring growth of the characteristic plasmon peak at 540 nm.

The system under study composed of gold nanoclusters confined within SMA nanotubes is shelf stable as a colloidal solution. Evaporative drying in air produces a well-ordered thin film through the alignment of nanotubes into higher-order structures of increasingly large scale[190]. In order to prepare the samples for examination of the structure as it exists in solution by X-ray

diffraction, a sample was flash frozen in a -80º C freezer and dried in a freeze drier.

Producing a dry thin film was accomplished by applying a bead of gold-SMA solution to a flat surface at STP and low ambient humidity to permit water to evaporate in air. Two different films were prepared and examined by X-Ray diffraction: one prepared from the original solution and a second from a sample that had been freeze-dried and later rehydrated to the original concentration.

Samples of the films were transferred by exfoliation to a carbon adhesive such that the underside of the film is exposed for scanning electron microscopy (SEM). Notably, the dry film adhered too strongly to polymer or glass surfaces to be usefully removed and an attempt on polished copper quickly and deeply oxidized the surface, spoiling the sample. Aluminum foil was found to provide weak film adhesion and, although some aluminum oxide was observed, the energy dispersive X-ray (EDX) scans showed that neither aluminum nor its oxides were present in the films described below.

Results and discussion

Stability – biomineralization-inspired composite material

We have found that gold nanoclusters formed within the SMA nanotubes are shelf stable in terms of size and position while the system remains in 1% aqueous solution. Increasing the concentration of the SMA in solution by evaporative drying in air alters its nanostructure so freeze drying was used to prepare representative samples of the system when in solution. The spectra below show that drying by this method is both slow and uniform enough that the forces generated by moving water molecules are insufficient to overcome the bonding interactions that hold the gold nanoclusters within their SMA host.

A sample of the gold-polymer system solution with both 2D gold nanosheets and embedded gold nanoclusters was prepared for powder X-ray diffraction analysis, shown in Figure 5.3. The spectrum is composed of broad peaks at 2θ angles 38.20°, 44.37°, and 64.76° corresponding to the (111), (200), and (220) planes of crystalline gold. Peak broadening is

proportional to the nanoscale crystal surfaces that produced them through the Scherrer equation: $\tau = K\lambda/\beta \cos\theta$. For shape factor K = 0.9 and X-ray wavelength 1.54Å, the full width at half-maximum β of 3.37° for the (111) plane gives a mean crystal plane size of 2.99 nm, consistent with the known size of gold nanocrystals formed within the nanotubes (solid line). In addition to the broad peaks, the 2D gold layers present in the sample produce a sharp peak only at the (111) position (dotted line).

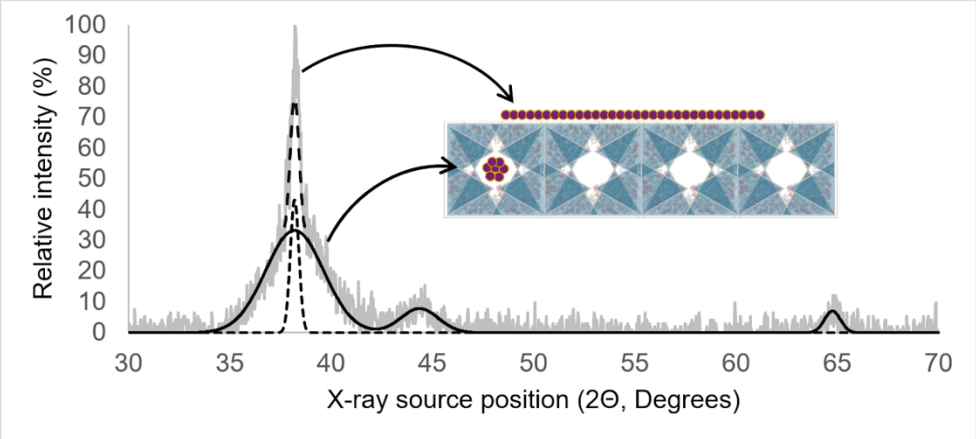

Figure 5.3: XRD spectrum identifying that both ultrathin gold nanosheets (source of sharp 111 plane peak) and gold nanoparticles (source of broadened peaks) are present in the sample.

Subsequent samples were prepared to favour the formation of nanoclusters in order to examine system changes through several dehydration and rehydration cycles (Figure 5.4). Because the gold nanoparticles remain interior to the polymer nanotubes after freeze-drying and do not aggregate during the process it suggests that sublimation of the bulk and confined water did not generate the forces necessary to dislodge them. The XRD spectrum is therefore indicative of the ratio of crystal surfaces on the individual nanoparticles: the (200) surfaces are 40% and the (220) surfaces are 23% as expansive as that of (111). Importantly, the gold nanoparticle-loaded nanotubes can be stored in either aqueous solution or dry powder until ready for use.

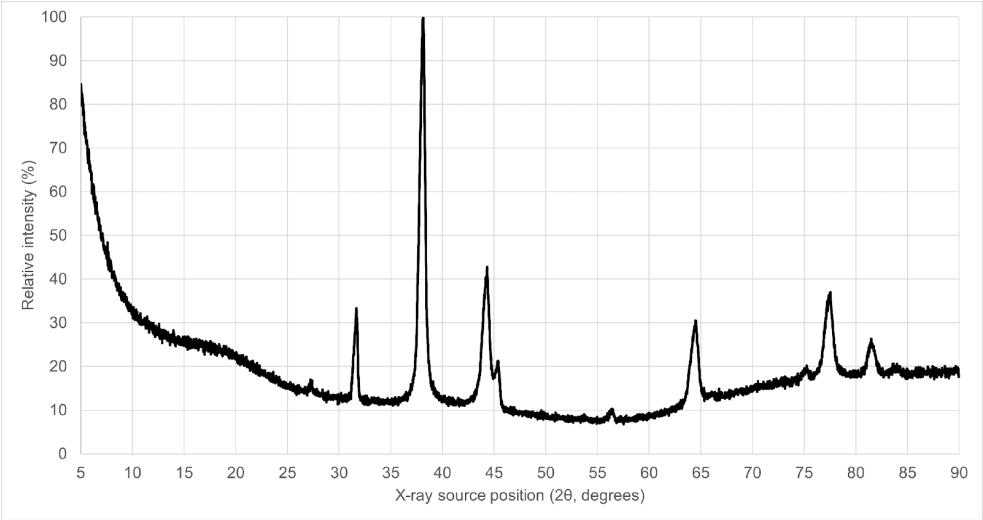

Figure 5.4: XRD spectrum of freeze-dried Au-SMA(20) film.

Pos. [°2θ]	FWHM [°2θ]	d-spacing [Å]	Rel. Int. [%]
38.2287	0.3838	2.35434	100.00
44.3399	0.1535	2.04300	39.98
64.5301	0.6140	1.44414	22.73
77.5304	0.6652	1.23127	23.38
81.4808	0.3070	1.18127	9.29

Table 5.1: XRD data for gold nanocrystals embedded in freeze-dried Au-SMA(20) film; peaks attributed to NaCl removed.

Mobility – transport and release of material for additive construction

In direct contrast to freeze drying, evaporative drying of the Au-SMA composite into thin films does produce microscale aggregates of nanoparticles in areas where the film is cracked or disrupted. The displacement of nanoclusters through the nanotubes and out of the confinement structure seen during evaporative air drying and absent in sublimated freeze-dries samples suggests that the flow of liquid water through the SMA nanotubes produces a motive force sufficient to displace the gold clusters from their confinement. Air dried films were produced by two methods: one sample was prepared from the original 1% aqueous solution and air dried on aluminum (Figure 5.5, black line); the second sample was prepared from the freeze-dried sample which had been rehydrated in ultrapure water to the original volume and allowed to stabilize before air drying (Figure 5.5, grey line). The similarity of the two spectra

indicates a high degree of stability of the gold-SMA system during freeze drying and reconstitution in solution.

The relative intensity of the (200) and (220) surfaces are reduced relative to the (111) surface as compared to the spectrum of the freeze-dried sample in Table 1, signalling preferential assembly on that plane. Naturally, any aggregation of nanoclusters will reduce the total surface area of the gold, but these spectra reveal that the snowflake aggregates retain a significant proportion of their higher order crystal planes.

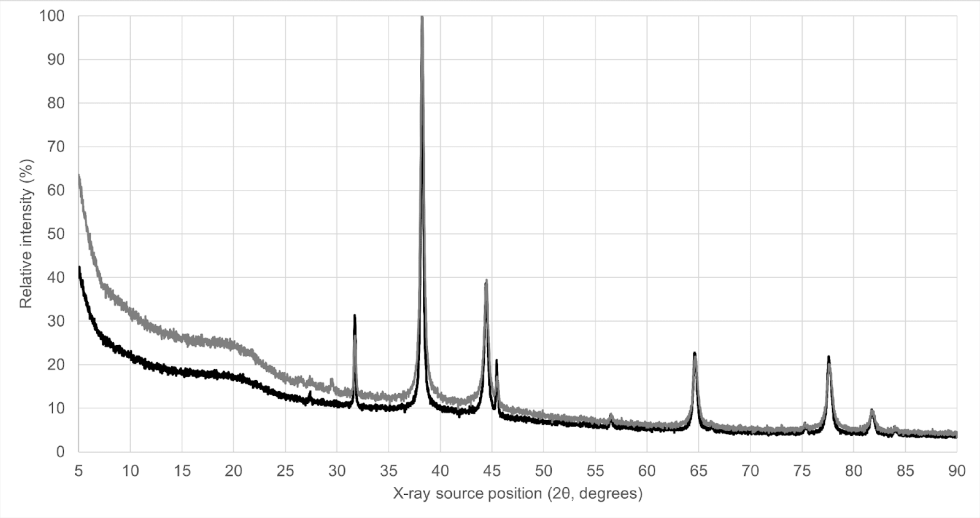

Figure 5.5: XRD spectrum of air-dried Au-SMA(20) film from the original solution (black line) and film produced after freeze-drying and rehydration (grey line).

Original solution			
Pos. [°2θ]	**FWHM [°2θ]**	**d-spacing [Å]**	**Rel. Int. [%]**
38.2197	0.2175	2.35486	100.00
44.3789	0.1023	2.04130	31.80
64.5911	0.2047	1.44293	19.21
77.5785	0.2047	1.23063	19.14
81.7296	0.1279	1.17831	6.11
Rehydrated solution			
Pos. [°2θ]	**FWHM [°2θ]**	**d-spacing [Å]**	**Rel. Int. [%]**
38.2974	0.2175	2.35026	100.00

44.3618	0.1560	2.04035	29.14
64.7213	0.2814	1.44034	17.69
77.5718	0.2047	1.23072	16.57
81.7102	0.4093	1.17854	4.77

Table 5.2: XRD data for gold nanocrystals embedded in air-dried Au-SMA(20) film, prepared from either the original solution or a solution that had been freeze-dried and rehydrated ; peaks attributed to NaCl not listed.

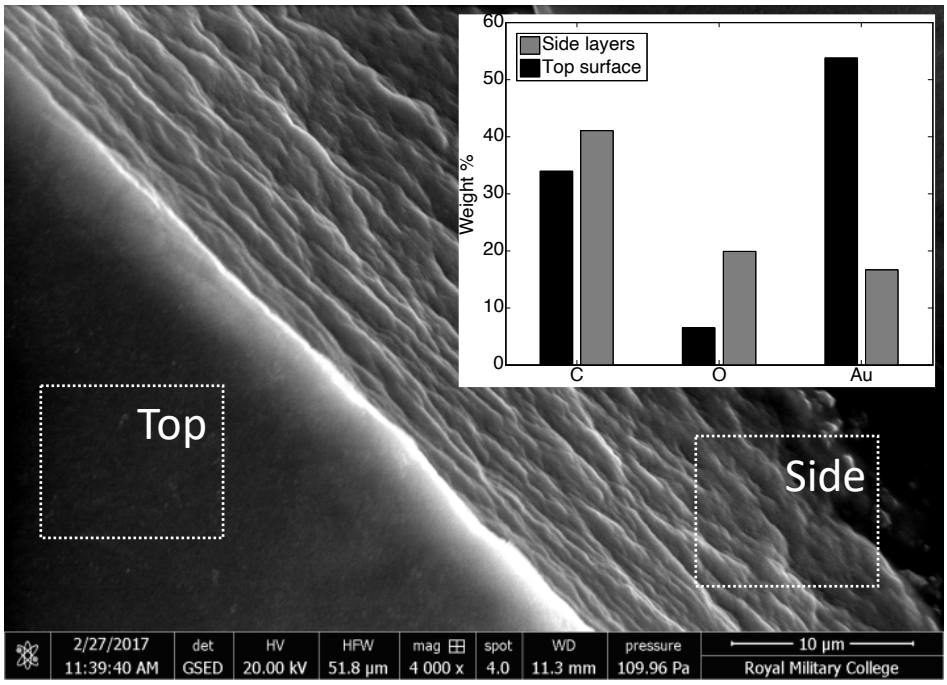

Figure 5.6: SEM image of the Au-SMA film dried in air, showing a smooth upper surface and layered side surface indicative of a well-ordered stacking of the polymer nanotubes during the drying process.

In solution, the nanotubes of the gold-polymer system can be found separate or weakly bound into parallel sheets. Higher-order assembly is dependent on concentration and temperature; at higher concentrations the nanotubes self-assemble into stacked layers interleaved with 2D gold, if present. The morphological changes to the nanotube system brought on the extreme concentration increase during evaporative drying were believed to be stable but had not yet been characterized. Micrograph images obtained by SEM confirmed that the gross structure of the film was comparable to that

observed in solution. EDX analysis revealed that the smooth outer surface of the film to be a layer of gold, as shown in Figure 5.7.

Co-location of oxygen was used to distinguish carbon present as SMA from that introduced by the carbon adhesive during sample preparation. As expected, the laminar areas on the side surfaces of the film revealed a higher concentration of carbon and oxygen than the uppermost surface (Figure 5.7). The 2D gold nanosheets ranged from 50 μm to several 100 μm, consistent with earlier findings. Both sodium and chloride ions are present in solution as counterions to the SMA and gold precursors, respectively; these formed a salt during the drying process and appear in the EDX scan as leaf-shaped frost on the gold surface in Figure 5.8.

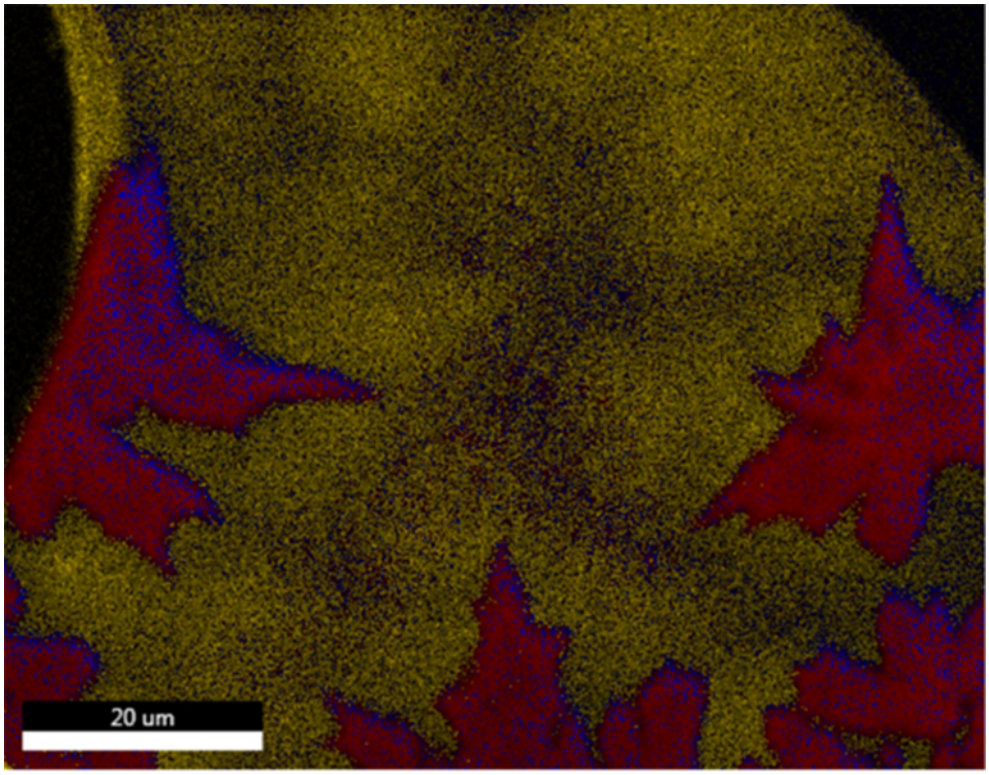

Figure 5.7: SEM image with EDX overlay showing locations of Au (yellow), Na (red), and Cl (blue) concentrations.

Richly textured ‘snowflakes’ were discovered at the edges and faults of the film that provide the following indications that they are formed through the additive assembly of gold nanoparticles driven free from the nanotubes;

examples are shown in Figures 5.9 and 5.10. First, EDX spot analysis of Figure 5.9 revealed that the snowflakes were composed entirely of gold. Second, smaller aggregates are visible, such as those in the upper right-hand corner of Figure 5.9, enhanced for sharpness and contrast. Third, the radially homogeneous increase in particle size and decrease in number on approach to the snowflake mesostructure visible in that image is consistent with the introduction of a monodisperse constituent particle at a regular rate. Finally, the branched, fractal structure is consistent with Brownian particle aggregation, strongly suggesting that the snowflakes were assembled from existing gold crystals during the drying process rather than grown from gold ions in solution and later revealed by the drying process.

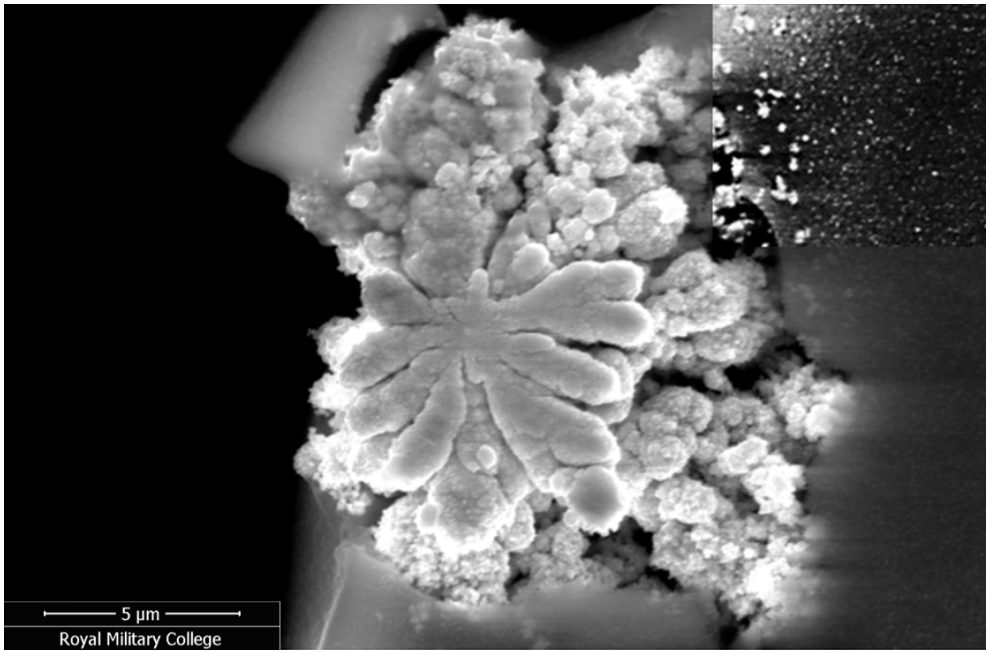

Figure 5.8: SEM image of gold 'snowflake' structure assembled from nanoparticles formed in and released trough the SMA structure.

Even though the gold-polymer layering is maintained through the drying process, SEM resolution is not sufficient to directly determine whether the polymer nanotubes' fine structure remained intact, was disrupted, or collapsed completely. Nanotube break-up could be responsible for the release of gold nanoparticles into solution and microfluidic flow for concentrating them into the last wetted areas. Free nanoparticles in solution could form similarly shaped dendritic structures in a drying droplet so the

presence of branched gold structures in the film would not normally suffice to demonstrate that the nanoparticles moved through the nanotubes to their edges. However, Figure 5.10 shows a snowflake partially embedded in the polymer whose linear structure is clearly demarcated by the straight and regularly spaced lines surrounding the snowflake from the lower left to the upper right. The striations marked by visible gold clusters in this and other SEM images signal that the nanotubular polymer structure is maintained during initial dehydration, although they may lose integrity as the nanoparticles progressively concentrate and aggregate in the final drying stages.

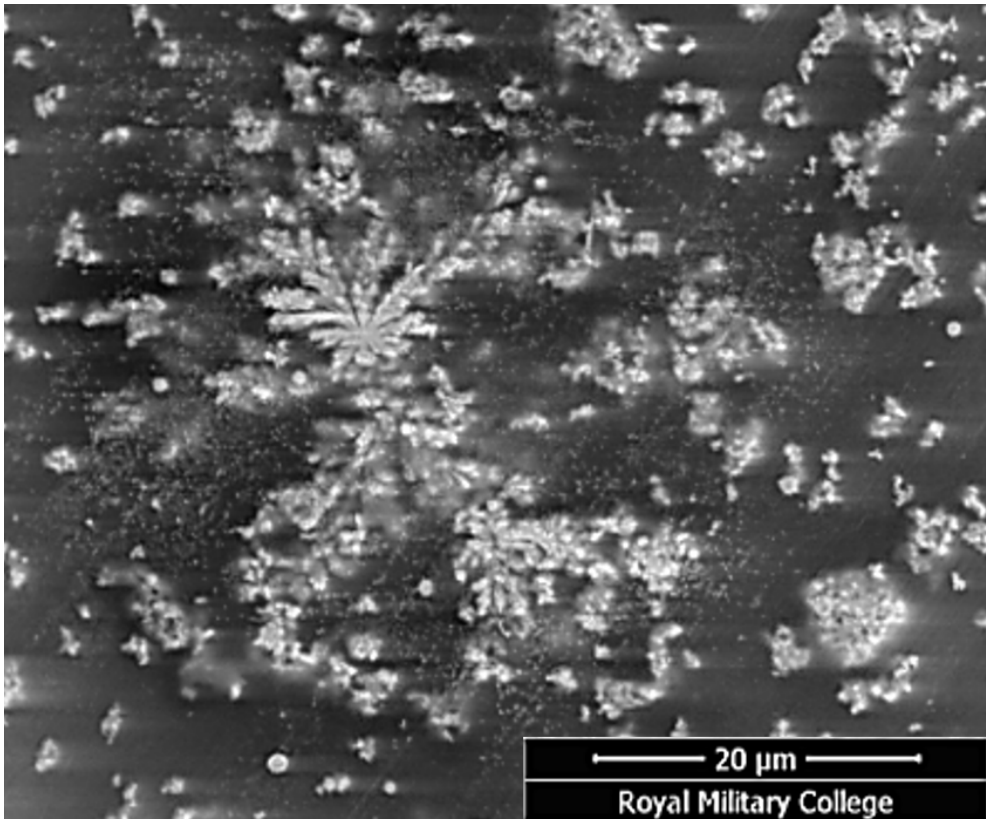

Figure 5.9: Micrograph image showing gold particles embedded in the polymer template that have aggregated to a scale large enough to be resolved by SEM revealing that the nanotubes which contain them are aligned along the lower left to upper right diagonal.

Conclusion

Biomineralization offers a rich ground from which we may draw inspiration for nanoscale hybrid systems with whose assistance we may synthesize,

store, and manipulate low dimensional crystalline materials. Here we have described a system of self-assembling polymer nanotubes that reduce gold chloride salt to monodisperse nanoparticles. The system demonstrates stability into a solid-state powder that can be readily reconstituted into aqueous solution. Alternatively, the system can be concentrated via evaporative drying in air to create thin films which discharge their nanocluster cargo in a controlled manner by dehydration-induced flow of water through the confining nanotubes. While the structures constructed by nanocluster aggregation described in this work are assembled through *uncontrolled* Brownian motion, developing additive fabrication techniques enabled by the *controlled* release of nanoclusters from polymer nanotubes presents an opportunity to achieve nanoscale resolution over the final shape and surface texture of higher scale multicrystaline structures. In future work, the technique we have demonstrated with gold should be attempted with other metals, minerals, and organic molecules to access the full range of mechanical and optical properties that nature tells us can be gained through the thoughtful bottom-up construction of hybrid, low-dimensional materials.

This and previous chapters show that supramolecular structures can impose order on reaction outcomes, rates, and the flow of reactants and products. The interactions between the reactant, the structure, and their environment are non-negligible and may indeed drive the effect of confinement. Learning to harness weak forces to our advantage within tailored nanoscale reactors, as biological processes do, will require new empirical data and theoretical tools to guide their design. The following chapter presents plausible directions for future work to that end.

6. Molecular sensors to characterize the effects of nanostructured reaction environments

Abstract

The potential for conducting chemical processes in nanostructured spaces, especially in wetted, self-assembling soft materials, is limited by the difficulty of measuring the thermodynamic properties felt by molecules within those spaces. Without sufficient data to refine a theory of entropy that adequately accounts for the shaping effects of confinement, designing an architecture to purpose will remain elusive. Spin crossover materials, particularly porphyrins, may be the reporter molecule we need to measure the effective pressure of the nanoscale volumes we wish to construct. This chapter serves to close the physical sciences section of the thesis with a look to future prospects of the work.

Introduction

Life on Earth relies on a tremendous wealth of complex and interdependent chemical systems to perform the myriad functions necessary for its self-sustainment. The majority of these occur within enzymes: proteins delicately tuned over four billion years of random, nearly imperceptible adjustments to optimize the size of the reaction chambers, the hydrophobicity, polarity, topology of the surfaces, and the presence and function of metal ions. While science and industry struggle to increase the rate and reduce the waste of bulk chemical synthesis, even the simplest living cells effortlessly produce high-efficiency nanoreactors able to correctly sense and respond to environmental signals using only the most commonly available elements. Although human artifice is entering the field many thousands of millennia behind Nature, we do have certain advantages: synthetic systems are subject to fewer interactions, are externally sustained, and the only limits on the use of exotic elements are cost and radiative decay. The “what” of the structures are the easiest questions to answer, but the “how” is more critical. By applying the same physical principles at work in biological systems while laying aside their specific atomic structures, taking inspiration rather than instruction, we may adapt the lessons of

protein evolution to non-living industrial processes while minimizing vestigial limitations.

Attention has recently turned to the role of water in and around these nanostructures. Due to the nearly intractable difficulties posed by the extremely small space and time scales the job of probing local fluctuations in temperature, pressure, and solvation generally falls to computer models of Newtonian motion, a method known as molecular dynamics (MD). Simulations track the movements of thousands of interacting molecules in an effort to calculate the properties under study. MD has been refined to a high order of fidelity to experiment, although it does have its limitations. First, the results are only as good as the mathematical model used to simulate molecular and solvent interactions and water, specifically, is a notoriously recalcitrant molecule. Second, systems simulated in MD are incapable of chemical reaction – molecules can move, vibrate, and rotate but will never change their number or species. Molecular dynamics simulation is a powerful but insufficient tool; results that claim to demonstrate some new understanding of how small changes in space and environment can affect reaction thermodynamics beg for legitimacy by comparison to real-world results. MD driven advances in bioinspired systems chemistry therefore depend upon experimental methods to legitimize the models that underwrite the theory.

Metal-ligand complexes that demonstrate a temperature and pressure dependant spin transition, or “spin crossover” (SCO) are the subject of active research as instructive cases in ligand field theory, but their small size and high sensitivity also hold promise of useful application in research and technology. The electrons which occupy the five d-orbitals of ligated metal ion complexes can either be alone in their suborbital or paired, one spin up and one spin down. Although enthalpy is lowest when electrons are paired, or “low spin,” additional entropy in the “high spin” unpaired state provides a competing benefit. In general, the energy advantage of either low enthalpy or high entropy is so great that a complex’s spin state is effectively permanently set in the low or high spin state. However, for those rare complexes whose two states are nearly balanced, a small change in temperature, pressure, or ligand electron density can be enough to influence

a dynamic and reversible spin transition. From this, one might imagine a technique for the non-destructive reporting of local thermodynamic quantities in nanoscale reaction spaces that employs individual complexes whose surface chemistry could be readily adapted for selective separation into a variety of interior surface topologies. Or, what may be more interesting still, spin crossover complexes incorporated into a synthetic nanoreactor as an active component in a catalytic system capable of sensing and responding to environmental cues.

Hundreds of SCO complexes and frameworks in one, two, and three dimensions have been identified; those relative few whose transition occurs in temperatures amenable to liquid water will be particularly interesting to researchers who seek to understand and take inspiration from the subtle inner workings of natural chemical systems. In this perspective, I will present the thermodynamics driving spin crossover in terms of ligand field theory, describe its sensitivities and methods to measure their response, provide a survey of example complexes, and finally speculate on how these materials might find application in systems chemistry involving reactions within advanced nanomaterials[1].

General Overview

The guiding principle underlying the spatial distribution of each orbital is energy minimization, best achieved by the homogenization of probability and so electron density. As the letter sequence rises through *s*, *p*, and *d* the orbital shapes become more complex and partitioned. The five independent divisions of the *d* orbital can host a maximum of ten electrons; three are X shaped and lie in the planes **xy**, **xz**, and **yz**, the fourth aligns to the **x** and **y** axes and is addressed as $\mathbf{x^2 - y^2}$. As an hourglass along the **z** axis, the final orbital, $\mathbf{z^2}$, resembles a *p* orbital except that it is ringed by a toroidal belt at its centre. Since two electrons may fill any given subdivision, the order in

[1] The book chapter by Philip Gütlich and Harold A. Goodwin, "Spin Crossover – An Overall Perspective" Top Curr Chem (2004) 233:1-47 DOI 10.1007/b13527 provides, as advertised, an excellent overall perspective of the methods of perturbation and detection for spin transition systems. It was cited in nearly every article cited here.

which orbitals fill becomes an important question that will be addressed in the following sections.

Ligands

Bonds to metals by non-metals are not typically treated as covalent, but rather ligand atoms donate their electrons into bonding molecular orbitals to form a complex. The molecular electronic structure determines the number and direction of bonding sites and thus whether a complex geometry is tetrahedral or octahedral. In the octahedral orientation, which is the more relevant to our current topic, the metal contributes *s* and *p* orbitals to molecular sigma bonds which become occupied with electrons donated by the ligands. Metallic valence electrons occupy its *d* orbital. Despite their differences in shape and orientation, the *d* sub-orbitals are energetically-equivalent until degeneracy is broken by ligation. With bonds aligned to with the three axes, an increase of electron density in those cardinal directions has a different impact on bonding than an equivalent increase does in others. Whether filled or unfilled, off-axis **xy**, **xz**, and **yz** *d* suborbitals are not aligned with donating ligand orbitals and so have little impact on sigma bonding. The $\mathbf{x^2 - y^2}$ and $\mathbf{z^2}$ orbitals, however, are oriented in line with the ligands. Filling these has the effect of further increasing electron density between bonding atoms, lengthening and weakening the bonds, and are therefore anti-bonding orbitals whose higher probability localization implies a higher energy level than the non-bonding divisions. The resulting energy difference is labelled Δ_o (as compared to Δ_t for tetrahedral complexes) and its quantity is a function of the strength of the bonding between metal and ligand: the more resilient the bond the more energy it will take to insert anti-bonding electron density. Closer metal-ligand distances and stronger electron-donating ligands will therefore increase Δ_o and vice versa. An ordered list of ligands in terms of ligand field strength Δ_o gives the spectrochemical series, an abridged selection provides an example:

$CH_2Se^- < CH_2S < I^- < Cl^- < SCN^- < NCS^- < H_2O < NCSe^- <$ phen $< NCCH_3 < CN^- < CO$

where metal bonding occurs through the leftmost atom in each species and 'phen' is 1,10-phenanthroline.

Opening Δ_o between the three lower and two higher d-orbital subdivisions affects the order in which they fill with electrons. As before, the first three electrons will each occupy one of the lower energy suborbitals. The placement of the fourth and fifth electrons is a question of balance: if electron pairing energy is greater than Δ_o the electrons will occupy the upper two suborbitals; if electron pairing energy is small relative to Δ_o then the next lowest energy orbital vacancy is to pair into the lower three. The first case is known as the high spin (HS) electron configuration; its occupancy of the upper anti-bonding suborbitals leads to longer metal-ligand bonds that absorb light in the infrared band while the greater number of unpaired electrons enhances magnetic susceptibility. If Δ_o is sufficient to insist upon electron pairing in the lower energy suborbitals the electron configuration is known as low spin (LS). Vacant anti-bonding orbitals produce shorter, stronger metal-ligand bonds that provide visible colour while greater spin pairing inhibits magnetic susceptibility relative to the HS state.

Lower field strength ligands tend to produce high spin complexes. For example, $[Fe(H_2O)_6]^{3+}$ is high spin and nearly colourless but when its ligands are replaced with carbon monoxide it becomes the low spin and brightly coloured Prussian blue. Nitrogen substituted heterocycles generally lie in the middle of the series and provide many possibilities for tuning their field strength through derivation and substitution or partial replacement. An illustrative example is $Fe^{II}(phen)_3$, a low spin complex. If one of its phen groups is replaced with two weaker field ligands, NCS^- or $NCSe^-$, the spherically averaged energy field decreases and the compound becomes high spin at room temperature[191].

Thermodynamic mechanism

The balance between electron repulsion and ligand field energies determines which metal-ligand complexes are high spin and which are low spin, but for those species where one is very nearly balanced by the other it is possible to induce switching from one electronic state to the other. Electron pairing produces shorter bond lengths, stronger bonds, and because they already

inhabit only the lowest energy sub-orbitals available, the low spin state is enthalpically favoured and remains stable as temperatures approach absolute zero. High spin states, alternately, produce longer, weaker bonds. This provides greater vibrational and rotational freedom and so is entropically favoured. As temperature increases, energy storage in these additional modes makes the high spin state the more stable of the two, although the temperature can be quite high before this becomes the case. The relationship between thermodynamic stability, enthalpy, entropy, and temperature is captured by the Gibb's free energy equation, $\Delta G = \Delta H - T\Delta S$.

The stable state is decided by the more negative term: if $\Delta H < T\Delta S$, low spin is preferred to high spin and vice versa. The balance point lies where $\Delta G = 0$, and so $\Delta H = T\Delta S$ which defines the critical temperature at which spin crossover occurs as $T_c = \Delta H/\Delta S$. By carefully tuning the ligand field strength to the metal, T_c can be placed at easily accessible temperatures, a useful feature as will be shown in the applications below.

A look at the typical temperature-magnetic response curve shows that kinetics also plays a role. Dilute species will occupy a variety of energy states according to a Boltzmann distribution while close-packed complexes experience co-operative and nearly simultaneous state switching. In cases where ligand steric hindrance or extensive geometric rearrangement results from the high to low spin change, $\downarrow T_c$ will be depressed, leading to the formation of a hysteresis loop. In other words, complexes warming into that temperature range will be thermodynamically stable in the low-spin state and those that cool into it will be kinetically stable in the high-spin state. Bistable molecules that demonstrate wide hysteresis centred about room temperature are an especially exciting development for their application to digital memory storage and to display technologies.

Metals

Chromium, manganese, iron, and cobalt ions with four to seven *d*-electrons ($3d_4$ - $3d_7$) are the best candidates for spin crossover[192]. Nickel (II) and other d_8 atoms can undergo the same spin transition but the geometric change between the two states is so great that they tend to be considered separately. The greater spatial extent of the 4d orbitals decreases the electron pairing

energy and increases the ligand field strength such that reaching the thermodynamic balance necessary for spin crossover becomes increasingly unlikely. Iron(II) falls into the energetic "Goldilocks Zone" and the large and easily measurable difference between its completely paired electrons in the low spin state and its four unpaired electrons in the high spin state have made it the most commonly reported metal centre in the literature[193]. Iron(III), Cobalt(III) and manganese(III) have also been described, as have complexes with two or more metals, both similar and dissimilar[194–196]. The focus and examples used in this paper follow the trend and draw heavily on complexes coordinated to a single iron(II) atom.

In his recent doctoral research, Dr. Sebastian Ovalle generated a dataset of 1024 porphyrin structures optimized through density functional theory to study the effects of iron or cobalt metal centre and ligand selection on oxygen binding affinity[197]. Among his early findings was that the different functionals and basis sets used in the modeling technique varied in how accurately they could predict the ground-state spin configuration and spin transitions of porphyrins, highlighting the sensitivity of their balance. DFT models do not account for environmental forces, so he experimentally measured oxygen binding by porphyrins confined within 20 kDa SMA nanotubes. His results reveal a remarkable sensitivity to the partial pressure of oxygen such that the system shows potential to serve as a gas transport mechanism. Additionally, the machine learning tool he created to model porphyrins will allow further tailoring of the system to act as a molecular pressure sensor, as described below.

Environmental Sensitivities

Typical reporting

Although the Gibb's free energy equation makes temperature the obvious metric for external influences on spin state, any sufficiently strong energy input could affect transition spontaneity, depending on whether it reinforces the enthalpy or entropy contribution. Thermal energy is baked into the original statement of the equation with entropy as its coefficient, but the work done by pressure, for instance, resists the volume expansion that results from bond lengthening and so serves to stabilize the enthalpy-favoured low spin state. Temperature is in fact the most common means to

test spin crossover properties and control spin state, but pressure, ligation, and irradiation are also reported[198].

Spin state transition results in several measurable property changes, most importantly magnetic susceptibility, colour, Mössbauer spectrum, and the release or uptake of heat. Volume changes are too subtle to be easily monitored in the quantities used for characterization. Since magnetism is a direct and well-studied result of spin state, spin crossover experimental results are usually reported by graphing the normalized magnetic susceptibility (as a proxy for the percentage of the population in the high spin state) as a function of temperature. Features of interest in the resulting curve include the critical temperature, hysteresis, transition slope, and completeness.

Solution v. Solid state

Spin crossover can occur in solution or in the amorphous or crystalline solid state. Most experiments have been performed on crystalline material in isolation to avoid confounding property changes in the complex with changes in the solvent. However, even in ideal and stable

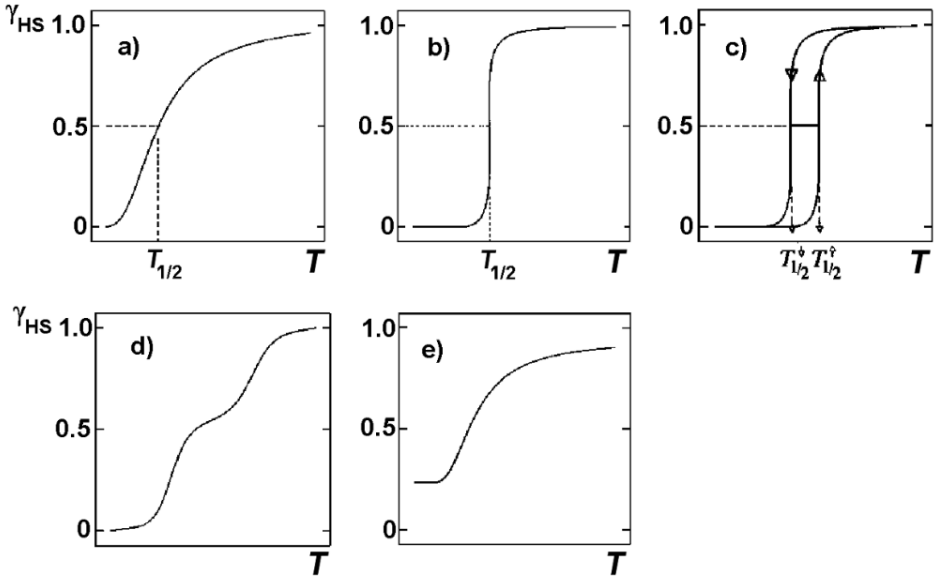

Figure 6.1: Examples of Spin Crossover charts. Reading from top left to bottom right: a) Boltzmann distribution in solution or amorphous solid b) Sharp transition in crystal c) Hysteresis cycle d) Multi-stage transition produced by two crystal phases e) incomplete transition[199].

solvation the resulting response curve will show significant differences. This is perhaps not surprising since the metal-ligand electronic structures have been specifically designed for sensitivity to local changes in the chemical or physical environment. The critical difference is whether the occurrence of spin transition in a single molecule has influence the kinetics of others.

Thermodynamic considerations decide whether spin crossover is favourable, but as with all other reactions there is no guarantee that the energetically spontaneous transition will occur immediately. Without a means of communication between the individual complexes, whether found in an amorphous solid or in solution, the precise moment of spin transition is a random, independent event and the percent of the population in the high or low spin state will follow a Boltzmann distribution for a given temperature range (Figure 6.1a)[200].

Crystalline spin crossover materials demonstrate a complete exchange of all molecules from one state to the other in a sharp transition range due to cooperation between neighbouring complexes (Figure 6.1b). Because the electronic transition is also expressed in the molecular geometry, transition kinetics in crystals are such that one complex can act as a nucleation site, transmitting the signal to its neighbours in a linked reaction that reaches the entire engaged population over a short time.

Intermediate curve slopes have also been reported due to colloidal behaviour. Each crystal will cooperate and transition independently of the others, narrowing the distribution in time and temperature. Accordingly, this effect is especially influential in those species that undergo larger geometric shift between the two states, either in bond length or direction. The same cooperative communication between complexes that nucleate a transition in one direction can provide resistance to transition in the other direction, leading to a split in critical point between the rising, ↑Tc, and falling, ↓Tc, temperature. Bistability in the temperature range bracketed by the arms of the hysteresis loop (Figure 6.1c) is therefore produced by thermodynamic stability in the rising direction and kinetic stability in the falling direction. The location, slope, and completeness of the transitions are do not show

fatigue across repeated cycles, a motivating property for a large part of current research into spin crossover materials[201]. It must be noted here that the measured width of the hysteresis loop is affected by the temperature scan rate – a slower scan produces a wider loop. While the scan rate is still reported only rarely it is necessary to accurately compare and reproduce results[202].

Cooperation between complexes in the solid state has been studied by replacing >90% of the SCO active iron centres with an intransigent zinc ion, a practice known as metal dilution[203]. Experiments have shown that while the crystal structure remains relatively unchanged, the transition signal will not be transmitted between iron centres and the response curve of the crystal appears like an amorphous solid or complexes in liquid solution. In my admittedly naïve opinion, the broad transition response curves attainable in metal-dilute crystals may be less exciting technologically, but have more scientific merit. Information about T_c (shown in Figure 6.1 as the point at which half the population is in each state: $T_{1/2}$) and the probability curve for a given metal-ligand combination in relative isolation are properties that are likely to define sharp transition locations under varying environmental circumstances as well as the theoretically maximum extents of hysteresis width.

If the material forms different crystal phases, transition in each phase may centre about different T_c, resulting in a response curve like Figure 6.1d or, in the extreme case, lattice forces may frustrate transition and result in incomplete response as in Figure 6.1e.

Thermally induced SCO

Classically, the Curie-Weiss law defined the relationship between magnetic susceptibility of permanent magnets to temperature:

$$\chi = \frac{C}{T - T_{Currie}}$$

Where χ is the is the dimensionless magnetic susceptibility, C is a material dependent Curie constant, and T_{Currie} is the temperature below which the metal displays spontaneous ferromagnetism in the absence of an external magnetic field. As temperature decreases, so too does the local vibrational

energy that could perturb the magnetic moment vector from alignment with other atoms and so susceptibility trends to a maximum as temperature approaches 0 K. Spin crossover materials were originally considered as an anomalous exception to this law: as temperature drops through T_c magnetic susceptibility *decreases*, in direct violation to Curie's principle. We now understand that temperature is related to the relative enthalpy and entropy of the low and high spin states, and since the law only applies to paramagnetic materials it is simply the case that Curie-Weiss did not anticipate that paramagnetism is itself temperature dependent.

Its reliable sensitivity to temperature makes spin crossover materials candidate molecules for application as a nanoscale switch or sensor, depending on whether the transition is sharp or Boltzmannian. Second, bistability in sharply transitioning crystals opens the possibility for binary memory and information storage, although the material would need to prevent inter-complex cooperation to avoid data bleeding into neighbouring cells. Temperature variation outside the relatively narrow hysteresis bounds would irreversibly erase any stored data, although that might be a desirable feature for a system temporarily working with particularly sensitive information.

Pressure effects

The transition from low to high spin moves electrons from the non-bonding orbitals into the anti-bonding orbitals and subsequently induce a lengthening of the metal-ligand bond by roughly 10% for iron (II) but translates into only a 3-4% total volume increase for a typical crystal. The change in volume demonstrates that the complex does work on its surroundings during spin transition, an amount of work that can be increased by increasing the external pressure. High pressure therefore has the effect of resisting low to high spin crossover, thereby stabilizing the low spin state and increasing T_c[204]. Under pressures on the order of GPa, T_c can be raised more than 100 K; for many compounds, the prototypical $Fe(phen)_2(NCS)_2$ complex included, this difference is sufficient to raise the critical temperature above the freezing point of water. Response curve slopes also tend to steepen as the increased pressure improves transition cooperation.

An interesting side note is that the simpler metal oxides and sulfides found deep in the Earth's crust are equally affected and that research into spin transition may have implications for geology and the global magnetic field[203].

Light induced excited spin state trapping

Irradiation by green light excites low spin electrons into the excited state which provides a radiationless decay pathway to the high-spin state. Once in this state at temperatures below T_c there is an activation energy barrier to relaxation in excess of thermal energies, trapping the complex in the high spin state. This process was first discovered in 1985 and is known as light induced excited spin state trapping (LIESST)[205]. Eventually, tunnelling permits a return to the low spin state but this process can take anywhere from seconds to thousands of years depending on the temperature and difference in lattice structure between the two electronic states, the principle source of activation energy.

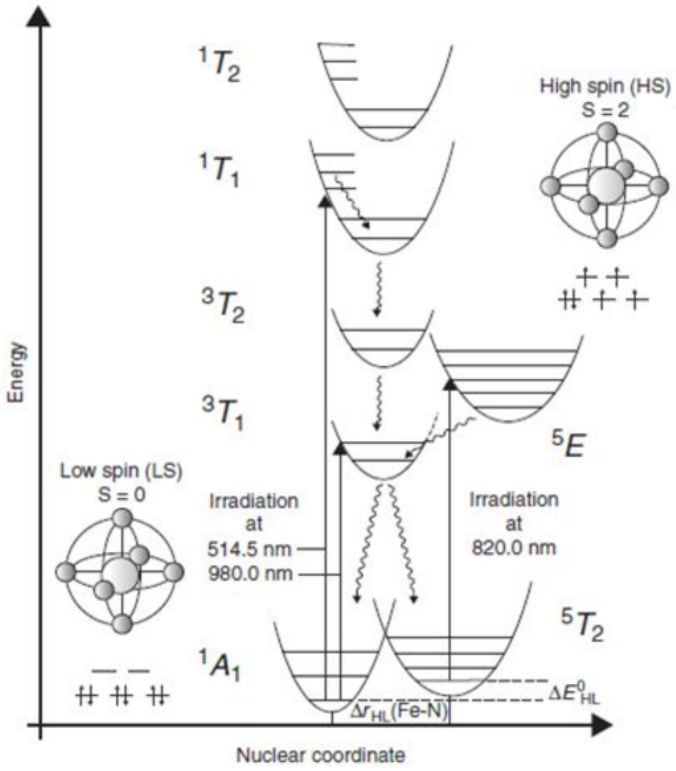

Figure 6.2: Schematic drawing of Light Induced Excited Spin State Trapping. From Halcrow, Malcolm A., ed. Spin-crossover materials: properties and applications. John Wiley & Sons, 2013.

Ligation

We have already seen that the spherically averaged ligand field strength impacts Δ_o, with low field strength ligands producing high spin complexes and vice versa. Because SCO depends on the balance of Δ_o vs electron repulsion it is possible that SCO susceptibility in a complex might be activated or deactivated by substitution of one or more ligands with one whose field strength tips the balance between the spin states. In the reaction

$$\mathrm{Fe^{II}(phen)_3, + 2\ NCS^{-} or\ 2\ NCSe^{-}} \rightarrow \mathrm{Fe^{II}(phen)_2(NCS)_2\ or\ Fe^{II}(phen)_2(NCSe)_2}$$

the initial iron complex is low spin and not SCO active, but on substitution of one 1,10-phenanthroline group with two lower field strength ligands it becomes high spin and SCO active. The electronic state change itself would not be considered an SCO effect since the shift is a result of a change in complex identity and not environmental conditions. However, it does raise the possibility of designing system that requires the presence of a signal molecule in sufficient concentration and thereby allow another lever of control over the timing of SCO effects.

Responses

We've discussed in some detail methods proven to induce spin crossover, but have only stated its common indicators: magnetism, colour, Mössbauer spectroscopy, and in certain special cases moderate changes in reactivity, geometry, and volume. In this section each will be discussed in greater detail.

Magnetic moment

The magnetic moment of octahedral transition metals can be adequately approximated by neglecting the orbital angular-momentum component and calculating according only to the number (n) of unpaired electrons:

$$m = \sqrt{n(n+2)}$$

For iron (II) that has zero unpaired electrons in the low spin state and five in the high spin state, the difference becomes easily measurable:

$$\Delta m = \sqrt{5(5 + 2)} - 0 = 5.92$$

The Evans NMR technique as adapted by Weber and Walker is the most common evaluation for SCO materials in solution, while superconducting quantum interference devices (SQUIDs) have generally replaced balance magnetometers for solids[203,206].

Colour changes

A secondary effect of spin transition is the change in appearance from colourless to pale high spin complexes to vividly coloured low spin complexes. As was shown in Figure 6.2, the ground state of low spin lies at a lower energy level and therefore its requires a higher frequency light to reach the excited state. An obvious colour difference arises in a single crystal of $[Fe(1\text{-propyl-tetrazole})_6](BF_4)_2$ cooled from high to low spin and exposed a spot of green light to invoke LEISST. Visible light spectroscopy shows that the colour change is quantitative in that area[207,208]. In other compounds, the HS absorption peak may be pushed into the near infrared and so appear colourless. Non-visible shifts in the infrared can also be indicative of spin crossover.

Examples

Iron(II)

Complexes of Iron(II) coordinated to six nitrogen donor ligands provide the richest variety of spin crossover materials with the desirable properties (sharp transition, accessible temperatures, wide hysteresis). This combination generates the largest known difference in M-L bond length between high and low spin states, indicative of the thermodynamic energy difference, the potential for cooperativity in solid state crystals, and the activation energy that drives hysteresis. This last property can be seen clearly in LIESST relaxation: iron(II) complexes trapped in the high spin state at low temperature remain so tens of millions of times longer than the analogous iron(III) species. Examples of ligands from monodentate pyridine to 6-coordinate nitrogen cages can be found in the literature, although bidentate heterocycles account for the majority of example ligand species. Halcrow 2007 provides a comprehensive review of some 420 heterocyclic N-donor ligand species and the spin states they induce[209].

Cobalt (II), Iron (III), and other ions

Of the other metal ions capable of spin transition, d_7 cobalt(II) and d_7 iron(III) are the most commonly studied, followed by manganese. Cobalt(II) tends to produce low-cooperativity and so gradual or incomplete conversion and show low sensitivity to pressure, although there are counter examples.

The tridentate pyrazine-imide ligand N-(2-pyrazylcarbonyl)-2-pyrazinecarboxamide (Hdpzca) forms an octahedral Co(II)(dpzca)2 complex that demonstrates a hysteretic spin crossover centred at 173.5 K with a ΔT of 11 K[195]. Although the paper title claims the transition is abrupt and complete, magnetic susceptibility continues a slow decline until 50 K when it reaches full transition to the low spin state. However, the sharp decrease of the magnetic moment from 4.0 μB to 1.7 μB in the higher temperature range cited should be sufficient for practical applications.
An interesting property of cobalt complexes not seen in iron is Jahn-Teller distortion up in transition from high to low spin state: equatorial bond lengths decrease significantly more than the axial bonds[201].

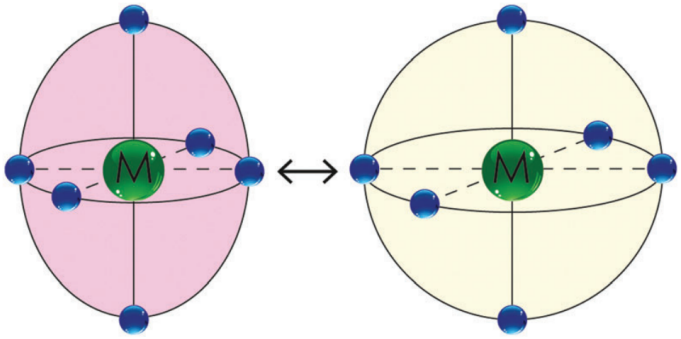

Figure 6.3: Jahn-Teller effect in Co(II) from Brooker, Sally. "Spin crossover with thermal hysteresis: Practicalities and lessons learnt." Chemical Society Reviews 44.10 (2015): 2880-2892.

Coordination polymers

An important class of SCO materials are those linking metal ions through covalent bonds into one, two, or three-dimensional networks. Structured materials are meant to improve cooperativity and fill specific functions, such as thin film displays or open framework sensors. Each have been produced but exploration of the possible structures and their characterization is early and ongoing.

One-dimensional SCO materials join metal centres by linking through a bidentate ligand, such as the iron and 4-amino-1,2,4-triazole coordination polymer shown in Figure 6.4. Despite predictions and initial indications that the covalent conjugation would promote cooperativity and therefore produce rapid transition materials, work by Dr. Birgit Weber exposed the limits of this method. Measurements on powder samples do show rapid spin switching as initially reported but the effect is lost when larger crystals are used. Their careful study revealed that the crystal alone was too strong to be overcome by thermal spin transition but solvent molecules interjected between the chains provided both the flexibility needed to restore SCO behaviour but also the hydrogen bonding network necessary for fast, cooperative transition.

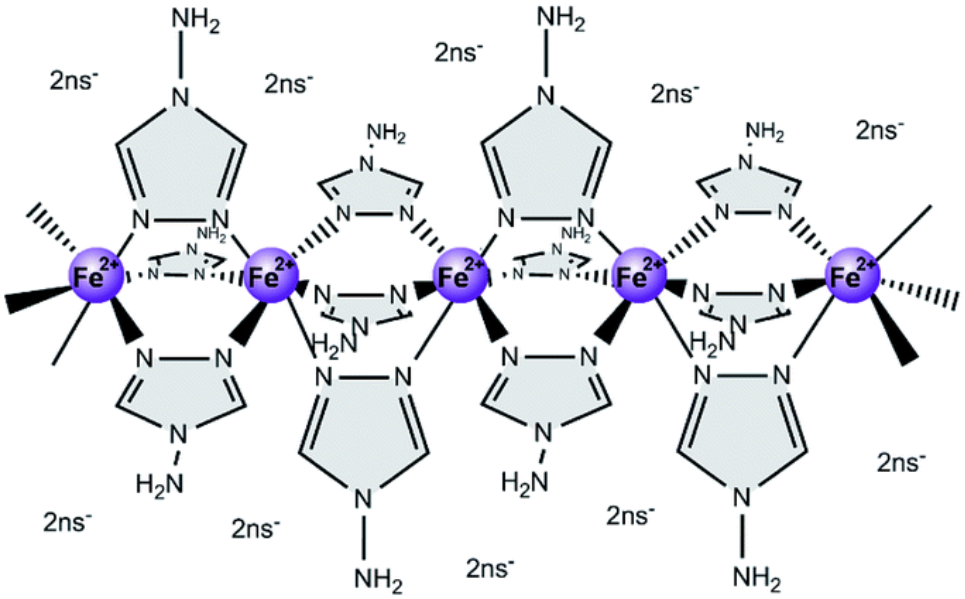

Figure 6.4: One-dimensional spin crossover coordination polymer

One distinction of the polyatomic chain is the insensitivity of the shape of its transition to changes in pressure, an advantage in any application where it is desirable to maintain its sharp switching capability across a wide range of temperatures and pressures.

2D networks

The first two dimensional SCO network was $[Fe(btr)_2(NCX)_2]\cdot H_2O$ where X = S or Se and btr = 4,4-*bis*-1,2,4-triazole, a linking molecule binding the complexes[210]. The crystal structure revealed that all NCX pseudohalide groups were oriented in the *trans* position. Like the one-dimensional example, the sheet lost its SCO activity once dehydrated, implying that hydrogen bonding was similarly responsible for balancing structural flexibility and coordination. Other examples have been produced through layer-by-layer deposition onto a metal surface[211]. This method has the advantages of relative ease, reliability, and homogeneity but is necessarily bound to a thicker substrate so while it may be a flat surface it cannot truly be called two dimensional[211].

3D Frameworks

Examples have now been reported of 2D nets interlocked into a 3D, mechanically linked structure[198]. The same method described for 2D nets has been adapted to produce 3D structures. In fact, the two dimensional example was converted into three dimensions by the displacement of axial pseudohalides from the *trans* to the *cis* orientation and allowing for additional bridging ligands[198].This arrangement can now be grouped into the large and ever-growing field of Metal-Organic Frameworks (MOFs). In certain cases, pore size has been designed to allow guest molecules; capture of small molecules and gases have long been a key feature of MOFs. A SCO MOF has been shown to exhibit spin transition due to the presence of a guest molecule[198].

Applications

Thermal memory and display technology

The most obvious application for a temperature sensitive material is temperature sensing, whether continuous as in those non-cooperative and in solution or switching as in crystals and bonded networks. Unlike other chemical colourimetric temperature sensors, the bistability of SCO materials endows it with memory - until it reaches a low enough temperature that all molecules return to the LS state, those that have been converted to HS will remain so. One can imagine mapping the loss of colour in an SCO sensor to

the thermal breakdown of a polymer provided its hysteretic loop covers the correct temperature range.

Confined within a nanoscale reaction space, the complexes should find themselves in close enough contact for transition cooperation or indeed crystallization[211]. This will sharpen the temperature transition depending on the total number of cooperative units. So if the shape of the transition curve at the two extremes of cooperativity are known, i.e. the single crystal and dispersed in solution, the experimentally derived curve would provide valuable data on the number and mean volume of the reaction chambers. Information that could then be used to corroborate or calibrate other sizing methods of particles in solution, such as dynamic light scattering.

Molecular pressure sensors

Pressure stabilizes the low spin state, so the appearance of colour or the disappearance of a magnetic response could act as a pressure-based switch or sensor[212]. Most relevant to the current purpose, a molecule-sized pressure sensor can act as a reporter molecule in systems too small for direct measurement, such as in the internal spaces held within of biological or synthetic nanostructures. With a SCO reporter whose T_c lies above 273 K, the effect of pressure on T_c could be directly compared to classical bulk pressure. A confounding factor could arise if the local organization responsible for the pressure differential is itself sensitive to changes in temperature. However, studies to date do not reveal deviation from zero-order reaction kinetics that would indicate that the internal pressure is a function of bulk temperature within the range of interest.

Chemical sensors

Spin crossover is directly associated to the strength of the ligand donor field surrounding the metal ion and so T_c of a complex is impacted by change in the ligand structure or their chemical environment[213]. Several groups report SCO initiation or control through differences in counterion or hydrogen bonding with other molecules in solution[214]. For example, MOF spin state can be altered by the nearby presence of certain guest molecules.
pH would be especially valuable, to discover intense but localized fluctuations in solvent pH depending on its chemical environment,

especially in confined spaces. Considering the possibility that the effective pressure fluctuations might be severe enough to cause hydrogen dissociation in water there is a possibility that confined spaces will present the possibility for ligand changes.

Spin transition for control of catalysis

One exciting challenge is the development of catalysts that can respond to chemical signals. Reactions that might be controlled in this manner include catalyzed reactions that depend on occupied or empty d-orbitals, or the lability of the ligands, for their mechanism to proceed. One recent example is β-hydride elimination in high-spin iron(II) and cobalt(II) alkyl complexes. A DFT study investigating how a mechanism that requires empty orbitals could occur in high spin complexes showed that C-H bond formation likely proceeds through a low-spin transition state that returns to high spin to give the product[215]. It would be interesting to explore the mechanism experimentally under external conditions either favouring or hindering the spin transition.

Nature provides several examples of transition metal N-donor complexes in the form of heme groups. Iron, generally, is ligated with a tetradentate porphyrin ring that may or may not be functionalized further. Increased electron donation or withdrawal in the ligands, displacement of water from the axial position, or other physical conditions as described above will influence the ligand field and therefore also on the Δ_o and spin crossover properties. If only to highlight the ongoing interest in this field, in an article published after this last sentence was originally typed measured spin crossover in an iron(II) porphyrin complex by mechanically straining the molecule using the tip of an atomic force microscope[216].

Instead of the experimenter's direct input, there is ample evidence that the electronic state of SCO materials can be controlled by peripheral alterations of its ligands and that this could be leveraged to allow or prevent another reaction. An important feature of biological catalytic systems is their ability to respond to chemical signals to direct their activity level. Exploration of abiotic signal-controlled catalytic pathways is a very interesting potential application for air and water stable SCO complexes. For example, if the

signalling molecule is itself directly involved in the reaction it could result in an oscillating reaction wherein the signal molecule concentration rises and falls by catalytic action. The cycle stability of SCO means that such a system would make a temperature and pressure-sensitive molecular clock. Since the spin state of the system would still be affected by changes in the environment, monitoring changes to the oscillation frequency could produce an extremely sensitive and precise sensor.

Finally, instead of a change to the ligand field consider a room-temperature low spin species that could be excited to the high spin state by light absorption, kicking off a reaction pathway. Or a combination of the two: ligand strength pushes to low spin, the reaction occurs, then light absorption drives the return to high spin and expulsion of the newly formed molecule.

Conclusion

This short perspective offered only an introduction to spin crossover systems. Although the literature is relatively young, the bulk published after 1985 and seemingly in waves as new characterization methods arise, it contains a wealth of fascinating instances of the effect. Whether individual complexes or bound into one, two, or three-dimensional structures, SCO materials very clearly demonstrate the fundamental principles of ligand field theory by teetering between the high and low spin electronic states. The electron-electron repulsion energy is nearly balanced with the field splitting energy; the enthalpic advantage of close, strong bonds balanced with the entropic advantage of increased vibrational modes. Environmental perturbations including temperature, pressure, radiation, or ligation changes easily and reversibly alter the electronic structure. The often sharp and obvious changes in magnetic moment and colour that result have made SCO materials notable subjects for those interested in their use as molecular sensors. Their small size is of special interest for application to systems otherwise inaccessible to measurement, such as the interior spaces of biological or artificial nanostructures. Of equal importance is their potential in controlled catalysis. Molecules able to sense and react to their chemical and physical environment are critical to the continued exploration and adaptation of Nature’s solutions to some of humanities most pressing concerns.

The previous chapters presented experimental work I have performed towards understanding how molecular structures can be designed and used to shape the entropy of a system and promote certain chemical reactions. These chapters are composed of peer-reviewed papers I have published in academic journals with the goal of communicating my observations within the chemistry community and advancing the science among its practitioners. While a journal article may be the vehicle recognized by the community to establish the legitimacy of the work, it is not an effective method to share knowledge across disciplinary boundaries. Technical language that can allows for rapid, precise understanding between experts can easily become indecipherable for readers whose background departs too far from the author's own.

The other exemplar of academic communication is the lecture – an expert explaining a subject according to their own understanding of its most important features: a 'speaker first' model. Foregrounding the speaker is best when communicating within a system of knowledge and practice where the common aims and values are already established. However, the same lecture fails when it is attempted across knowledge systems – one must first establish what features are most important to the listener and may then expand from there: an 'audience first' model. When the goal is to promote an innovative new material for commercial development or clinical use, to convince students of the value of an academic subject, or to show politicians the value of research for public policy, the choice to establish a connection first may be the difference between success and failure. The next chapter illustrates the costs of failing to connect by example and suggests a remedy. The lesson may be generalized to garner wider benefit from the difficult and critical work of research.

7. Nanomaterials for Targeted Drug Delivery

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Abstract

The first nanomedicine was approved for clinical use over 20 years ago. In the intervening time, our ability to engineer materials at the nanoscale has advanced immensely, yet a revolution in targeted drug delivery remains elusive. Nowhere is this more keenly felt than in the treatment of multidrug resistant cancers, where nanotechnology's fine control over drug release rate, location, and sequence promises a suite of tools for the effective long-term management of disease. Existing nanocarriers in development incorporate a variety of materials and properties designed to transit through the circulatory system, concentrate at tumor sites, selectively bind to cancerous cells, and release their drug payloads. So why have these advances in materials not led to advances in treatment? This chapter surveys the physical, educational, and political systems needed to transform a nanomaterial into a drug delivery system. Increasing the success rate might be achieved by paying greater attention to the intersections of chemistry, medicine, and policy: a 'disease-first' design strategy, closer integration of materials and physiology during training, and early coordination with regulatory policy makers.

Introduction

The ability to view and manipulate matter on the smallest scale has influenced the direction of research across all fields, and medical technology is no exception[217,218]. Regulatory bodies vary in their definitions of medical nanotechnology but in general the term comprises materials or material components designed to perform some medicinal function with at least one dimension between 1 and 100 nm. Nanoscale objects are small enough that they can interact with biological structures, yet large enough that they may exert a level of control over their surroundings and, often, encapsulate a

payload[219]. Microsilica particles, for instance, often extend to 400 nm but are included in this category because it is the nanoscale pores dotting their highly textured exterior, and not their overall diameter, that provide the advantage[220]. However, most nanoparticles (NPs) under investigation for use as targeted drug delivery vehicles described in this chapter do maintain at least one dimension below 100 nm.

Nanoparticles as a Vector

It would be misleading to describe the medical nanotechnologies presented here as drugs. While the structure or its components may impart some therapeutic effect, it is more accurate to consider these nanomaterials as vectors or delivery vehicles for the therapeutic agents they contain. Just as the spread of vector-borne disease is determined by the physiology and mobility of its host, so the fate of a drug payload vehicles is a function of the behaviour of its carrier within the body. Encapsulation of a drug by a nanocarrier provides a means to control the direction, duration, concentration, and destination of chemotherapeutic agents with far greater accuracy than the systemic release of the free drug[221].

In addition to precise control of the location of payload release, targeted delivery by nanoparticle may permit co-delivery of treatments whose timing or concentrations would be difficult to coordinate without a common carrier. For example, if a chemotherapeutic drug acts on a pathway for which two or more phenotypes exist, tumour cells may circumvent the drug by up-regulating expression of a compensatory pathway, developing heterogeneity and possibly drug resistance. A well-designed nanoparticle could carry and release a variety of drugs to address each possible pathway without the need to recharacterize a tumour or produce toxic concentrations or interactions at the systemic level[220]. Adjuvants may also be loaded and released at the optimum time, place, and concentration to maximize their effects. Finally, the carrier itself may incorporate a physical treatment modality which could act in concert with the chemical it carries. For example, the use of gold nanoparticles as a thermogenic treatment might carry a drug that makes local cells more susceptible to heat stress.

This chapter will address the common nanomaterials under investigation for application in targeted treatment and the potential methods they may employ to avoid or overcome drug resistance in tumour cells. First, the existing classes of nanomaterials under investigation for application in targeted delivery of therapeutic or imaging agents will be described. A survey of the physiological barriers to precise targeting will help justify why some of the promises of medical nanotechnology remain unfulfilled. This survey will be followed by a discussion of the real motivations for continued effort towards the successful translation of tumour-targeted nanocarriers for combating multiple drug resistant (MDR) cancers. We will conclude by offering some considerations for future directions in the design of materials and policies.

Current Systems

Several classes of nanoparticles are being developed for medical applications[222–224]. Liposomes and polymeric structures are the most common, followed in no particular order by micelles, dendrites, and inorganic nanoparticles.

Liposomes Liposomes are simple self-assembling spheres of fatty acids. The surface forces that drive assembly draw the hydrophobic tail groups towards each other, aligning the hydrophilic head group towards the aqueous exterior, giving liposomes a spherical shape. They have the virtues of being biocompatible, self- assembling, and easily characterized. Liposomes were the first type of nano- medical drug delivery system approved by the United States Food and Drug Administration (FDA)[225]. While liposomes are susceptible to capture and break- down by the immune system, their surface chemistry makes it possible to deco- rate them with molecules such as polyethylene glycol (PEG) that disrupt the body's defenses.

Micelles Micelles share numerous similarities and limitations with liposomes. They do, however, have more versatility in chemical composition and accessible shapes. Indeed, micelles formed by self-assembly of amphiphilic copolymers can generate exact shapes ranging from spheres to rods or lamellae as seen in Figure 7.1. The shape of the self-

assembled structures is often dictated by solvent composition and the ratio between water and an organic solvent. The shape of the drug carrier or the prodrug has been shown to influence the internalization pathway, blood circulation, cellular uptake, and observed cytotoxicity[226]. The influence of the shape of the nanocarriers on the release of the drug has also been highlighted in a review by Venkataraman and colleagues[227]. They found that changing the shape from a spherical to a filamentous micelle increased circulation time from 2 days to a week and resulted in a significant relative decrease in tumour size given an identical initial drug concentration[228]. The diverse chemical composition of the amphiphilic molecules permits different functional groups on the surface of micelles and allows for great versatility of the nanocarriers produced. Such facile functionalization opens direct and active targeting of the cancer cells to reduce side effects linked to the chemotherapeutic drug[229].

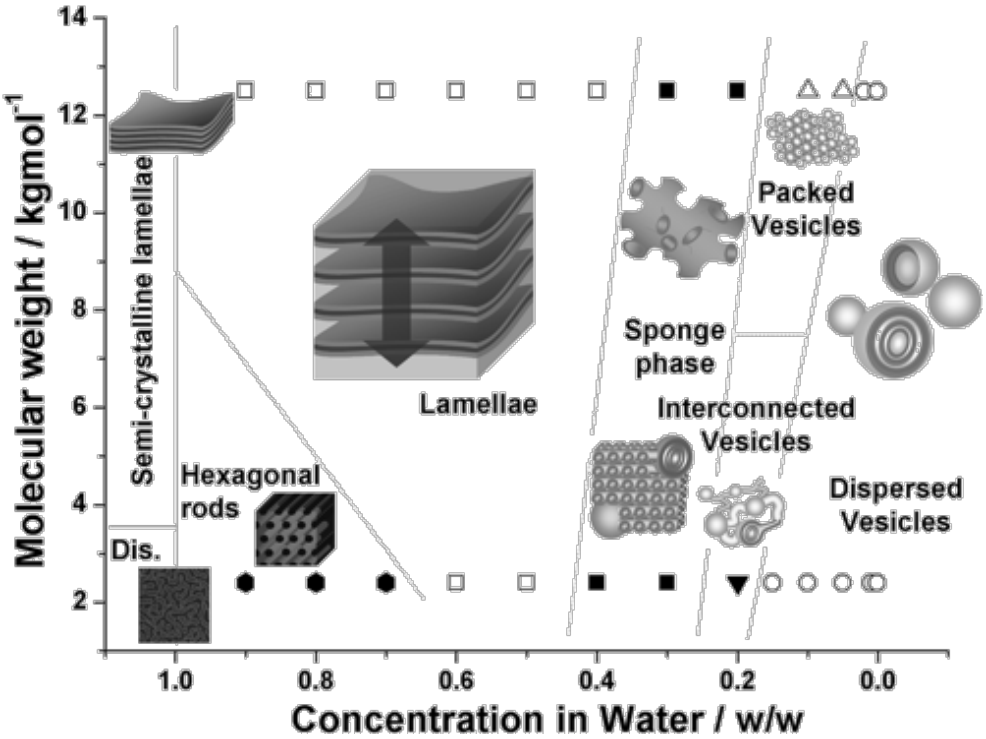

Figure 7.1: Like many polymeric materials, the shape and size of the self-assembling nanostructure of this block copolymer can be simply controlled by small alterations in the molecular mass and concentration. Isothermal phase diagrams of poly(ethylene oxide)-co- poly(butylene oxide)/water reproduced with permission from ACS Publications (Reference 16).

Polymeric Nanoparticles Polymeric structures offer much more physical and chemical versatility, forming anything from a amorphous gels to rigid crystalline structures[230]. Generally, polymers present a much more complicated toxicity profile but size, shape, inner and outer chemistry may each be tailored according to the application. Due to their easily-altered physical properties, polymers are the most investigated nanostructured material[231].

Dendrites Dendrites are polymers that branch from a common point to form fractal volumes with well-defined interior cavities and are another class of polymeric structure that shows promise for drug delivery applications as seen in Figure 7.2[232,233]. Dendritic cavities can provide physical entrapment of guest molecules, a property that could be translated into drug capture and delivery, although this delivery system has not yet been clinically observed. Indeed, dendrites are sought for applications in drug delivery as well as gene transfection[234], bioimaging[235,236], and tissue engineering[237,238]. Like other polymeric structure, dendritic structures could potentially undergo chemical functionalization of the interior and exterior structure for an increased range or specialization of biological applications. However, the cost of production can be prohibitive, and problems with scalability, biocompatibility, and biodegradability, have limited the number of *in vivo* studies[239,240].

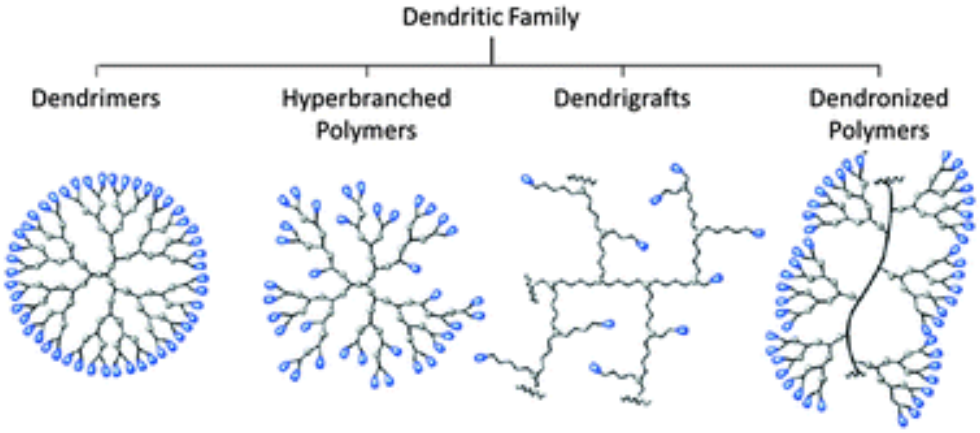

Figure 7.2: Polymeric dendrimers – regularly branching polymer nanoparticles – can be designed to take on a variety of shapes and sizes. The size and number of internal spaces or pores, which act as containers for drug payloads, are separately controllable. Reproduced with permission from RSC Publishing (Reference 25).

Inorganic Nanoparticles Inorganic nanoparticles include a broad range of materials from relatively large and porous silica to small metallic gold nanoparticles[241]. Most inorganic particles are non-reactive and rarely introduce challenges in toxicity. Inorganic nanoparticles such as quantum dots (CdTe or CdSe/ ZnS), iron oxide, silver (Ag), zinc oxide (ZnO) or gold (Au) NPs are often functionalized to improve solubility and reduce aggregation. Cellular intake via endocytosis and combination with a lysosome exposes the NPs to a low pH environment. This change in pH, combined with low-specific enzymes, degrades the organic coating and induces NP aggregation and degradation[229]. While these may be detrimental to performance during transport or delivery, degradation of CdSe, Ag, or ZnO has also been associated with the production of cytotoxic ions[242]. Cytotoxicity linked to degradation has not been observed with Au NPs which can be used for both diagnostic and therapeutic purposes. The therapeutic effect of these nanoparticles can be fine-tuned and adapted to drug-resistant tumours.

However, some challenges in the development of Au NPs remain. For instance, surface plasmon resonance is a function of NP size and surface coating, factors which are limited in range by their impact on cellular intake and circulation time. Silica NPs are also widely studied and present unique controllable physical properties that can be precisely tuned[243,244]. Indeed, it is possible to control the size, shape and porosity of the NP while functionalizing the surface of the particle to a precise circulation time or drug release profile[245]. Also, silica NPs can be modified to present different functional groups within the same NP for imaging, targeting and drug delivery[246]. In general, organic and inorganic multifunctional drug carriers present an advantage for targeted drug delivery and imaging especially in the case of drug-resistant tumour cells.

Mechanism of delivery

Nanocarriers promise to increase the efficacy of traditional chemical, biological, and radiological treatments by creating a platform for the rational design of an accurate and precise targeting system. Despite the robust research activity in the decades following the first FDA approved nanomedical cancer treatment, all currently approved therapies remain

limited to relatively low-precision, passive targeting[247]. Arguably, nanotechnology's most significant impact on therapy has come from relatively simple materials that stabilize their drug payload during systemic circulation, reduce the exposure of healthy cells to cytotoxic agents, and tailor particle size to accumulate in a tumour preferentially. The following sections provide an overview of characteristics currently under study, which future nanocarriers may incorporate either individually or in combination.

Enhanced Pharmacokinetics and Stability in Circulation

Many chemotherapeutic drugs are small molecules with low water solubility and are subject to rapid renal clearance. Nanocarriers are used to increase circulation time and total exposure[248]. For example, doxorubicin is an effective anti-cancer drug used to treat a variety of cancer types. However, due to rapid clearance and non-specific uptake by healthy cells, a high dose is required to achieve an effect on a tumour. Encapsulation within a liposome, micelle, or polymer structure creates a nanocarrier system with a diameter large enough to avoid the renal clearance pathways that affect particles under 5 nm while also remaining small enough to passively accumulate in the tumour microenvironment due to the enhanced permeability and retention (EPR) effect depicted in Figure 7.3[249]. EPR arises because the vasculature that feeds rapidly growing tumours may be poorly formed and so suffer a higher rate of seepage between their endothelial cells. Particles in the 30–400 nm range are more likely to exit the bloodstream through the fenestrations (enhanced permeability) and less likely to be carried into the lymphatic system, again due to the underdeveloped support system (retention)[250–252].

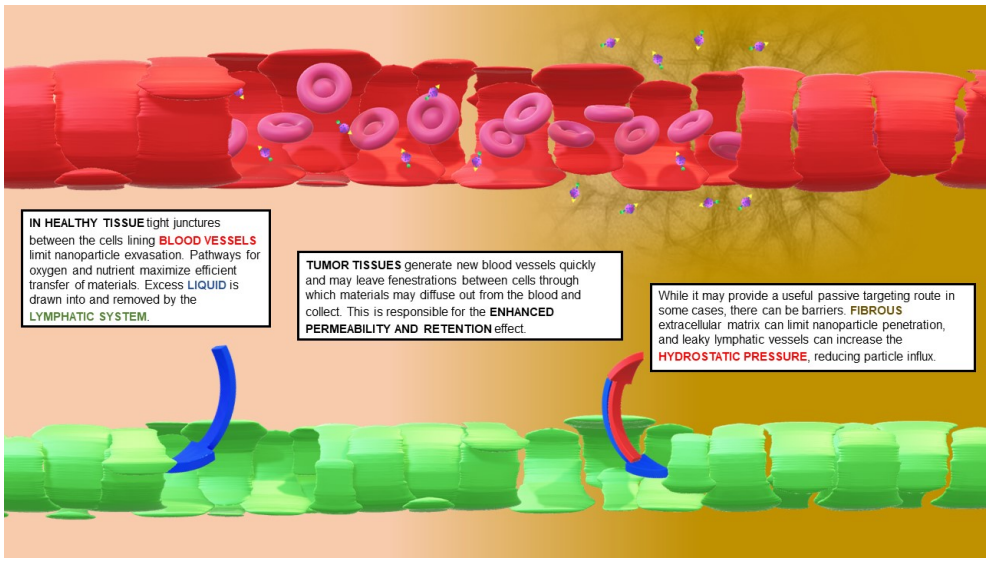

Figure 7.3: Schematic of the Enhanced Permeability and Retention (EPR) effect in leaky tumour vasculature. Rapid tumour growth may lead to poorly-constructed blood and lymph vessels which permit nanoparticles to be preferentially deposited in the tumour microenvironment.

Passive targeting by EPR is often the only method incorporated into a nanocarrier's design. However, it is important to remember that there exist significant differences between cancers and heterogeneity within a given type of cancer[253]. Not all tumour vasculature produces the EPR effect to the same degree, and some tumours may not present the effect at all[254]. Low tumour drainage is itself a double-edged sword; while treatment carriers that manage to enter the tumour extracellular fluid are retained for a longer time, the pressure gradient works to resist particle inflow from the blood. Furthermore, longer exposure times do not improve outcomes in-and-of themselves but must be paired with a reliable method for extravasation and drug release[255]. Regardless of the method of encapsulation, some fraction of the drug payload is released in the bloodstream due to non-specific interactions, mechanical disruption, or another rare and randomly-occurring event[253]. Prolonged circulation time therefore increases the risk of exposure to a low concentration of the free drug and the likelihood that tumors can develop drug resistance before receiving an effective dose[256].

In addition to the diameter, the exterior chemistry can be tailored to promote or avoid interactions with colloidal proteins found in the bloodstream[257,258]. Aggregation of proteins on the nanoparticle's surface will change the

solubility and hemodynamic profile and may also mark it for removal by macrophages in the blood vessels, liver, or spleen. Protein aggregation reduces systemic availability and increases non-specific accumulation in the organs[259]. Liposomes are typically subject to protein interactions, but conjugation with a short polymer chain, such as PEG, or another surface group sterically hinders protein access to binding sites on the lipid surface[260].

Drug encapsulation can, therefore, increase the circulation half-life from minutes to hours and the total exposure by orders of magnitude while eliminating the initial spike in serum concentration, allowing for the administration of dose amounts that would otherwise be toxic to patients[248,249,261,262].

Active targeting

Active targeting of tumour cells by nanocarriers implies that the delivery shell incorporates a mechanism to recognize the treatment target[247]. For example, a diseased cell known to express a much higher concentration of a certain mem- brane protein may be a candidate for active targeting of that protein. Depending on the type of nanocarrier, an antagonistic binding molecule or moiety for the membrane protein can be incorporated onto the exterior surface. Of course, the presence of reactive surface features complicates the task of unimpeded systemic transport. Recent work by Jin and colleagues addresses the need to protect or ‘camouflage’ the binding ligands until in proximity to the target receptors[263]. Once the nanocarrier reaches the cell, the targeting ligand will recognize and bind to the target receptor. This interaction could be made to initiate payload release in the ECM next to the cell membrane or to induce endocytosis and have the drug-loaded carrier into the cell interior[217,264]. Once the drug delivery system is encapsulated within the cell, intracellular targeting of specific organelles may be possible[265].

Challenges to delivery

Vascular Kinetics

Systemic travel from the point of injection to the target site poses numerous challenges to the drug-loaded nanosystem[266]. Clinical trials of unsuccessful

carriers have nevertheless helped identify unknown or underappreciated challenges associated with effective delivery of chemotherapeutic agents to their intended targets. The following summarizes some of the pharmacokinetic issues posed by systemic circulation, navigating the tumour microenvironment and extracellular matrix, gaining access to the cell and drug release. The concordant considerations for the design of nanocarriers are discussed for each segment of the journey.

Hydrodynamics

In the first approximation, blood is merely a liquid medium inside tubes of varying diameter and pressure. In this simplified model, the behavior of nanocarriers when carried along by the blood flow is a matter of fluid dynamics. The flow velocity is slower against the vessel walls and faster in the center. Particles that concentrate towards the center of the vessel have less contact time with the walls, demonstrating increased circulation times but decreased extravasation. The distribution of particles within the blood vessel is mainly determined by their physical dimensions of size and shape[267,268].

Size is a biologically relevant measure due to the physiological systems in place to ensure rapid clearance of small molecules and foreign cells as well as the nanocarrier's ability to take advantage of the EPR effect[252,255]. Size is also physically relevant because it affects how a particle will move within a liquid. The proper size of a particle in a liquid is not its hard diameter but instead its hydrodynamic diameter, which is determined by how much water moves with the particle inflow. Fluid in contact with the walls of the vessel will be slow relative to the center due to the higher resistance to flow[269]. The faster moving inner molecules will have more influence on smaller nanoparticles and will quickly sweep them along, concentrating them in the center of the vessel and limiting their exposure to the vessel walls. This approach will increase circulation time but restrict access to their target tumours. The gradual breakdown of the nanocarriers in circulation creates the extended low-dose release that may incite drug resistance.

The shape is an equally vital but less discussed physical dimension of the nano- carrier regarding its hydrodynamic impact[227,228]. Just as the shape of a

falling object will determine its path and velocity through the air (consider the difference between a closed and opened parachute), so too will a particle's shape determine how it travels in the blood[270,271]. Spherical nanoparticles are common due to the relative ease of their manufacture but tend to flow in the middle of the vessel, reducing opportunities for extravasation. Rod-shaped or fibrous particles fare better due to their higher aspect ratio. Disc-shaped particles spend the most time in contact with the vessel walls and therefore are the fastest to discover fenestrations large enough to escape the bloodstream[267]. It is perhaps unsurprising given that disc-shaped particles mimic the shape of platelets, blood components whose purpose is to find and block leakage from vessels. Liposomes are primarily limited to their spherical shape because of the radially symmetrical self-assembly of their phospholipid subunits. Polymers may be designed to take on an array of shapes, or in some cases to change shape in response to chemical or physical signals in their surroundings.

Extravasation

Extended circulation times are a good outcome only insofar as they promote extravasation of the nanoparticles at the targeted sites. For example, if the target tumour's vasculature is relatively well constructed and EPR effect is moderate, then the longer circulation time provides opportunities to interact with the target site and therefore a greater chance that the carrier will enter a tumour. One must also recognize that the more extended circulation period equally enhances the opportunity for nonspecific accumulation or other system clearance methods to take effect. If the probability of all other methods of exit for the drug delivery system remains lower than the one that delivers the drug to the target, then the longer circulation time is understandable and desirable. Better still are methods to increase the probability of the desired outcome, such as those that include adjuvants that attack the tumour vasculature itself.

Tumour heterogeneity is a complex problem that is often ignored during the design phase of nanoparticles[272,273]. Oversimplification or generalization of the physiological characteristics of diseased areas has failed when otherwise promising delivery strategies are translated to the clinic. To minimize this

risk, Hare and colleagues suggest four changes of focus during the development process:

1. Begin with a greater understanding of nanomaterial interactions with tumour tissues,
2. Develop more representative animal models and testing protocols,
3. Pre-select patients with a higher likelihood of response, and
4. The shift from material-driven to disease-driven development[272].

The tendency to develop nanomaterials based on a general delivery strategy before considering which disease it might suitably address has led to many new materials but few effective treatments. This may be symptomatic of the scientific backgrounds of those leading the search for formulations. Training programs that straddle the nanomaterial-pathophysiological divide may realign nanomaterial innovation with the patient- and disease-focused development and improve rates of clinical translation.

Penetrating the Tumor Microenvironment

Size and shape are just as, if not more, important with regard to penetrating the tumour microenvironment (TME) as they are in contending with systemic circulation. The extracellular matrix (ECM) may be far more closely packed than healthy tissue, limiting incursion by particles optimized for relatively free-flowing blood vessels. Furthermore, poor vasculature can restrict fluid drainage, increasing the local hydrostatic pressure[274]. Under these conditions, smaller particles or filament- shaped nanocarriers are likely the most effective. A larger particle that degrades into or releases smaller particles in response to environmental cues at the edge of the TME may also prove to be more effective at reaching its target[275].

The tumour microenvironment is often moderately acidic, so pH-sensitive release mechanisms are likely to begin to deposit their payload here[276]. If the drug reaches its effective concentration in the ECM as well as inside the cells, then drug release before cell entry is acceptable and may even be preferred. In this case, cancer cells have a reduced capacity for developing resistance since the target is the general tumour environment and not a specific marker on the surface of the cell. Other environmental cues that

could trigger drug release include light, magnetic field, ultrasound, and heat[277]. Nanocarriers can be engineered to generate or enhance these conditions in concert with external stimulation.

Entering the Cell

Another targeting strategy is to decorate the surface of the nanocarrier with ligands that recognize and bond with a receptor on the cellular membrane which then initiates endocytosis[269]. Precise delivery is therefore dependent on the relative overexpression of the target molecule on cancer cells as compared to healthy cells. For example, both healthy and diseased cells may express folic acid receptors on their surface[229]. However, some cancers are known to significantly overexpress the receptor. When coupled to the EPR effect, the target cells will internalize the nanocarrier in a proportionally greater frequency than healthy cells[267]. While this strategy does allow for more precise targeting than passive collection and drug release by the EPR effect or the acidic tumour ECM, it also presents the potential for cells to develop resistance to it by downregulating expression of the target protein. Strategies to avoid this undesirable side-effect are discussed in more detail below.

Defeating the Lysosome

Once the targeting ligand binds to a receptor protein on the cancer cell's surface, the nanocarrier may be transported through the membrane via endosome[231]. The cell may then begin to pump protons into the endosome or combine it with lysosomes to reduce the internal pH and degrade the endosomal contents. The nanocarrier can be designed to remain stable in the slightly acidic tumour ECM but respond to stronger acidity, ensuring preferential drug release inside the target cells. The nanosystem must also be able to protect the payload from acid damage and incorporate some mechanism to free the drug from endosomal encapsulation. An elegant solution to accomplish both is to use a proton absorbing polymer that expands as it collects a positive charge on its surface[269]. The proton sponge ensures that the payload is not subjected to an acid attack while the build-up of repulsive electrostatic forces causes the polymer to push against the endosomal envelope until it bursts, freeing the intact drug. Other strategies

include the inclusion of cationic polymers to induce membrane inversion or membrane-destabilizing peptides[267].

Applications in Multidrug-Resistant Cancers

As a fundamental design concept, nanocarriers for cancer treatment should be engineered to avoid or overcome the possible triggers for drug resistance concurrent to their release of the payload. Strategies include co-delivery and staged deployment of complementary drugs and adjuvants, the use of the nanocarrier itself as a sensitizer to a physical treatment method, and incorporation of drug efflux pump antagonists or disruptors. The application of any, or better yet all, of these methods in a targeted drug delivery system should act to reduce the incidence and impact of drug resistance in tumours.

First, nanocarriers are ideal for the accurate delivery of precisely dosed cytotoxic drugs and their adjuvants, ideally those with complementary target pathways[278–280]. By creating contemporary challenges to the cell, co-delivery designs overwhelm possible routes for the rise of resistance and increase the probability of cell death[281–283]. To fully realize the potential of this approach, ongoing efforts address two significant challenges: loading drugs with reliable and repeatable stoichiometric ratios and loading molecules with significantly different solubility profiles into a single carrier. While polymeric structures are attractive carriers due to their relatively well-controlled size, shape, and chemistry, non-covalent encapsulation leads to relatively high variance in drug loading[267]. Prodrug-polymer covalent conjugation is one solution to improve reproducibility, though the introduction of a linker and the requirement for hydrolysis to activate the payload at the release site increases system complexity. Microfluidic methods that measure and coat droplets to generate synthetic vesicles may be another avenue for a reliable polymer or liposome drug encapsulation. The second challenge is to combine different drugs in a single delivery vehicle or set of vehicles[284]. For example, liposomes tend to have a hydrophilic interior while polymeric micelles and dendrites tend to be hydrophobic. Block- or alternating- copolymers that self-assemble into ordered structures that incorporate regions of different solvation properties present a potentially viable solution that accommodates both hydrophilic and hydrophobic species[229].

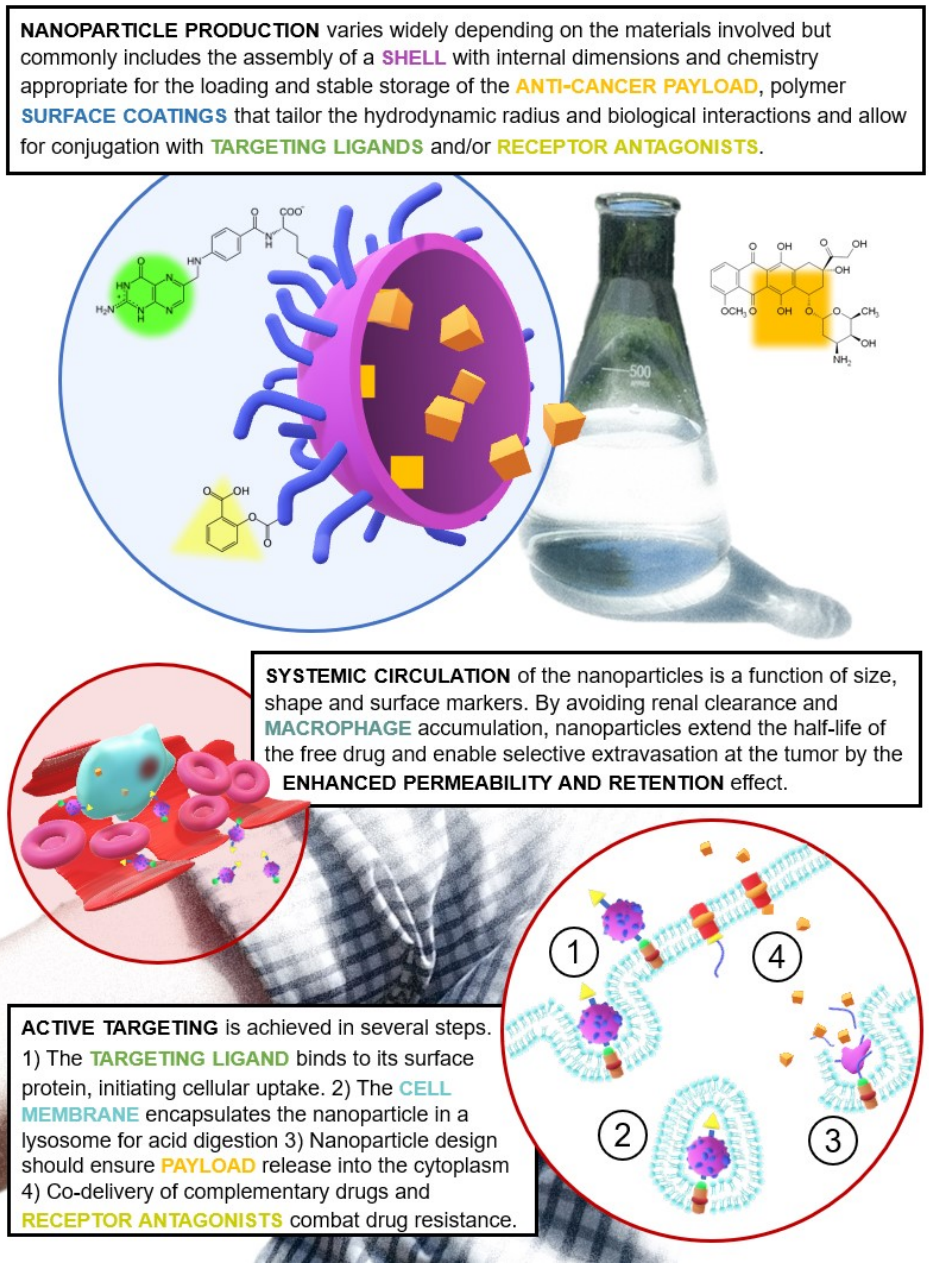

Figure 7.4: Schematized life of an archetypal nanocarrier from synthesis to drug delivery. Nanocarriers incorporate a number of design considerations including encapsulation method for the drug payload; shell material, size, shape, and chemistry; surface coatings; and targeting ligands. These design characteristics must be optimized for transport through systemic circulation and selective payload delivery at the diseased cells. Once the drug is released, the carrier can contribute to overcoming drug resistance by acting as a transport antagonist or be enhancing complimentary physical therapeutic methods.

Staged drug release is a challenging but potentially powerful strategy to defeat the rise of resistance in cancer cells. Zhang and colleagues reported the co- encapsulation of pro-apoptotic drug doxorubicin with antiangiogenic curcumin in a pH-sensitive copolymer delivery vehicle[285]. The antiangiogenic action of the cur- cumin targets the tumour vasculature to entrap the cytotoxic drug with its target, increasing uptake and decreasing cell migration from the tumour site. Similarly, a multi-component staged release nanocarrier first releases the antiangiogenic factor combretastatin followed by cellular uptake of polymer-linked paclitaxel[286]. Lastly, Hu et al. note in their review that the timing of dose delivery against the cell cycle can have a significant impact on drug efficacy[279]. Sequentially timed-release functions could present a mechanism to control for this previously uncontrollable factor[287].

Second, inorganic nanocarriers concentrated in the proximity of the diseased tis- sue could also act as sensitizing agents to physical therapies once they have released their chemotherapeutic payloads. For example, gold nanoparticles and nanoshells are already employed for imaging and light-induced hyperthermia[149,288]. By modifying the gold nanoparticles for targeted drug delivery, they incorporate two distinct treatment modalities, and the combination is more effective than either alone[221]. Other nanocarriers built around an inorganic nanostructure sensitive to light, magnetic fields, or ultrasound can fulfill the same function[289,290]. Nanocarriers that simultaneously deliver complimentary treatment agents and modalities to their targets demonstrate a significantly lower risk of multiple drug resistance in tumours[291,292].

Third, nanocarriers, especially polymeric structures, can be engineered to incorporate efflux pump inhibitors whose antagonistic interaction disrupts the cell's ability to decrease its drug loading. Because more of the drug remains in the target cell, efflux inhibitors allow for lower total dosing, faster tumour shrinkage, and decreased cytotoxicity of surrounding healthy tissues. This strategy may also prove to be fertile grounds for the application of biological agents such as short interfering RNA for silencing efflux pump expression[293].

In summary, by offering a path towards delivering the right dose of the right therapies at the right time in the right place, nanoscale drug delivery vehicles present an undeniably promising mechanism for cancer treatment that avoids or over- comes drug resistance.

An integrated approach for future development

The fact that much of the potential of nanomedicine remains unrealized may be at least partly explained by a large number of previously unknown physiological encumbrances discovered by the research program over its 30-year history[294]. Figure 7.5 highlights the progress of studies relating to nanotechnology and cancer. Cell, animal, and clinical trials of nanosystems for diagnostics and therapy have succeeded in probing the complexities of the path that a drug must follow from insertion into systemic circulation to its target inside the cell[264]. Past challenges suggest some measures that can be taken to hasten the future development of drug delivery systems.

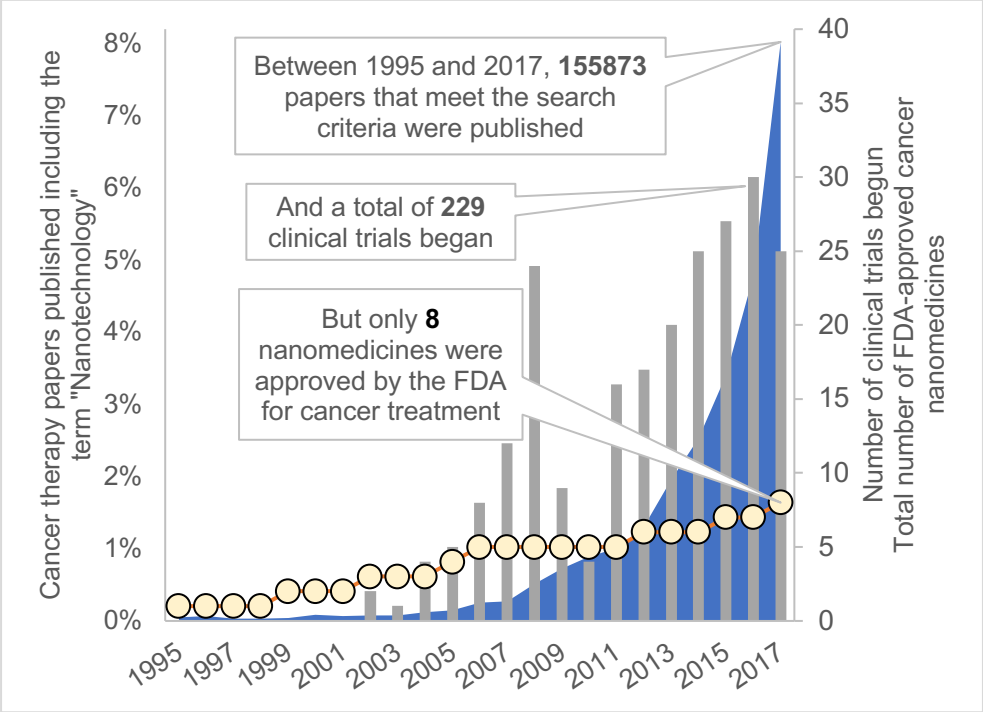

Figure 7.5: Total number of papers published that contain the terms “nanotechnology AND cancer AND treatment” as a fraction of “cancer AND treatment” [Google Scholar] (left-hand scale, blue curve), the number of clinical trials begun per year [Interventional trial for the treatment of “cancer”, “tumor”, “neoplasm”, or “malignancy” containing the search term “nanoparticle” 2002-2017;

National Institutes of Health, clinicaltrials.gov] (right-hand scale, grey bars), and the total number of FDA cancer nanomedicines approved, Reference 32 (right-hand scale, orange dots) from 1995 to 2017.

First, the overall carrier structure should be optimized according to what is known about nanoparticle distribution in the body. Size, shape, and surface coating are particularly important factors for effective systemic transport. Second, co-delivery of multiple drugs and adjuvants reduce the likelihood of resistance by simultaneously attacking multiple response channels. Third, after delivering its pay- load, the carrier shell itself should be pressed into service as a sensitizing agent in the tumour environment to external therapy sources. Moreover, finally, more specialized training is necessary to ensure sufficient knowledge of both nanoscience and physiology as well as practical experience with the regulatory process and standards a delivery system would be expected to surpass before approval for widespread use.

Material Properties

Designing a single self-assembling, biocompatible and degradable material that can self-tailor its size and shape according to the environment and conduct a targeted, staged, multimodal attack on the tumour site must, for now, only be imagined as a theoretical ideal[295]. Reality still falls short of this goal.

Twenty years of advances in nanomaterials and their dispersion characteristics in the body have left us with a set of general principles. In summary of the findings cited above, the maximum cross-sectional size of the nanocarrier should lie between 40 and 200 nm for prolonged systemic circulation and under 20 nm for extravasation and penetration into the tumour microenvironment. This approach could be accomplished by a multi-stage delivery vehicle that degrades into smaller units in response to environmental cues or by crafting disc or worm-shaped nanocarriers whose hydrodynamic radius is larger than its minimum diameter. These shapes have the additional advantage over spheres by increasing contact with the vasculature walls and increasing the EPR effect. The scaffold may be liposomal, micellar, polymeric, metallic, or non-metallic depending on its target, but so much the better if it can contribute to the attack by sensitizing the target to an external energy source. Surface treatments serve different

purposes depending on the stage of delivery: it should minimize protein accumulation in circulation, contain recognition and binding molecules for target membrane receptors and drug efflux pores, protect the payload from early release or degradation while being itself sensitive to environmental stimulus for drug release. The storage chambers should be able to hold precisely ratiometric amounts of various drugs and adjuvants of arbitrary hydrophilicity. And finally, release should be coordinated for location in or around the cell and sequence of drug action.

Clearly, the ideal hybrid nanomaterial may be as complex a structure as the biological structures it targets. Several components present highly challenging technical problems, some likely proving to be mutually-exclusive or intractable. All evidence suggests that material science will continue to press incrementally closer to the goal above. If we are to achieve higher rates of success in the treatment of patients, which is, ultimately, the goal of the material design programme, the field must look past the material formulation and place more focus on the disease targets. While materials scientists cite general tumour properties to evaluate the 'promise' of their formulation, nanomedicines currently in clinical use are approved for specific pathologies, demonstrating that the specific target cell should be taken into account earlier in the design process[272].

Training

In that same vein, dedicated bio-nanoengineering graduate-level training programs are increasingly necessary to connect the disparate fields of material chemistry and physiology[247,296]. Increased rates of success in the translation of nanocarriers into clinical cancer treatment will depend on a greater understanding of the complex interactions of complex nanostructures and complex pathophysiologies. Materials-driven development has made remarkable advances, but the disease-driven clinical application requires a level of biological expertise lacking in most chemistry and material science programs, nor do regular medical and microbiology programs teach chemical synthesis or characterization. The intentional interleaving of these specialties presents enormous potential for innovation to those able to approach the problem equally well from both sides of the interaction.

Regulation

Nanocarriers present a new class of treatment tool, lying between drug and device. Regulators may be challenged to adapt existing rules to control the testing and promote the safe manufacture of emerging materials and technologies[297,298]. If a nanocarrier is to be responsive to the differences between cancers, patient physiologies, and heterogeneity within a tumour cell population, then bolt-on targeting ligands may be the key. However, considering the number of materials, targeting mechanisms, and payloads available it is self-evident that separate trials for every possible combination would be impractical.

Optimally, medical adaptation would be as rapid as cellular adaptation, although this would be a daunting standard to achieve. First, it would require affordable and rapid access to genetic testing to allow monitoring of the tumour phenotype and rise of resistance[299,300]. Second, the nanocarrier would have to be conceived to permit rapid exchange of its surface decoration with minimal impact to its assembly, stability, or pharmacokinetic profile. This would be the synthetic equivalent of the influenza virus' ability to rapidly exchange its surface markers to work around vaccinations. Lastly, the regulatory framework would have to be flexible enough that each of the possible nanocarrier surfaces could be approved without the need to test each combination in a clinical trial. Not only would the sheer number of combinations be an insurmountable challenge, but it would also prove impossible to recruit a sufficient number of patients in any single combination to achieve statistically significant results. Of course, cancer nanotherapeutics are not the only field edging toward personalized medicine so policy may yet lead innovation.

Conclusion

Our ability to design reliable and precisely assembled medical devices no larger than some cellular organelles presents an enormous potential, though much of it has yet to be realized. For improved translation from lab bench to bedside requires disease-driven materials development, training programs to include equal weighting of chemical synthesis and characterization with

microbiology and pathophysiology, and for regulatory bodies to begin considering their approach to the expanded applications of medical nanotechnology on the horizon.

The preceding example demonstrates that chemical knowledge is necessary but insufficient for success, even for a use as universally sought as improving the safety and effectiveness of cancer treatment. To continue proceeding as though a chemical problem is isolable from its physiological, social, pedagogical, and regulatory circumstances is to ignore decades of evidence to the contrary.

In more general terms, the chemistry community overlaps with other knowledge gathering communities whose own traditions, nomenclatures, and skills inevitably contain, constrain, and influence how the chemical specialties behave. So how do chemists situate ourselves within the epistemic ecology? A full answer lies outside the scope of this work but, as I argue in the introduction, a study of the intersections of our discipline with others is necessary for adoption of chemical knowledge by outside actors or institutions. As demonstrated by the slow translation of entropy from mechanics into the chemical sciences, and of nanomaterial science into nanomedical treatments, scientific knowledge requires active transport across disciplinary interfaces.

Two areas in which I have worked directly to bridge distinct communities of knowledge and practice are teaching chemistry to military students and introducing scientific researchers to political decision makers. With the remaining chapters I intend to show that applying a pluralist, pragmatic approach may help us better understand the ways that different communities develop, validate, and employ knowledge, thereby hastening the transition from discovery in one to impact in another.

8. Chemical Education in a Military Context

This chapter draws from talks presented at the Canadian Chemistry Conference and Exhibition 2021 (Online, link to video: https://youtu.be/1tfr_ojhAAE) and 2022 (Calgary, AB); and the International Society of Military Sciences conference 2023 (Copenhagen, DK).

Abstract

In 2017, the instructors and laboratory coordinator of the first-year Introductory Chemistry course at RMC undertook a restructuring to highlight the role of chemical concepts and practices within military knowledge systems. Priniski, Hecht, and Harackiewicz' relevance framework was applied within Eccles' situated expectancy-value theory of student motivation to design learning interventions that target our students' chosen military career path, and the common set of interests and values it implies. Lab and lecture content has been updated to include examples, demonstrations and experiments relevant to the students' chosen military identity. Structural changes similarly reflect values of teamwork, clarity, consistency, and care for the well-being of subordinates. The inclusion of military faculty lent credibility to the military contextualization. Inclusive team building exercises were included to foster trust and ease communication while dividing the class into smaller sections for tutorial discussions afforded the chance to explore chemical problem-solving in greater depth and variety according to the student's interests. These experiences have strengthened student identification with chemistry, improved motivation to study course material, and steadily increased enrollment in Chemistry and Chemical Engineering.

Introduction

As at other universities, students arrive at the Royal Military College of Canada to pursue a four-year degree in the field of their choice. Unlike other universities, RMC undergraduates are also members of the Canadian Armed Forces and, while many will choose to continue on to graduate studies or

take a civilian career, most graduates go on to a career in the Royal Canadian Navy, the Canadian Army, or the Royal Canadian Air Force. This distinction in the student body has led to distinctions in the structure of the academic program. All students complete a 'core curriculum' of liberal arts subjects to ensure that Canada's future military leaders leave with a foundational knowledge of literature, history, and military strategy; theoretical frameworks in psychology, organizational behaviour, and moral philosophy; and facility in mathematics and scientific reasoning. RMC cadets are also expected to maintain physical fitness, develop skills in their second language, and demonstrate ethical leadership. However, neither the university's mission nor placement within a military organizational structure interferes with the academic content. RMC faculty maintain their academic freedom to teach, perform research, and serve their discipline with the same integrity they would expect from the equivalent appointment in another university.

That being said, a modern military is not as one dimensional as it is sometimes portrayed. The Canadian Armed Forces comprise a subset of Canadian society that is no less complex as the whole, with additional logistic and technical needs to ensure the highest levels of mobility, reliability, and preparedness from our materiel and personnel. To deploy a unit is to move a small town into a remote, if not hostile, location with all the demands for construction materials, water and sewage, food preservation and preparation, fuel storage and distribution, electrical generation and distribution, medical support, environmental protection and remediation, not to mention ammunition and weapon system maintenance, safety, and security. Military systems of cultural, practical, and material knowledge overlap significantly with knowledge systems of scientific, engineering, and humanities disciplines and for those motivated to engage with the intersection can provide a rich context for academic expression.

Students entering RMC arrive with diverse backgrounds, interests, values, and goals but have shown a common interest in military service. For many students, their will to serve is their principal motivation for attending university classes at all, undermining educational interest and performance. Students and instructors could therefore benefit from interventions that

credibly demonstrate that academic excellence can assist them in their efforts to grow into an effective military member.

Constructing a social identity

Developmental and education researchers recognize that transition periods are potent times for interventions affecting student values and sense of belonging[301,302]. Orienting oneself in a change of role and environment prompts a re-evaluation and realignment of one's values and goals in light of the new circumstances. Incoming Officer and Naval Cadets at RMC are experiencing a double transition into both undergraduate and military career and so need to develop their social identity as a member of both groups separately and in their combination.

Social identity theory was developed by Tajfel and Turner through the 1970s as a model for attributing behaviour to group, rather than individual, motives[303–305]. Social identity is defined as "that part of an individual's self-concept which derives from [their] knowledge of [their] membership of a social group (or groups) together with the emotional significance attached to that membership.[305]" As students who attend classes in uniform, their identity as a military member remains apparent even in the classroom setting, and as recent voluntary recruits they are likely to value that association as a positive social identity. Moreover, the strong organizational hierarchy stratifies the intragroup identity by experience and rank, which places a first-year Officer or Naval Cadet at the outermost edge of the group. By being constantly confronted with the knowledge that they are relatively undifferentiated from their civilian peers, an individual is encouraged to seek out and engage with avenues by which they may gain military-relevant knowledge so that they can deepen their legitimacy in their desired social identity.

It is less obvious that new Cadets should be strongly motivated to develop a social identity connected to their field of study. Our students are recruited into their military element and occupation *before* arriving and only select their faculty and major program *after* the first term, so their entry into the profession of arms takes precedence in time and prominence over their entry into a scholarly, scientific, or engineering profession. The student's choice

of academic discipline is partly informed by how well the information presented during the first-year introductory class in the topic satisfies their interests, fulfills a predicted need, and aligns to their values. In other words, its relevance.

Expectancy and Relevance

We can also examine the role of systems thinking on student motivations through expectancy theories of motivation. In an early iteration, Vroom suggests that if a person 1) believes that increased effort will lead to better performance (expectancy) and that 2) performance will lead them to receive a reward (instrumentality) that they 3) personally value (valence), then we should expect the person to be motivated to increase their effort[306].

Figure 8.1 Vroom's Expectancy theory of motivation

Eccles situated expectancy-value theory (SEVT) of educational development is a related but much more deeply developed framework outlining the objects and linkages that feed into an individual's values and estimation that their effort will successfully generate performance outcomes[307]. Vroom's reward valence is further categorized into subjective task values (STVs): interest value, utility value, attainment value, and perceived cost. Interest value is the intrinsic pleasure an individual takes from the activity. Utility value fulfills Vroom's instrumentality: the principal value of accomplishment is its contribution to another goal. Attainment value was originally conceived as closely held needs and values. Since 2009, it is attributed to tasks that affirm positive personal and social identity[308]. These motivating values are balanced against the physical, practical (opportunity) costs, and psychological costs of the task. Eccles affirms that activities that correspond to one's identity are more likely to be

pursued and thereby reinforced as part of self-concept but admits that the newer conception has not yet been fully explored.

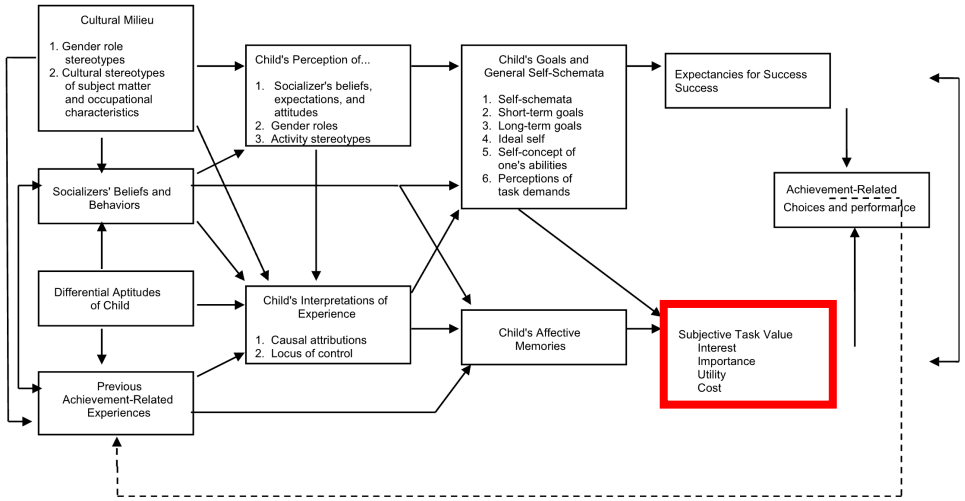

Figure 8.2 Eccles situated expectancy-value theory (SEVT) of educational development, highlighting the location of Subjective Task Value in the model.

Priniski, Hecht, and Harackiewicz define relevance as "a personally meaningful connection to the individual," where the degree of 'meaning' is determined by whether the activity signifies an association, usefulness, or identity along a continuum from weakest to strongest connection[309]. These categories map reasonably well onto Eccles' subjective task values. Priniski et al remark that their relevance continuum applies a hierarchy to the STVs, particularly to utility-usefulness and attainment-identity, that is not made explicit in SEVT – although I think that directly-motivating attainment values are implied to hold more power than indirect utility values. Both Eccles and Priniski note that interventions in utility are most common and best researched, having been proven accessible and successful, with Eccles suggesting that more attainment-focused interventions should be developed, such as those that reinforce the "link between potential associated job characteristics with the students' goals and identities."[307,309]

RMC students embark on an undergraduate degree program for many reasons, not least of which is to explore their identity and engage in professional growth that resonates with their personal values. By situating the knowledge and skills of the academic discipline within military

knowledge structures, instructors can help Cadets develop their positive social identities as both soldier and scholar, highlight the relevance of class materials, and motivate student learning.

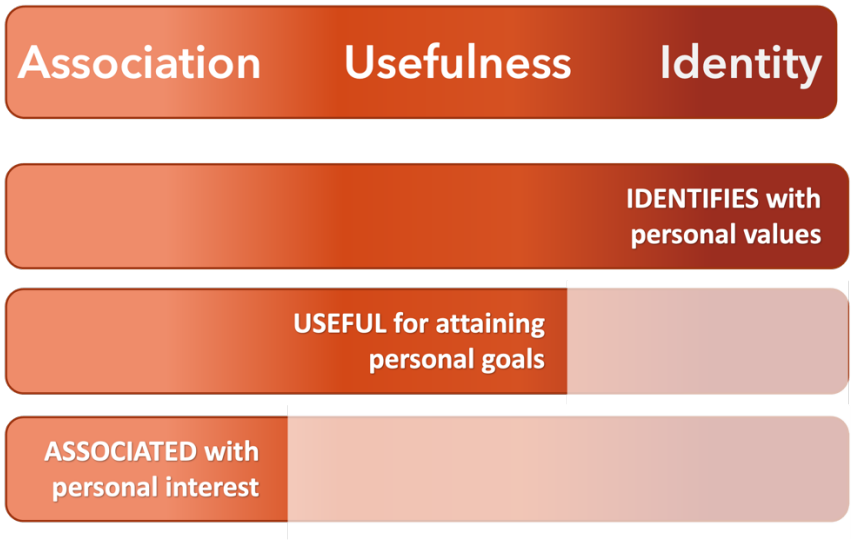

Figure 8.3: Priniski, Hecht, and Harackiewicz framework for relevance with respect to motivation

Implementation in first-year general chemistry course

While delivering fundamental theoretical knowledge, creating opportunities to practice chemical skills, and assessing student ability to use those tools to solve problems, the first-year introductory chemistry course also establishes student beliefs regarding the culture of chemistry. The representation of chemistry students encounter in their first, and often only, chemistry course will come to stand for what all chemists do, value, and hope to accomplish. Students will form their assessment whether instructors make their values explicit or not. Under this model, choices that might have been considered aesthetic, such as the framings of example questions, lab demonstrations, or real-world application, become significant course content. Points of intersection that situate chemistry within wider cultural and technological contexts contribute to how students view the utility that chemical knowledge is likely to have for their future, and how their personal values and priorities align with those that they come to associate with chemistry.

Introductory Chemistry is a mandatory course in all science and engineering programs at RMC, comprising between 100-130 students at the start of term

in a roughly 20:80 split between the science and engineering faculties. We know that our first-year students have chosen to enter a military career, so from 2017-2022 the classroom and laboratory instructors of the Introductory Chemistry course sought to credibly demonstrate that a chemical or material approach to problem solving will aid their progress toward their desired role as a military officer. By applying a relevance framework to SEVT, we identified elements of class content, laboratory work, and supplementary activities that insert chemical competencies into the chain between our students' personal values and professional goals.

Class content

Worked examples of theory offer plentiful opportunities to connect fundamental chemical and military knowledges across the relevance continuum. By remaining consistent in discussing at least one military application for every major topic and maximizing variation across military functions, in-class discussions impress the advantages of scientific skills for military operations.

For example, we explore a fictional scenario that may be encountered by Canada's Joint Incidence Response Unit (CJIRU) to teach methods for calculating the amount of product that can be generated from a set amount of precursor materials. Two chemical warfare agents, phosgene and diphosgene are first introduced as examples after the discussion on empirical and molecular formula and, in addition to going through a worked example, an accompanying video contains information regarding the development of both molecules, their use in gas attacks in WW1 and the strategic significance of the switch from phosgene to diphosgene.

In this video, a sample of the unknown liquid undergoes combustion analysis to produce a certain amount of CO_2 and H_2O, and the worked example shows how to determine the empirical formula from this information, and the formula is determined to be CH_2O. The students are given additional information to determine that the unknown compound is methyl methanoate. Other important observations of the scene are then highlighted, drawing their attention to the cylinder of chlorine gas and the presence of a UV reaction chamber. This information is then used in the

next video to work through an example of limiting reagents using the reaction of chlorine and methyl methanoate to produce diphosgene.

After working through the example to determine the theoretical yield of diphosgene, the discussion is expanded to include toxicity information, like its LC_{50}, and the ultimate threat posed by that amount of diphosgene to the general population, both in an outdoor and an indoor setting. Again, this is a fictional scenario - but serves as an example of the type of plausible threat that a sound understanding of chemical practices helps to defeat.

This example is taken from our early review topics and similar discussions are integrated into the teaching material throughout the year. Chemical warfare agents and their treatments are revisited during other topics, including structure and bonding, kinetics, organic, and gases. While chemical, biological, and radiological weapons are typically interesting for students, it's worth noting that they are only handled by a small number of highly specialized personnel and then rarely. In other in-class discussions on water purification, corrosion prevention, and the heat content of fuels, we would note how much more common and critical those material processes are for real-world application, engaging higher-order relevance categories.

Laboratory skills

The weekly three-hour laboratory session is an opportunity to apply chemical skills to practical problems. Certain demonstrations lend themselves more naturally than others, of course, and not all labs are explicitly paired to operational needs. In at least one case, however, we were able to frame the entire exercise through an operational lens.

After learning about heat and calorimetry and performing a lab on solution calorimetry in a coffee-cup calorimeter, students are divided into teams and tasked to assess the potential for flameless ration heaters to heat water from ice to a palatable temperature for a section of twelve on exercise in the high Arctic. Students receive a set of orders formatted according to CAF standards that outline their objectives, constraints, and reporting requirements. Students must perform calorimetry experiments to correctly identify the amount of reactants they would need to accomplish the task,

providing justification for any assumptions they made along the way. experiment. Group leaders are encouraged to delegate responsibilities to solve the problem during the allotted time.

They soon realize that they are faced with several questions besides the obvious ones pertaining to how to set up and perform the experiment. Some questions are objective and measurable (What is the ambient temperature? What is the temperature of the ice?) but others are subjective (How much water is required? How warm should they make it?) Their choices have material and moral repercussions. Ultimately, their solution should tell them that chemical ration heaters are logistically unjustifiable, so the experimental results provide them with justification to propose more efficient methods to heat water, such as naptha-burning stoves.

Ultimately, students are using the relationships and equations of heat learned in class, techniques learned in the lab, and guidance provided during the exercise to solve an operational problem and to recognize that human and economic factors may play as large a role as chemical factors in real decisions. By enacting the chemical principles in a simulated military application, students may come to appreciate the utility of chemistry for developing military proficiency. Ideally, they might identify expertise in chemistry as a military trait in itself.

Supplementary events

To invite first-year Cadets into community with practitioners and researchers in the Department and the CAF, we mark three special events during the year.

At the end of the Fall term, the Department hosts its annual “Winter Extravaganza,” an open-house event with demonstrations, tours, and games. The first-year class assembles an hour before general admission to tour the displays, talk with upper-year students in chemistry and chemical engineering about their student projects, see examples of research being led by our faculty, and witness the passion that potential role-models bring to their work.

During the first week of the Winter term, we welcome students "In with a Bang!" Presentations, tours, and a hands-on introduction to dummy ammunition allows students, military faculty, and invited guests to connect materials and techniques they will encounter in the field to the chemistry knowledge they are gaining in class. Guest lecturers present their ongoing research in ammunition science and engineering, chemical protection, remediation of firing ranges, and the challenges of unexploded ordnance on the sea floor. Topics are approached from the chemistry side and incorporate discussions of the regulatory and operational environments within which their research is performed. Ammunition and explosives experts are on hand to answer student questions about training and employment opportunities that will be available to them after graduation.

Lastly, late in the year, students take part in an extended role-playing scenario, Exercise: Volatile Storm (Appendix B). Guided by mentors, student groups confront the aftermath of a serious storm in the chemical sector of a fictional city. Playing as members of the "Rapid Emergency Assistance Coordination Hub (REACH)" students are asked to assess the information provided to them as the scenario progresses and recommend what responses (if any) the national government should take. The event is set in a completely fictional location so that students can focus on the big-picture factors, principles, and consequences at work. The scenario opens with fairly straightforward questions of investigating a health risk associated with a leak from an affected chemical plant. Subsequent developments introduce complications around political sensitivities, mis- and disinformation campaigns, emergency supply distribution, and national security risks. The mentors with each group guide discussions and help students to think through the implications of each new and partial piece of information. After each time step, groups report their findings and advice to the "Minister for Public Safety," played by a guest whose real position at the university heightens the stakes for participating students. Before the next time step is introduced, the whole group is invited to discuss and compare their approaches. In the end, the central chemical question is resolved but other outcomes may remain ambiguous. Students are led to reflect on the impacts that expertise, leadership, communication, and trust had throughout the scenario. For students who anticipate becoming scientists and engineers

in positions of military leadership, the exercise is an opportunity to see how technical knowledge complements competencies across disciplines and sectors to address complex problems.

Impacts and lessons for future work

Between 2017-2022, we introduced interventions aimed at promoting student motivation to learn chemistry by demonstrating that building ability in chemistry knowledge and skill is a legitimate and effective pathway to establishing their military identity and career. According to Eccles' SEVT and Priniski's relevance framework, intentionally situating chemical theory and application to engage student interest, highlight material utility, and align with positive social identity should lead to an increase to the subjective task value of learning chemistry and, ultimately, increased motivation to study within the chemical sciences.

We had not prepared instruments to measure the outcomes on student learning and engagement before those efforts were disrupted by the pandemic emergency response. With all the major concurrent changes that took place, disentangling the effect of our interventions from other impacts is impossible. We introduced class-specific start- and end-of-year student surveys in 2020 to confirm our students had adequate access to necessary network equipment and services, and that our approaches to remote teaching were as effective as possible. In 2021, questions were added to measure student affect toward chemistry, including their beliefs about the impacts of discovery and advances in chemistry on their quality of life (Figure 8.4), their health and well-being (Figure 8.5), the environment (Figure 8.6), and their military career (Figure 8.7). The surveys are included in this document as Appendix C.

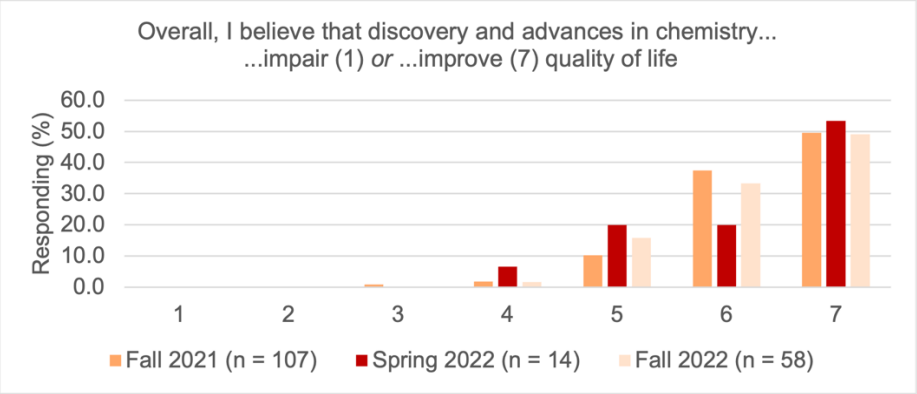

Figure 8.4 Survey results showing the change in student beliefs on the impact of chemistry on quality of life before and after completing Introductory Chemistry

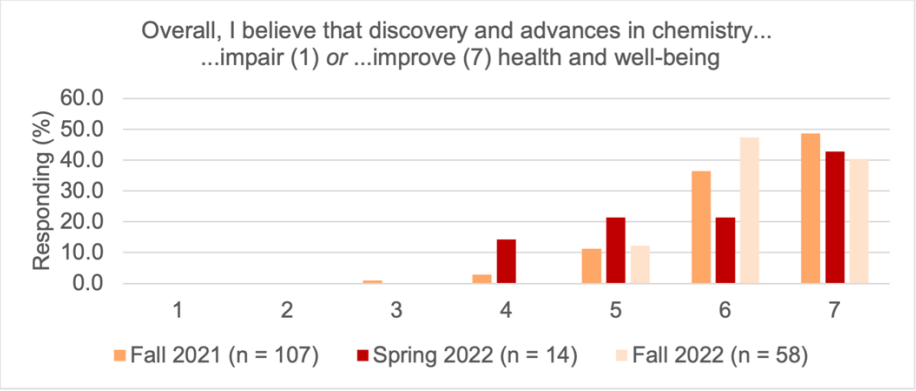

Figure 8.5 Survey results showing the change in student beliefs on the impact of chemistry on health and well-being before and after completing Introductory Chemistry

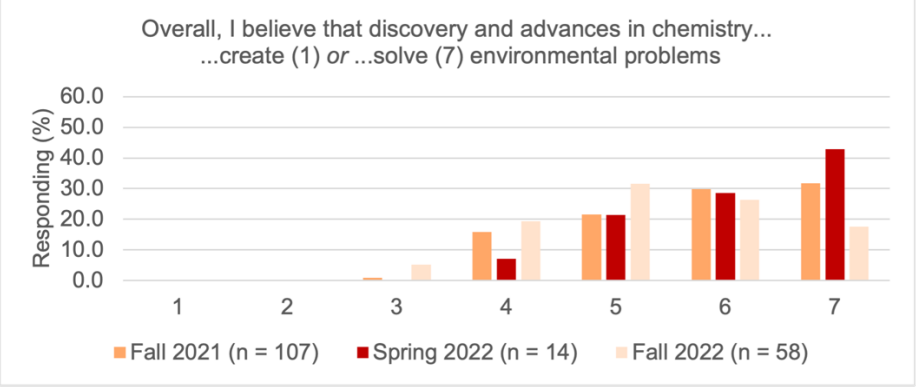

Figure 8.6 Survey results showing the change in student beliefs on the impact of chemistry on the environment before and after completing Introductory Chemistry

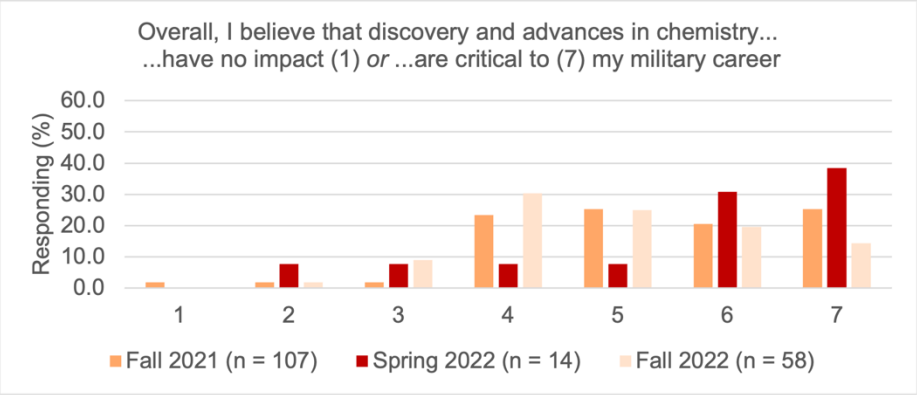

Figure 8.7 Survey results showing the change in student beliefs on the impact of chemistry on their military career before and after completing Introductory Chemistry

The figures above show the results from start-of-course Fall 2021 and 2022, and end-of-course in Spring 2022. Students were not surveyed in Spring 2023 or later so those data are not available, curtailing our ability to decisively conclude our intervention had the intended impact. However, the stability of the two start-of-term impressions suggests that the departure seen in the single end-of-term result indicate a real effect that could be sought should student surveys return. The reduced number of end-of-term respondents also raises the possibility that the results are biased because students who like chemistry are more likely to have responded to the survey; the fact that the Spring 2023 response is not uniformly positive reduces but does not eliminate that concern.

Bearing these interpretation limits in mind, the four charts tell an interesting story about changing student attitudes towards chemical advances before and after their exposure to the first-year chemistry course. The mainly positive beliefs that chemistry brings improvements to quality of life, health, and well-being in Figures 8.4 and 8.5 remain mainly positive, although the possible emergence of a bimodal positive-moderate split opens an intriguing possibility that introductory chemical education leads to more nuanced or cautious acceptance of the benefits offered by new materials and processes. Similarly, the turn towards belief in chemistry's ability to solve, rather than cause, environmental problems seen in Figure 8.6 may illustrate how education encourages students to re-evaluate their existing opinions. Student

beliefs regarding the connection of chemistry to their military career shown in Figure 8.7 are the most relevant to our discussion and least ambiguous results. The mid-scale peaks of the pre-intervention, start-of-course samples in both Fall 2021 and 2022 demonstrate significant doubt that chemistry will be relevant to their future. The post-intervention, end-of-course measurement for the Spring 2022 is not only more positively aligned than the Fall distribution but also the most strongly positive of all four questions. Although insufficient on its own to confirm the effectiveness of the program changes, it is a strong enough signal to justify its continuation and routine monitoring.

If the survey results are correct and the program interventions have influenced student beliefs in the relevance of chemistry to their military career, there is still the final step between the positive change to subjective task value and students' motivation to study chemistry. Since we have implemented these changes, the number of students joining the chemistry major program has consistently exceeded its long-term average (Figure 8.8). The total number of students enrolled in science programs fluctuated between 34 and 59 over this period, peaking in 2021-22, which would contribute to the rise in absolute numbers. However, the percentage of science students choosing chemistry over the other science programs doubled post-intervention from 12.2% to 24.3%. This rise offers evidence that the efforts to link personal relevance to motivation and motivation to changed study preferences had been successful.

Implications for and beyond the Military College

As stated earlier, identity-based interventions in motivation for academic education are under-studied[307–309]. The very obvious common touchstone among our otherwise diverse undergraduate population eliminated any uncertainty over which system of knowledge would be most salient for our students. In this and other respects, RMC and other military academies provide a good trial site for identity- and relevance-based education research since the relevant property among its student population is, figuratively and literally, uniform. Indeed, RMC may be uniquely suited among Canadian institutions for further research into student motivations for academic study when confounding variables such as job prospects, housing and food

security, exercise levels, and workload are as consistent as could be reasonably expected.

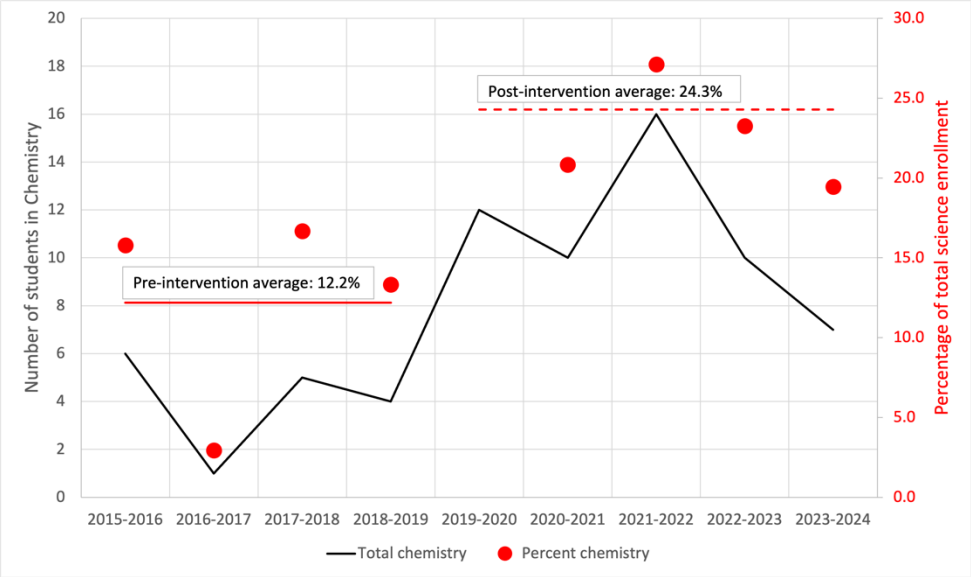

Figure 8.8 Student enrollment in RMC Chemistry and Honours Chemistry programs, 2015-2024. Accounting for the fluctuation in total enrollment across all science programs shows that a significant rise in chemistry student numbers occurred in concert with implementation of relevance-based program changes.

That said, the desire to self-categorize and identify as part of a group, or to gain greater legitimacy within a group, is not limited to the Canadian Forces. The first year of university is a liminal time for all students and, if anything, civilian students enter into a larger decision space with fewer signposts. Engaging with student expectations about the skills they will need to fit the roles they want has helped us to situate chemistry within the larger social knowledge framework to effectively shape and satisfy their first-year experience. We have nested chemical knowledge within military knowledge systems because we recognize that our students are motivated by their desire to identify as military members and to gain competencies that can be applied within a military context. The RMC experience is exceptional but not unique. Our focused approach may be a limiting case, but other contexts should accommodate the same motivational framework, based on specific student values, future expectations, and departmental strengths. Example systems of knowledge and practice that could be engaged through chemical education include industry and entrepreneurship,

environmentalism, and Indigenous ways of knowing, with cross-cutting categories such as sustainable industry, or environmental remediation policy and technology.

Conclusions

At the Royal Military College of Canada, we know that most students in our first-year class will serve as officers of the Canadian Armed Forces upon graduation. Before they arrive in their first class, our students already expect to become leaders who will make decisions under highly uncertain and often dangerous conditions. A motivating first-year experience is one that demonstrates how their academic framework will assist them in understanding and contributing solutions to the wide scope of complex challenges their concurrent military training leads them to anticipate. By aligning the aims of chemistry education to student aims in the construction of their desired social identity, we are able to identify and amplify the relevance of chemical knowledge to their development as effective military members. Situating chemistry within a larger set of values and meanings encouraged our students to find meaning and value in chemistry.

Motivating military students to undertake a program of chemical knowledge requires understanding both knowledge systems well enough to show how their values, priorities, and goals can align, reinforcing one with the other. In the next chapter, we apply this idea to connect scientists with political decision makers to help maximize the public benefit of academic research.

9. Science Meets Parliament

Sections of this chapter have been previously published as:
Zhao, Jiaying, Meghan B Azad, Erin M Bertrand, Cole Burton, Valorie A Crooks, Jackie Dawson, Adam T Ford, Angela Kaida, Arjun Krishnaswamy, Chikin Kuok, Catherine L Mah, Matt McTaggart, Amanda J Moehring, Dominique Robert, Albrecht Schulte-Hostedde, Heather Sparling, Mary A De Vera, Stephanie Waterman, Trushar R Patel. "Canadian Science Meets Parliament: Building relationships between scientists and policymakers." *Science and Public Policy* 48.4 (2021): 447-450.

And:
Robert, Dominique, Adam T. Ford, Albrecht Schulte-Hostedde, Amanda J. Moehring, Angela Kaida, Arjun Krishnaswamy, Catherine L. Mah, Cole Burton, Erin Bertrand, Heather Sparling, Jackie Dawson, Jiaying Zhao, Kin Chan, Mary A. De Vera, Matt McTaggart, Meghan Azad, Sheldon Williamson, Stephanie Waterman, Trushar R. Patel, Valerie A. Crooks. “De l'importance des relations entre politiciens et scientifiques.” *The Conversation* 14 April 2020. https://doi.org/10.64628/AAP.96xnncwaj

Abstract

Science Meets Parliament is a training program designed to prepare researchers to build relationships with Canada’s Parliamentarians and to create spaces for those relationships to grow. Since the first Canadian event in 2018, Science Meets Parliament has grown to become an established and nationally recognized leader in this space. Participating researchers in the natural and social sciences, engineering, and humanities report a higher likelihood to engage public policy through their research, their teaching, and outreach activities. By building a community of scientists and political decision makers who share the experience of seeing one another as good faith partners working toward the general benefit, Science Meets Parliament contributes towards a cultural norm favouring the creation and application of scientific evidence in Canadian political life.

Background and social context

Strictly speaking, knowing whether and how a thing can be done is independent from deciding on what thing to do and acting on that decision, but those two functions can closely influence each other: knowing how a thing is done informs decisions on what to do, while deciding what to do includes decisions on what and how much knowledge to generate in support. Science – which in this chapter I will use in the broadest sense to include all knowledge-generating fields of research, scholarship, study or practice across the physical, formal and social sciences, humanities, arts, and engineering – is our method for 'knowing that' and 'knowing how'. 'Deciding to' is the role of politics – the activities associated with how a group chooses to distribute and govern its resources, according to what values, and to what ends. Science and politics are special social functions that together create the futures that a society can realize. Political action without scientific knowledge is at best wasteful due to avoidable inefficiencies and at worst actively harmful due to unlooked-for outcomes. Scientific knowledge without political action is at best wasteful by being doomed to obscurity and at worst actively harmful due to unethical experimentation.

Although both science and politics are essential for the effective, responsible, and sustainable function of society, they are not equal partners. As the mechanism for the exercise of social power, political decisions have a level of control over knowledge creation that science cannot reciprocate. Governments have it within their power to dictate their nation's scientific enterprise, even into disaster[310]. Conversely, no level of scientific consensus can force a government to act[311]. Claims by political actors that they have surrendered authority and are "only following the science" on a given issue, for example social distancing and mask mandates during the COVID-19 pandemic response, do not hold up to scrutiny: they cannot cede responsibility or accountability for their decision to accept scientific advice. Too much control or too little support inhibits the work of science and thereby leaves society vulnerable to the unknown. Political decision makers therefore ought to temper their influence over the scientific enterprise in order to optimize its public benefit. Institutional norms of governance (for example, norms of communalism, universalism, disinterestedness, and

organized skepticism) provide useful guardrails to stabilize the balance of power to protect scientific integrity and its advantages from political overreach or neglect[2,312]. Policies that depart from the norms of scientific governance are likely to face backlash from the scientific community and affected segments of the broader population.

Such was the deteriorated relationship between Canadian science and political decision makers in 2015. Since forming government in 2006, Steven Harper's premiership had kept a close, centralized control over information that led to antagonism with the national press early on[313]. Concerns that political control would extend to the release of scientific data arose in November 2007 after Environment Canada promulgated a new Media Relations Protocol, reported by the Ottawa Citizen in February 2008 under the front page headline "Environment Canada 'muzzles' scientists' dealings with media"[314,315]. The policy mirrored the language used to govern communications between other public servants or military members and external organizations and its stated intention was to ensure consistency and coordination and avoid anything appearing in the press that could surprise the Minister or senior managers. Consideration was made that "Scientists will still be encouraged to speak directly to the results of their work" although, as reporting noted "They "shall not," the presentation says, "speculate about events, incidents, issues or future policy decisions." Whether this prohibition covers speculation about the impacts of phenomenon such as climate change, which is reshaping Canadian and global ecosystems, is not clear"[314,315]. That the protocol was to include any discussion on scientific findings and their impacts was made clear in time. The popular and scientific press reported cases in which government scientists were prevented by their departments from speaking about their research, and in 2012 Environment Canada dispatched "media relations contacts" to monitor their scientists' engagement with the press at the International Polar Year Conference in Montreal [316–319]. These reports led the Professional Institute of the Public Service of Canada (PIPSC) to assess the extent of political influence on scientific communications through commissioning a widescale survey of scientists across the federal government. Despite assurances to the contrary in Environment Canada's 2007 Media Relations Protocol, 90% of respondents felt they were not free

to speak with media about the work they do, 86% fearing censure or retaliation even in cases where their knowledge could prevent harm to the public interest. Over a third claimed that they had been prevented from responding to a question from the media within their area of expertise and 24% report that they had been asked to exclude or alter technical information or conclusions in a government document for non-scientific reasons[320]. A complaint that the government was systematically inhibiting access to scientific information was also lodged with the Information Commissioner of Canada[321]. The Commissioner found that the communications policies of departments under investigation complied with the principles of access to information as written but not as practiced. As applied, the policies had impacted the public's ability to access information, had created the chilling effect as reported by the PIPSC, and were not consistent with the federal government's formal commitment to open government[322].

Political actions that limited the flow of scientific knowledge out from government departments coincided with decisions that limited the creation, access, and distribution of scientific information within government. The National Science Advisor's position that had been created in 2004 to coordinate the collection and use of evidence within cabinet was first moved from the Privy Council to Industry Canada in 2007 and then discontinued in 2008[323]. Between 2008 and 2013, $596M and 2,141 full time equivalent positions were cut from the budgets of science-based departments[324]. Federally-run research labs including the Polar Environment Atmospheric Research Laboratory (PEARL) and Environmental Lakes Area (ELA) had their budgets severely reduced or eliminated, libraries were closed and their documents destroyed[324,325]. These changes were enabled by the Jobs, Growth, and Long-Term Prosperity Act of 2012, an omnibus bill whose ostensible purpose was to implement that year's federal budget but also strongly impacted the government's scientific capacity through alteration or repeal of acts including the Canadian Environmental Protection Act, the Species at Risk Act, the Nuclear Safety Control Act, and the Kyoto Protocol Implementation Act.

Although the budget cut funding for environmental and fundamental sciences, it did provide new spending to encourage more industry partnerships. In fact, overall science and technology funding had grown since 2006, particularly in support of business-led research, in alignment with the *Mobilizing Science and Technology to Canada's Advantage* strategy[326]. The document positions the government's relationship to science in the context of its philosophy of governance: "This S&T Strategy recognizes that the most important role of the Government of Canada is to ensure a free and competitive marketplace, and foster an investment climate that encourages the private sector to compete against the world on the basis of their innovative products, services, and technologies." Accordingly, the communications and funding policy decisions described above followed from the guiding principle that "Science and technology is not an end unto itself. It is a means by which we can pursue sustainable development." As written, this approach to scientific governance departs from longstanding norms of communalism (by restricting the release and discussion of data) and disinterestedness (by predetermination of economic development as its outcome)[327]. These violations were made more severe in practice since they targeted specific scientific knowledges that political decision-makers viewed as impeding the growth of a specific industries. Because it could not be known in advance whether scientific inquiry into e.g. climate and environmental protection would lead to greater economic advantage than would naïve expansion of the oil and gas industry, the policy interferes with the work of science within the range it claims to permit. It is not only anti-scientific but fails its own test.

The Canadian scientific community was sensitive to the challenge to its norms presented by the government during that period and expressed their opposition through editorials, surveys, letters, and most dramatically on 10 July 2012 when two thousand scientists marched on Ottawa's Parliament Hill to mourn the "Death of Evidence[328]." The demonstration did not lead to a change in policy but the sight of lab-coat clad scientists marching was surprising enough to bring the use of scientific evidence by political decision makers into the wider public consciousness. It inspired a day of "Stand Up for Science" rallies in 17 Canadian cities in 2013[329]. In January 2014, the Canadian Broadcasting Corporation's weekly news magazine the

Fifth Estate aired an episode entitled "Silence of the Labs[330]." The organizers of the 2012 march founded a non-profit advocacy organization, Evidence for Democracy, that continued to apply pressure and raise public awareness through the 2015 federal election. The effect of activism by scientists and their supporters is evident by the promises to "restore Canadian public science," to ensure that "scientists are able to speak freely about their work, and that scientific analyses are considered when the government makes decisions," and "reversing the Conservatives' policy of muzzling scientists" that appeared in the platforms of the Green, Liberal, and NDP parties. For their part, the Conservative party recommitted to "help Canadian businesses adopt advanced technologies and carry out research and development[331]." Given that the government's strategy had been a departure from longstanding cultural norms, the tensions it had caused with public service and academic scientists, the rise of public support for evidence based decision making, and that Canada was one of the few countries in the Organisation for Economic Co-operation and Development (OECD) whose business and government research and development expenditures declined over the 2006-2015 period, the consistency across opposition platforms is understandable[332]. Whether or not advocacy for scientific integrity impacted the results of the 2015 election, it undoubtedly influenced the early policy changes implemented by the incoming Trudeau government.

Two days after the swearing in of the new cabinet, which included Ministers for Science and for Innovation, Science and Economic Development, the government announced that "government scientists and experts will be able to speak freely about their work to the media and the public[333]." However, administrative processes change more slowly than governments. In August 2016, Science Minister Kirsty Duncan and President of the Treasury Board Scott Brison wrote a letter to their fellow ministers to enforce the change in policy within their departments[334]. In Summer 2017, Canada signed collective agreements with two of PIPSC's science-based employment groups enshrining their right to speak about their research[335]. In a follow up to their 2013 Survey, PIPSC found that 53% of respondents still believed they could not speak freely[336]. In September, Mona Nemer was appointed as Canada's Chief Science Advisor with a mandate to provide advice on

"guidelines to ensure that government science is fully available to the public and that federal scientists are able to speak freely about their work" and on "creating and implementing processes to ensure that scientific analyses are considered when the Government makes decisions.[337,338]" It was with this background in mind – a scientific community estranged from federal policy spaces by a decade of government interference or neglect, a public policy community demonstrating its intent to change, and a support and capability gap between the two – that I first encountered Science Meets Parliament as an intervention that could help to revive Canada's foundered science-policy relationship.

Program development

Science and Technology Australia (STA) is an umbrella organization for the nation's scientific societies, representing the interests of its membership to government. Since 1999, STA has operated Science Meets Parliament (SMP), a program that invites its member societies to send delegates to the seat of the Australian federal government to learn about political processes, engage with fellow researchers, and meet with Members of Parliament and Senators. I heard of the program through a former delegate, Dr. Gemma Anderson, at the Royal Society's Commonwealth Science Conference in 2017. Through her, I was able to discuss the program in detail with the STA CEO Kylie Walker, program lead Dion Pretorius, and SMP founder Dr. Ken Baldwin. The STA team were open and generous in answering questions about all aspects of their program. Some advice they offered to re-create SMP in a new jurisdiction was that the program must:

1. Avoid lobbying. Many special interest groups arrange "day on the Hill" events to generate political support for their organization or issue. Participating Parliamentarians are necessarily presented with an "ask," whether for increased funding, support for a project, or another action to promote their goal. SMP Delegates are instructed to avoid making any particular request from the MP or Senator they meet, instead offering to support them in their work. This small change helps to differentiate the program and begin to affirm that scientists can be good-faith partners in working towards the public benefit.

2. Demonstrate non-partisanship. A core principle of STA is that access to high-quality scientific knowledge improves policymaking on every part of the political spectrum. By targeting the legislature, as opposed to the government, SMP enacts this principle by inviting participation from members in all parties, taking care not to show any real or perceived preference for one over others. As a result, SMP had remained a staple of the Australian parliamentary calendar through changes to science policy as drastic as those experienced in Canada.

3. Focus on building relationships. The program's greatest impact is on the long-term stability of the relationship between science and public policy. While Delegates are encouraged to share their research, meetings are not intended to be a one-way presentation. Instead, by encouraging organic conversations that aim towards understanding each other's goals, challenges, and values, the meetings create a space for honest reappraisal of and new appreciation for both the person in front of them and the institutions they represent.

4. Provide professional development for the Delegates. There is no reason to expect that someone who has devoted years to advanced scientific training should also have acquired the ability to operate effectively in a policy environment. Our failure to prepare Delegates could risk reinforcing prejudices about scientists being out of touch or politicians being unresponsive. Workshops dedicated to science communications, political structures, and other relevant topics help Delegates develop the skills they will need to connect across sectors.

5. Ensure equality, diversity, and inclusiveness. While SMP Australia had always performed an advocacy function, STA realized that it had also become an important capacity building program for their nation's scientists. Former Delegates were more likely than their peers to continue to engage with policy, whether through their elected representatives, participation in parliamentary committee or budget processes, or writing op-eds for popular publication. Accordingly, they took greater care to ensure that participation adequately represents the population and avoids re-producing demographic biases. Since capability-building across

different regions, languages, etc would be one of the primary goals of SMP in Canada, we would need to be thoughtful in developing our application and selection processes.

Three meetings in the following months then cemented the core elements of the program and its organization. First, Dr. Malardier-Jugroot and I met with our Member of Parliament, Dr. Ted Hsu, who not only confirmed that SMP could work in Canada but that we should aim to run the pilot program within the year. Second, I spoke with Dr. Mehrdad Hariri, CEO of the Canadian Science Policy Centre (CSPC), who told me that the CSPC was already intending to develop a training opportunity in Parliament for researchers, modelled after the Library of Parliament's week-long Teachers Institute on Canadian Parliamentary Democracy program[339]. While Science Meets Parliament would be different in format and scope, we agreed that there were practical advantages to tailoring the Australian model for the Canadian landscape. As the organization behind Canada's largest science policy conference, CSPC held the volunteer and logistic power to make a Canadian Science Meets Parliament practicable. Third, Dr. Hariri met with Canada's newly-appointed Chief Science Advisor Dr. Mona Nemer who felt the program would provide a valuable mechanism for her to exercise the mandate of her office to connect the scientific and political communities.

Event programming

2018 Pilot

The first Science Meets Parliament took place in Ottawa over two days in November 2018. Due to practical concerns over the limited capacity of our small organizing team, eligibility was restricted to Tier II Canada Research Chairs. We agreed that this afforded us a large enough candidate pool of active researchers in Canada whose experience on the program could be related to their students and mentees, creating valuable secondary and tertiary effects. 28 Delegates were selected from over 70 applications, based on their responses to questions regarding their motivations (principally to gauge their alignment to the non-lobbying and non-partisan nature of the event) and on our commitment to ensuring a representative sample of Canada's diversity. We made no attempt to solve the demarcation problem of what is and is not included in "science," rather we hoped to attract as

diverse a group as possible for a radically interdisciplinary event. Realizing that our eligibility criteria had unintentionally excluded Inuit researchers (at the time, no CRC Tier II researchers identified as Inuit), we worked with Polar Knowledge Canada to find a suitable participant.

On the first day, the scientists met with the Chief Science Advisor who shared her personal experience of facilitating interactions among scientists, politicians, and policymakers. She also discussed the roles of scientists in advancing evidence-informed policy and provided tips for communicating with legislative representatives. Following this meeting, the delegate scientists attended a policy workshop to learn about the structure of government and legislative processes in Canada and methods for effective political communication. In particular, experienced legislators from across the political spectrum advised scientists on how to adjust their communication methods from source-oriented to audience-oriented. Scientists then received the guidance of communication experts, including current and former MPs and senators, in an interactive session where they practiced research dissemination speeches aimed for a lay audience.

For the second day practical exercise, Delegates were paired with one or more of 43 participating MPs and Senators. Some had several-hour long conversations with policymakers or shadowed MPs for the morning/afternoon sessions. Others attended committee meetings such as the Standing Committee on Health and Finance or the Standing Committee on the Environment and Sustainable Development. In several instances, the paired scientists and policymakers embraced different political ideologies. Despite these ideological differences, many pairs were able to find forward-thinking common ground through their discussions. The Standing Committee meetings were relevant to a wide range of scientific disciplines, and policy themes, including climate change, fisheries protection, energy access in Indigenous communities, small rural businesses, big data, the new relationship between Canada and First Nations, Inuit, and Métis people, advancing gender and health equity, and healthcare funding. Some discussions focused on how science can be most useful to policymakers, the types of evidence that policymakers need for effective decision-making and procedural details on how policymakers seek out scientific evidence. In

some cases, both sides also agreed to host events focused on teaching scientists about working with the media to influence policy. Later in the day, the scientists attended Question Period in the House of Commons and the day concluded with a networking reception, where delegates, the Honourable Dr. Kirsty Duncan, (Minister of Science and Sport,) Dr. Nemer, MPs and Senators from all four political parties and invited guests came together to celebrate the inaugural event.

Adaptation and Enhanced Training

The general federal election of November 2019 caused us to move the second event to a date in May 2020, which we then had to delay indefinitely due to the COVID-19 pandemic. By the time the severity of the disease had emerged and government responses began in earnest, we had already announced the selection of our second Delegate cohort. To maintain engagement, seek benefit from the enforced elongation of the timeline, and take advantage of the explosion in remote video conferencing, we developed an ad hoc series of webinar training sessions. Subject matter experts and leaders of organizations in Canada's scientific and policy communities were invited to host discussions on topics ranging from the mechanisms of parliamentary democracy, the role of the Library of Parliament, funding agencies, and equity, diversity, and inclusion in science among others. Mid- and post-program Delegate surveys were performed to determine which sessions were most valuable and should be retained as work-up training in future events. Among those selected are a government 101, the machinery of Parliament, EDI in science, meeting the Triagency heads, a panel discussion with former MPs, and a workshopping session for Delegates to share and refine their "elevator pitch" short introductions. We had discussed arranging remote meetings with MPs and Senators to close out the 2020 cohort, but ultimately decided that there too much value would be lost. Welcoming scientists into the physical spaces of Parliament makes their invitation to engage with the formal processes of Parliament more concrete than would a phone call or video meeting. In-person federal events were successfully held in May 2021, followed by a return to routine in 2023 and 2024.

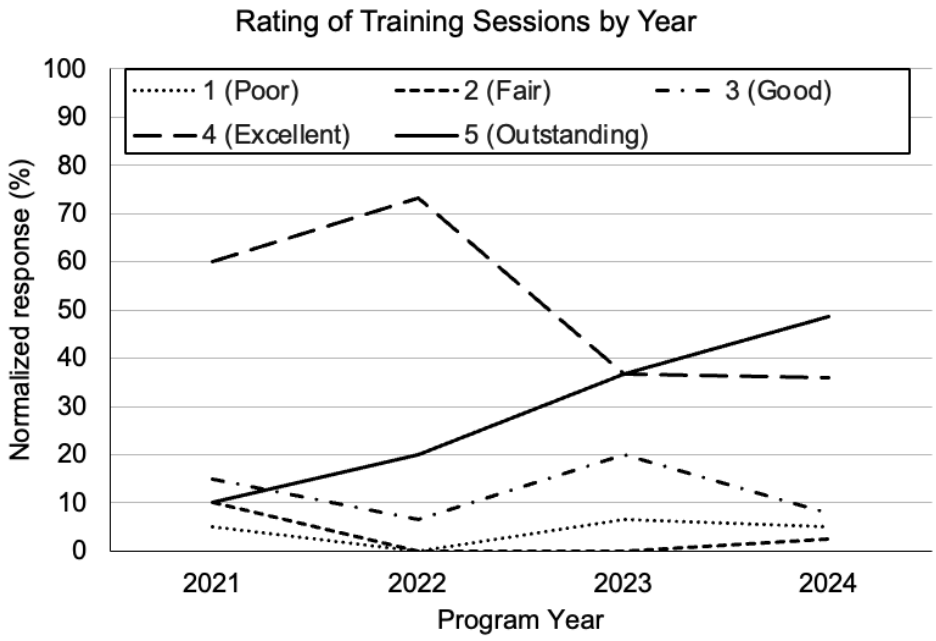

Figure 9.1: Survey responses from Delegates rating their overall experience with the training program in 2021 (n=20), 2022 (n=15), 2023 (n=30), 2024 (n=39)

Provincial Expansion

By 2023, the organizing committee had grown to include several past Delegates, CSPC volunteers, and members of the Office of the Chief Science Advisor so when we were invited by the Speaker of the Legislature of British Columbia to develop Science Meets Parliament BC we were ready to accommodate. Delegates selected from BC's research centres joined the federal delegates in common remote sessions. The two days' event in April 2024 followed the established pattern but also included a reception by the BC Lieutenant Governor at Government House. The good will with which this program was received was communicated by the Speaker and Lieutenant Governor's staff to their counterparts in Ontario, leading to the second provincial program in Queen's Park, March 2025. Both are expected to continue annually.

Impacts and observations

The difficulty of assessing the impact of this program on the Delegates, parliamentary participants, or on the culture of science in Canada is

significant. In the first case, the researchers whose applications are accepted are rising leaders in a competitive, strenuous occupation who have nonetheless chosen to take on new challenges by engaging with public policy. Which is to say that Delegates are already high-achievers and deconvoluting the specific influence of SMP from the myriad traits, decisions, and opportunities that influence their career trajectory is impossible with any level of objectivity. To assess the impacts of SMP on the 2018 cohort, SMP committee member Dr. Trushar Patel and I drafted and sent a questionnaire to those Delegates who authored a 2020 paper that documented their immediate impressions, in the belief that the most reliable source of information on the impact the program has had on participants is the participants themselves.[340]. The problem of impact assessment on MPs and Senators is as challenging, with the additional practical impediment they are far less likely to respond to participant surveys. CSPC does receive a few responses after each program, although the limited responses may not be representative. Evidence for Democracy (2019) and CSPC (2021) both surveyed federal Parliamentarians on their access to and use of scientific information.

Impacts on scientists

In our 2018 perspective paper, Delegates from the first SMP cohort claimed that it was "no longer sufficient to allow the products of science to 'speak for themselves' and rely on traditional means of dissemination." Five years later, all nine survey respondents retained or deepened their commitment to that position. It is relevant that the questionnaire was sent while the pandemic response was still fresh in people's minds. The former Delegates reported that their experience in the program helped attune them towards public perceptions of science and encourage them to make active contributions to discussions outside of academe, while also making them more sympathetic to the difficulties policymakers encounter in trying to balance the needs of all constituents and stakeholders. In fact, an appreciation for the demands placed on Parliamentarians' time and attention was the most common (3/9) response to their self-reported most impactful lesson that they took from SMP. The other responses, equally valuable during the intervening years, were their belief in the possibility for impact through policy engagement, their practicable knowledge of government

organization and processes, and the skills they developed for communicating their research to new audiences (2/9 each). Each respondent felt that SMP had influenced their degree of engagement on policy issues (one who had engaged prior to participation responded ‘somewhat’), and most had connected their research to policy development (7/9; one other who expected to do so shortly).

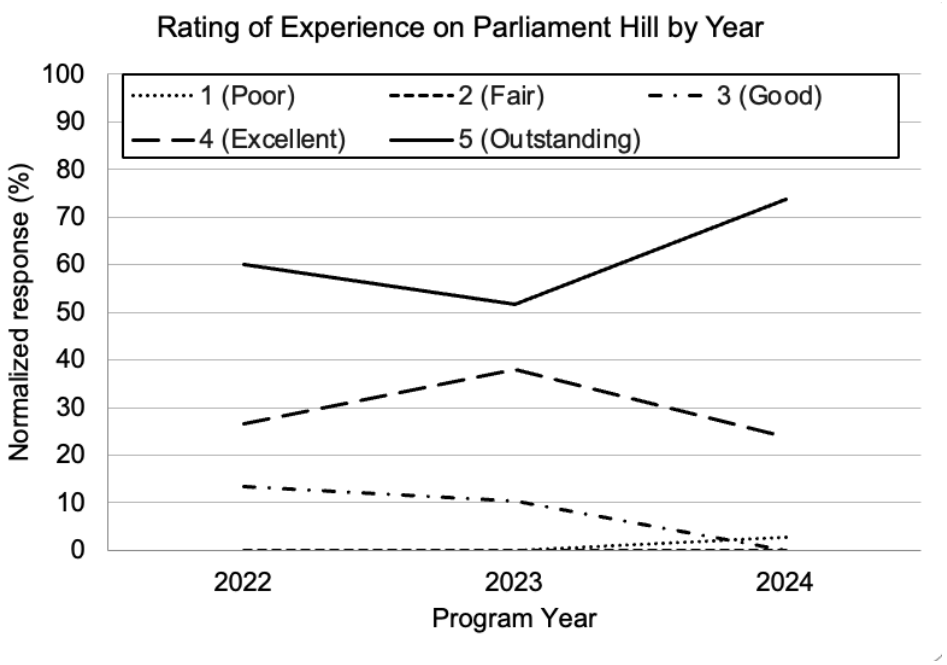

Figure 9.2 Delegate survey responses indicating the value of their experience meeting with Parliamentarians during the SMP program 2022 (n=15), 2023 (n=30), 2024 (n=39).

Impact on mentorship, teaching, and service

Most respondents report that their engagement with public policy has influenced how they approach mentorship and teaching (7/9) and service or administrative duties (6/9). These responses help to validate our decision to tailor eligibility criteria for early career researchers since the possibility for secondary and tertiary impacts through mentorship was an explicit aim. Delegates encourage their graduate students to get involved in outreach and advocacy (5/9), to seek careers in government policy or science (2/9), and to discuss science and policy in seminar or classes (3/9). One notable impact is the development of a graduate training program called “Research meets

Policy" (RMP@SFU) by a former Delegate at Simon Frasier University, directly inspired by their SMP experience. The week-long program has run annually since 2021 and resulted in its own spin-off events[341].

In terms of service commitments and university administration, Delegates felt that SMP encouraged them to continue in their pre-existing intentions rather than inspiring a new direction. This response illustrates the difficulty in isolating the influence of SMP training and experience on self-nominated participants. Two respondents who did claim a more direct influence both expressed that they felt more confident to carry their identity as scientists into policy discussions, rather than leaning on administrative titles that may seem more naturally at home in governance spaces.

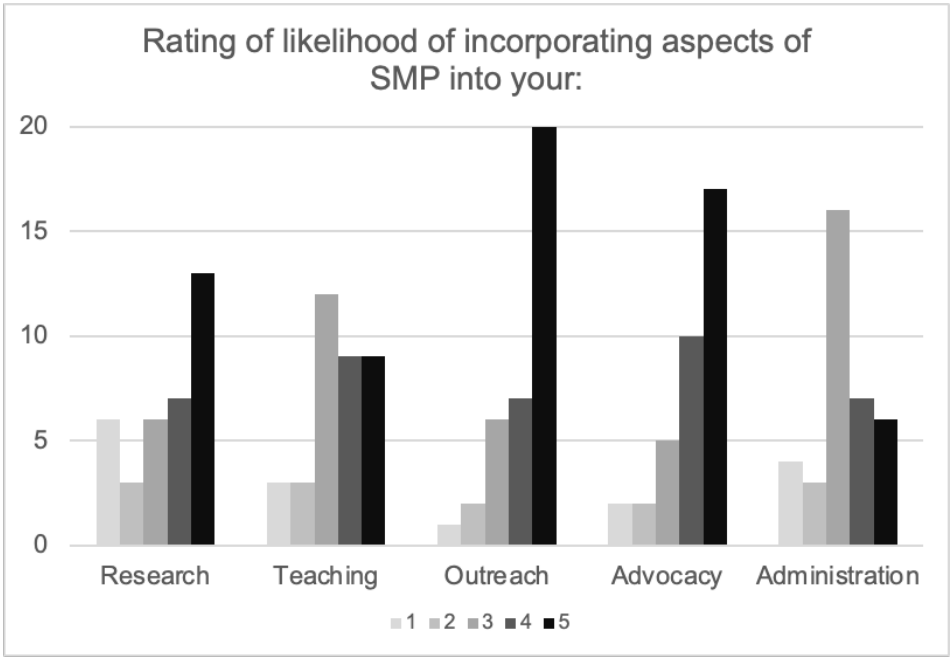

Figure 9.3 Survey responses from Delegates indicating their likelihood of incorporating lessons and experiences from SMP into various aspects of their work (n = 36).

Non-traditional research outputs

Our 2018 article noted that the additional work required to engage with policy or to translate research for extramural audiences deserves to be recognized and incentivized alongside journal articles or conference

presentations. For instance, committee testimonies, budget submissions, and briefing notes can be important communication vehicles for scientific knowledge that are often undervalued by exclusion from curriculum vitae, grant applications, promotion packages, and similar measures of academic merit. Accordingly, we asked the former Delegates whether they are now more likely to produce non-traditional research contributions and to include them on summary documents intended for academic audiences. The majority of respondents (8/9) have expanded the research outputs they consider legitimate for their field and included those contributions in professional documents, some receiving feedback that such inclusion was viewed favourably. The majority report that their fields have become more receptive to non-traditional research outputs since 2018 (7/9), although most of those (4/7) see it as the continuation of an existing trend toward encouraging public engagement in parallel to standard publishing practices. Discouragingly, two respondents, one who is noticing a change and one who is not, expressed doubt that alternative research products are receiving the same evaluative weight as traditional output.

Impacts on Policymakers

CSPC sends post-event surveys to participating MPs and Senators, but since response rates are no more than 10% and universally positive they do not provide a reliable record of the program's real or perceived value to Parliamentarians, or evidence of its impact on policymaking. In 2019, Evidence for Democracy (E4D) surveyed MPs on the real practices of information gathering and use in Canadian Parliament. One question addressed the role of public outreach programs as formal pathways for knowledge mobilization – naming Science Meets Parliament as an example[342]. Quoting from the report:

> "In terms of public outreach events, many MPs described that they enjoyed attending them when they could, and that they viewed the events as fun, good networking (both with constituents and other MPs), and a great opportunity to learn about something they might not know about. Although some MPs described picking up information from some of these events that did end up factoring into their work, more MPs

> described that these events are not information-gathering exercises *per se*, unless the event was directly relevant to files that the MP was already actively seeking information on. However, a few MPs did discuss following up with individuals they met at public outreach events later on when they needed an expert opinion on a particular topic. This indicates that, although public outreach events might not be the most effective way to present MPs with new information, they can be important as a key first step in building trusting relationships between experts and MPs, which is a key ingredient in the evidence-gathering cycle."

This description of SMP as a space to establish and nurture relationships across the research and policy sectors, rather than to provide specific evidence on any one policy topic, aligns with the aims of our program and the Delegate experience. The potential effectiveness of this approach is attested to elsewhere in the E4D report: "Particularly when MPs are overloaded with a huge amount of information, MPs described the benefit of relying on their established trusted relationships as a way of getting relevant, credible, and verifiable information quickly and effectively." Echoed in a further section on sources of reliable information: "As well, several MPs discussed the benefits of gathering information from a person they trusted — several MPs had a number of scientists, experts, or trusted individuals they felt they could call to get easy access to research information."

In 2021, CSPC completed a survey of Canadian MPs and Senators on their use of scientific information during the COVID-19 pandemic[343]. It did not ask about SMP in particular, but their respondents noted that reliable access to trusted experts to provide plain-language explanations of the latest research provide an important counterbalance to mis- and disinformation. By widening the scientific networks available to a greater number of Parliamentarians, SMP leverages trusted relationships to indirectly strengthen the use of evidence in policymaking.

Discussion and recommendations

Following the adage to "let the science speak for itself" is no longer sufficient and can become dangerously negligent when mis- and disinformation are being actively mobilized. Strengthening ties between researchers and the communities who benefit from scientific work is vital to enable evidence-informed policy, generate technical and social innovation, combat disinformation, and attract young minds to pursue higher education, among other strategic needs. Of all the impacts that Delegates trace to Science Meets Parliament, their appreciation for the urgency and gravity of strong, diverse connections between members of the research and policy communities has had the most impact. However, new partnerships with policymakers, industry, educators, or other members of the community can bridge the gap between scientific knowledge and societal impact, but effective communication beyond disciplinary and sectoral boundaries requires ongoing, active engagement.

Overall, delegates report that their participation in the SMP program was influential and beneficial to their careers. Learning to tailor their message to meet both audience needs and scientific fidelity has improved their communication with policymakers, peers, and community stakeholders, leading to enhanced knowledge mobilization inside and outside of their discipline. Understanding the workings of government and the challenges faced by politicians provides a valuable perspective that informs their strategies for advocacy and engagement. They continue to use the training they received during the program and pass on that knowledge to students and mentees. Five years after their experience, Delegates confirm that the program enhanced their ability to engage effectively with policymakers and navigate the complexities of science-policy interactions. It is too soon to tell whether or not our strategy for encouraging many small-scale interpersonal relationships will secure the large-scale science policy relationship against falling back into disrepair when once again challenged. Our program's influence on Canadian cultural norms for its scientists' involvement with policy or expectations for its leaders to employ scientific knowledge in their decision making is still more difficult to assess. However, the survey results we have seen and the invitation from provincial legislatures are encouraging signals for the future.

In our 2020 article for The Conversation, 19 SMP Delegates and I offered six recommendations to further strengthen the science-policy relationship in Canada. Some have already been realized in whole or in part, but all remain relevant.

1. Integrate public policy communication into academic training: Effective communications with policymakers is a key skill that researchers must develop if they are to facilitate the incorporation of science into policy. Yet this element is missing from most graduate programs and faculty training. Including policy communication skill development into professional training will provide the current and future generations of scientists with the tools necessary to engage with policymakers and other community knowledge users.

2. Develop incentives for policy engagement: Researchers have identified the lack of professional incentives for policy engagement as an important reason why a gap exists between science and policy. Policy inputs, such as briefing notes or committee testimony, should be recognized by institutions as valid research outputs and service for the purposes of promotion and funding applications. Additionally, university public outreach offices could support faculty engagement with the policy process by monitoring parliamentary committee agendas and alert researchers to opportunities to contribute their expertise.

3. Establish and support forums for public engagement training: Science Meets Parliament has demonstrated the potential for programming to grow capacity in this area. Opportunities for scientific researchers to develop knowledge and experience in policy spaces have increased but are still relatively rare. Reliable funding, especially from public sources, would increase the number of scientists from diverse disciplines and backgrounds with the will and skill to engage with the policy-making process.

4. Create a research chair at the Chief Science Advisor's office: Visiting research chairs within the Office of the Chief Science Advisor and like

offices would allow scientists to learn and develop new strategies for integrating science into politics. A four month to one year tenure would offer a path for former SMP Delegates who have now 'met' Parliament to make more in-depth contributions to science policy. As the Science Advisor network is built within government departments, visiting chairs would create a pipeline for early and mid-career researchers to gain experience and develop expertise to take on those roles in the future.

5. Establish training opportunities for MPs and Senators: Parliamentarians should be offered structured opportunities to enhance their science literacy through campus and community visits, targeted training and workshops, or pairing with scientists. For political representatives who have no or little experience in research, training experiences would enhance their understanding of the scientific landscape in Canada, including how research funding benefits their communities and how credible information is generated by the scientific community.

6. Extend Science Meets Parliament to other levels of government: While we have adapted and delivered SMP in British Columbia and Ontario, other regions and jurisdictions may yet benefit from the introduction of the program. Instituting a version for the east coast or prairie provinces, the North, or for municipalities each present their own challenges and exciting possibilities. Additionally, SMP Canada has become sufficiently established that we could assist other nations to develop their own versions or to re-connect with Australia and work towards multi-national or global opportunities.

Conclusion

As hazardous as it is for government to take too much interest in the actions of its scientists, it is also dangerous for scientists to take too little interest in the actions of its government. A relationship in which both science and policy communities understand and respect the other makes mutual support possible; the more people willing and able to reach across the divide, the more probable it becomes. Both research and policy professionals require long study and apprenticeship to develop the knowledge and skill they need to succeed in their chosen career. There ought to be no expectation that

someone who has committed their time to one path should be an expert in the other; however, the Science Meets Parliament experience demonstrates that it is possible to produce a training package that delivers a sufficient level of familiarity for effective engagement without placing undue burden on the participant. Science Meets Parliament Delegates feel more confident engaging with policymakers and better able to see that the impact of their work reaches beyond the confines of their discipline and sector.

10. The kind of problem sustainable entropy *is*

If we are going to advance a concept of entropy to serve as a useful tool to construct sustainable chemical processes, then we are going to need to let go of the tradition that tells us entropy embodies the inevitability of death and search for its role in the kaleidoscopic evolution of life. As discussed in the opening chapter, entropy developed from its roots in mechanics into classical thermodynamics of Clausius, Gibbs, and Planck and the statistical thermodynamics of Maxwell and Boltzmann. Classical thermodynamics contemplated the divorce of physical properties from the materials that exhibit them: the relationships between (largely) independent variables are analyzed into simple sets of equations. Sadi Carnot would have approved of its careful application of mathematical reasoning to induce universal principles from specific observations. Statistical thermodynamics, on the other hand, sought to locate the cause of physical properties in the material itself—demonstrating how a large number of complex, disorganized actions by microscopic objects can give rise to predictable behaviours in macroscopic objects. Lazare Carnot would have appreciated its attention to the contribution of infinitesimally small parts to the larger workings of the system. Both perspectives have proven their immense usefulness to understanding the material world, both approaches improve the techniques we use to manipulate and build, and both theories stand affirmed, as Einstein suggested, "within the framework of the applicability of [their] basic concepts."

But there are questions remaining outside of those basic concepts. Principally for this discussion, problems involving complex interactions within well-organized structures: circumstances that can neither be reduced to simple relationships nor modeled as disorganized complexity. Molecular-scale architectures shape the immediate chemical environments they contain, creating preferred proximities and orientations which influence which guest interactions become more or less likely. Unlike a gas or large volume solution, the small-but-sufficient resistance generated from the interior walls confine a guest molecule's movement according to the layout of the structure. In cases where a potential energy gradient further establishes a bias in favour of one direction of motion over its reverse, the

net result can be a predictable, spontaneous movement of the guest towards a lower entropy state. Structures at the molecular scale are no more able to create perpetual motion than any other – energy must still be exchanged with the surroundings – but there is significant ground to explore between the extremes expressed in “all spontaneous processes must move in the direction that maximizes entropy” and *perpetuum mobile*.

Machine learning is an effective optimization method for meeting a well-defined outcome from a complex environment, and so is well suited to model the complex relationship of a large number of highly interdependent variables that obtain within nanoarchitectures. Theory-informed models will be as invaluable to navigate the large space of possible molecular architectures in search of the sizes, shapes, surface composition, and catalytic inclusions that best support target reactions as classical and statistical mechanics have been for developing bulk scale reactors.

Experimental synthesis and characterization of soft, self-assembling structures in an aqueous environment presents its own set of challenges. Establishing more accessible methods to quantify the thermodynamics governing the behaviour of small molecules within nanoscale reactors offers an exciting prospect. We have recently seen early evidence that certain porphyrins will sensitively and reversibly respond to subtle changes under confinement. We have only characterized the changes using UV/visible light spectroscopy so far, but there are several other physical responses that porphyrins may express, as described in Chapter six. The combination of reporter molecules with instruments capable of sensing chemical shifts with high spatial and temporal resolution, guided by appropriate theory, provides the toolset to explore a science of entropy-shaping nanoarchitecture. Furthermore, using methods developed on relatively simple artificial reactor systems to characterize more complicated biological systems would allow for direct comparison and improved mimicry. Our application of new and existing techniques to target enzymes while taking account of the ways in which ‘molecular machines’ deviate from classical mechanics will open the range of examples we can apply to a program for sustainable chemistry.

I have already said that understanding the chemistry is necessary but insufficient for the success of a program targeting a complex social need. Sustainable chemistry certainly meets that threshold, both in the ways that industrial chemistry can be made more energetically and materially efficient and the ways that chemistry can contribute to the sustainability of other fields. A programmatic focus on tools and materials that act on the entropy of a reaction situates itself at the intersection of chemical, biological, and physical approaches to the problem. Each discipline could legitimately claim title to the task and it would therefore benefit from their collaboration. Additionally, the specific purposes to which the benefits are targeted will implicate other expert communities, whether decontamination of recalcitrant chemicals (e.g. environmental scientists and engineers, local community members), fine chemical synthesis (e.g. industrial engineers, agriculture scientists, botanists, nutritionists; plus medical chemists, pharmacists, and physicians if drug related), or clean energy (e.g. chemical engineers, materials scientists, climate scientists). Each of these application areas also carry social and political consequences that deserve attention from the outset. Coordinating the with impacted groups and their representatives is both ethical and practical, since doing so would have a tangible impact on the success of the scientific enterprise. I also enjoy the irony that entropy, the physical property most associated with disorder and drifting apart, could provide an occasion to get together and organize.

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Appendices

Appendix A: Questionnaire to 2018 Delegates

Questions that directly follow from the earlier paper:

1. In 2018, we claimed that it was "no longer sufficient to allow the products of science to 'speak for themselves' and rely on traditional means of dissemination."
    a. Has your view on this statement changed since 2018?

    b. Have you connected research (your own or others) to policy development, as we suggested? If so, briefly share your story.

    c. Do you believe that your participation in SMP influenced whether or not you engaged with policy development in your professional life and engaging with the community at large, if so, your approach?

2. We suggested several benefits to scientists who participate in SMP or similar programs. Respond to each of the questions below with a yes or no, and if yes please provide some details.
    a. Did you remain connected or have you established additional connections with one or more political decision makers as a result of your participation in SMP?

    b. Has your exposure to the policy space influenced how you approach teaching or mentorship with students?

    c. Has your experience changed what research outputs you recognize as legitimate for your field (e.g. budget submission, committee testimony, etc.)? If so,

        i. Have you included any non-traditionally academic outputs on a document intended for an academic audience (e.g. CV, knowledge mobilization plan,

grant application, recruiting or promotion package, conference proceeding, etc.)?

ii. Have you noticed any change in what your field recognizes as legitimate research output?

d. Have you remained connected with the other Delegates in your cohort, personally or professionally?

i. Do you believe that your experience in SMP led directly or indirectly to a new collaboration or research direction?

Question areas for open discussion:

3. What was the most impactful lesson you took from SMP2018 and how did it benefit your academic and/or non-academic initiatives?

4. Are there changes to your understanding or approach to research/teaching/service that you would credit in whole or in part to SMP? Possibilities include:

- How you propose/plan/execute your research;
- How you approach graduate or undergraduate recruitment and training;
- Communications plans and stakeholder engagement;
- Hiring, promotion, and other appointments; either as the candidate or assessor;
- Engagement within your field or with other academic/non-academic communities;
- Negative effects: were there unforeseen consequences you would've sooner avoided?
- Non-effects: do you feel that the event had no measurable impact on your development?
- Any other aspect that we missed in topics listed above.

5. Naturally, inevitably, if and how did your experience during SMP influence your response to the Covid-19 pandemic? Did an ‘inoculation’ of science policy help you navigate government, institutional, or personal responses? Do you feel that you better understood the possibilities and constraints on science advice or political action?

6. Finally, please include any other stories you feel are relevant to the discussion.

Appendix B: Exercise: Volatile Storm

Background

Lonsdale is a small, high-income country that gained independence from its large neighbouring country Braggmark in 1927. The largest city in Lonsdale is the capital, Bernal, located near the Braggish border, followed by the port city of Mocatta.

Economy of Lonsdale

Although today Lonsdale has a population of nearly 3 million and an advanced technological infrastructure, it was considered an obscure hinterland in its early modern history due to its relative distance and poverty compared to Braggmark's central, resource-rich states. The primary economy of Lonsdale was sheep and barley farming up until the 19th century; coal mining became a secondary activity in the 17th century to support steel manufacture in the central states. As Braggmark grew into the major political and military power in its region, Mocatta became a more important, if remote, trading port. Its textile industry developed substantially as ships brought silk and other new materials into the city during the 18th century. After the discovery of synthetic coal-tar dyes in 1856, the combination of existing coal processing and textiles manufacturing sites produced an industrial boom in the region. Labour unions established during this period eventually gain the controlling interest in the largest of these enterprises; socialized ownership of the major industry would pave the way for Lonsdale's later political reformations.

In 1881, Mocatta became the site of Braggmark's first operational steam engine, marking a turning point in the history of Lonsdale. As local industries quickly adopted the new technology, the state grew richer - economically, certainly, but also in the arts and sciences. Lonsdale's close connection between technological and economic development attracted top academic researchers to its schools. Bernal Technical University is now regularly listed among the top three research institutions in the world for chemistry, nanoscience, genetic engineering and chemical engineering.

Early and rapid adoption of industrial technologies was not all positive, however. Smoke from the heavy concentration of coal-powered machinery covered the area surrounding the cities in black soot, by-products from the chemical industries leached into the waterways, and the increased human demands on farm production exhausted the soils. Lonsdale's history of pollution hit its lowest point in 1960 when a series of serious birth defects was linked to effluent from a pesticide plant. The highly publicized trial that ensued, plus the publication of Rachel Carson's *Silent Spring* in 1962, led to important environmental reforms including acts to protect air and water quality, and public spending on ecological rehabilitation. Chemical production and refineries remain important industries for the region. While hazardous material storage and disposal is much better regulated than in the past, public funding for inspections and enforcement has not kept up with inflation since the turn of the century.

Politics of Lonsdale

By 1912, Lonsdale's economic independence had grown to match its cultural and geographic independence from the other states of Braggmark. The socialist parties that swept to power in the state government in that year confirmed its political independence as well. Depending as they did on international trade, science, and cooperation, the people of Lonsdale did not identify with the growing militarism and xenophobia in other parts of Braggmark. When Braggmark announced its entry into the Great War in 1914, Lonsdale announced its exit from the federation. Braggmark's federal government denounced the move as regrettable. The national press was more blunt, calling Lonsdalers a "treasonous and cowardly sub-class of people". However, Lonsdale's separation was within the state government's legal power and supported by a strong majority of its own citizens so its independence was ratified.

Lonsdale had never been a strategically critical area so Braggmark had never established land fortifications in Lonsdale; however, the Navy had a resupply station in Mocatta that was taken over and closed by Lonsdale following independence. In what Lonsdale saw as an act of retaliation but Braggmark claimed as a necessary act of coastal defense, the Braggmark navy established a naval blockade on Mocatta. With its port effectively

closed, Lonsdale was forced to rely on overland trading with Braggmark for essential goods. By the time peace returned in 1918 the tables had turned: a heavily bombarded Braggmark needed Lansdale and its ports to receive relief from overseas. Lonsdale extracted heavy taxes on goods moving through the country and regained their lost wealth quickly. The experience left Lonsdalers with a lasting mistrust of the Braggmark military and confirmed their repulsion for armed conflict. From its inception as an independent nation, Lonsdale has been without a military and officially committed to pacifism.

Despite its controversial opening act, diplomatic relations between Braggmark and Lonsdale have been peaceful and mostly friendly. Lonsdale continues to depend on Braggmark for a large portion of its trade in food and building materials and, although neither country would acknowledge it, for defense. This has occasionally flared into a point of tension between the countries, most notably marring Lonsdale's centenary celebration in 2014. In Lonsdale, historians uncovered evidence that the nationalized chemicals industry had manufactured and supplied the Braggish military with chemical weapons and their precursors throughout the Great War, continuing right up until the environmental reforms of the 1960s. New questions arose over the agents actually responsible for the infamous birth defects. Political pundits asked whether or not the country could continue to identify itself as dedicated to peace while it profited from war. On the Braggish side, opportunistic political groups tied the revelation to the centre-left party in power at the time, painting their opponents as "hypocritical and deceitful as the socialists in Lonsdale", while also claiming that Braggmark had been "cheated" out of money by their "free-riding" neighbour. Fringe elements went as far as to claim that the news invalidated the reason given for independence and so Lonsdale's separation was never legal and just used as cover for Braggmark to "do what needed to be done" during the war. A claim of sovereignty over Lansdale or "One Braggmark" has become a common conspiracy theory among far-right groups in Braggmark. No major political party takes the idea seriously, though some notable politicians have made comments in the press and reposted memes on social media that hint at support.

Scenario

In March 202_, Lonsdale was hit with a massive and uncharacteristic storm. Winds of up to 140 km/h disrupted power to a half a million homes while the storm surge flooded many low-lying areas, including most of Mocatta. The heavy rains that followed washed out roads and impeded emergency response. The storm was responsible for at least 18 deaths. The Lonsdale Red Cross and Corps of Civil Volunteers (Lonsdale's national service organization, a non-militarized reserve force) were activated to manage housing, rations, and public health measures for approximately 25,000 displaced persons throughout the country. International disaster assistance teams from Braggmark were invited to help clear and repair critical infrastructure while a team from a third country, Crowfoot-Hodgkin, was asked to send technical teams to help secure the oil and chemical refineries in Mocatta's flooded industrial sector.

You are a member of Lonsdale's Rapid Emergency Assistance Coordination Hub (REACH) responsible for coordinating efforts between national agencies and international partners and to advise the Lonsdale national government. During the response to this event, you report directly to the Minister for Public Safety. Your role is to make recommendations on issues relating to the disaster response including employment of the available resources and public communications.

Situation updates (distribute as the scenario progresses)

Situation clock: 0 hours
You have received a phone call from an evacuation site near Mocatta. Triage nurses report that people are arriving complaining of extreme muscular weakness and shortness of breath. Treatment for exhaustion and dehydration has had no effect. One person with these symptoms suffered a seizure and was airlifted to Bernal General Hospital. Family members from some patients have identified a connection to Yardley Chemical Works. The physician in charge of public health at the site believes their symptoms could be caused by exposure to a toxic material.

Questions for discussion:
What is the problem you're trying to solve?
What are your options?
What are your constraints?
What information will be required to make a decision?
How will you get this information?
What recommendations, if any, will you present to the Minister?

Situation clock: + 6 hours
Within hours, news about possible toxic chemicals in the floodwater has trickled onto social media. A family member of one of the Yardley workers noticed doctors donning protective suits and confronted them while streaming on Facebook. The video was reposted on Twitter, inspiring a long thread claiming that evacuees from Mocatta show telltale signs of nerve agent poisoning. One Braggish volunteer clearing debris for the technical team recorded one in conversation saying that they "don't have the right gear for chemical weapons". Although the team member was simply responding to a direct question about the capabilities of their protective equipment and made no suggestion that chemical weapons are present, the volunteer shared the video clip on Instagram. The hashtags #NerveGas and #OneBraggmark are now trending worldwide.

You have spoken to the director of operations at Yardley who confirmed that all tanks and lines are secure. They added that they do produce an organophosphate, tributyl phosphate, but it's not known to cause acute poisoning at low concentrations. The support element leader from Crowfoot-Hodgkin acknowledges the company's assessment but refuses to deploy a team to Yardley until the cause of Bernal patient's illness has been identified. Medical staff at the evacuation site have requested nerve agent countermeasures including oxime and atropine.

Questions for discussion:
What is the problem/problems you're trying to solve?
What are your options?
What are your constraints?
What information will be required to make a decision?

How will you get this information?
What recommendations, if any, will you present to the Minister?

Situation clock: + 12 hours

An explosion at a fuel depot was caught on film by a news helicopter and picked up across network coverage. Braggish fueling crew were on site loading trucks to resupply construction vehicles and generators at the displaced persons camps. All personnel are safe and fire did not spread but further operations were closed out of concern for safety. The Braggmark government held a press conference to say that despite the risks that Braggish workers face, their country is proud of the long history of friendship and cooperation between the two countries - a friendship which they will gladly reaffirm in Lonsdale's time of need. Nevertheless, Lonsdale opposition parties are calling for an investigation into the incident before allowing foreign nationals access to other critical infrastructure.

Questions for discussion:

What is the problem/problems you're trying to solve?
What are your options?
What are your constraints?
What information will be required to make a decision?
How will you get this information?
What recommendations, if any, will you present to the Minister?

Situation clock: + 18 hours

No more evacuees have shown signs of paralysis or breathing issues, nor did any other patient require hospitalization for their symptoms. The cause of the Bernal patient's illness has not yet been identified, but nerve agent poisoning has been definitively ruled out. However, the number of people reporting sudden moderate illness, especially nausea and headaches, has increased steadily - even from unflooded neighbourhoods. Public health authorities are worried that water treatment may have been interrupted or water lines damaged, allowing untreated water into the drinking water supply. In response, they have released a boil water or filtration advisory for any area that has been without power since the storm. Given that there are

still many homes without power, residents were also reminded not to light fires indoors due to the risk of carbon monoxide inhalation.

Bottled water immediately became the most in-demand commodity at shops and response centres and supplies are quickly being exhausted. This is only the latest item to add to the list of shortages: what gas stations were still operating are running dry and grocery shelves are growing bare. Cash donations to the Red Cross from neighbouring states have been generous but sourcing and distributing essential supplies takes time to coordinate. Material donations from charities in neighbouring states have too often been misguided, delivering materials like clothing or medical supplies that match the organization's mission rather than Lonsdale's needs.

Questions for discussion:
What is the problem/problems you're trying to solve?
What are your options?
What are your constraints?
What information will be required to make a decision?
How will you get this information?
What recommendations, if any, will you present to the Minister?

Situation clock: +24 hours
Workers at the fuel depot, with assistance from the Crowfoot-Hodgkins technical assistance teams, confirm that the source of the explosion was a temporary storage tank that had been holding commercial hexane. The tank became unmoored during the storm and ruptured when it settled sometime later, causing a significant leak under the waterline. The patients presenting with weakness and difficulty breathing suffered from acute hexane toxicity after exposure to this initial high concentration. Shifting winds allowed air to mix into the tank and once the mixture reached a certain fuel-oxygen ratio, scraping metal on metal at the rupture site was enough to cause the detonation caught on film. Low-level hexane exposure to hexane can cause headache and nausea and so as public health suspected contaminated drinking water may have been the source of those symptoms. Boiling or activated charcoal filtration would have eliminated the hexane as well as biological contaminants.

Questions for discussion:
How does knowledge of the underlying cause of the illnesses, explosion, and water issues change your approach to the problems? How does it change your messaging?
What long-term effects do you think the storm and its aftermath might have on Lonsdale, both internally and internationally?

Mentor Discussion guide (not for distribution to students)

Stakeholders from whose perspective the problem should/may be considered:
Governments of Lonsdale, Braggmark, and Crowfoot-Hodgkin
Municipal administration of Mocatta and Bernal
NGOs assisting in the emergency response
Affected population of Mocatta region
Affected industries (Yardley, fuel depot and others)
Media: national TV, radio, newspapers, social media
Emergency services in Lonsdale (hospitals, policing, fire, rescue)
Businesses and large organizations in Lonsdale (including stock market, tourist board etc.).

Ask, "Who *else* could be affected by this decision?"

Additional questions for consideration:

Expertise To what extent is a problem a technical/scientific issue or a social/political one? How can people with different expertise (especially sciences and social science/humanities) work together to solve problems? How do the different aspects of a problem constrain the possible solutions?

Leadership What is the role of leadership in managing uncertain situations? How does leadership operate at different levels (e.g. as a technician vs. advisor vs. Minister)?

Communication What is the role of traditional and social media? How can narratives impact the outcomes of "purely technical" problems?

Trust What is the role of trust? (trust in science, in government, in media, in partners, etc). How can trust be built or eroded in the scenario? How are the various stakeholders satisfying their own needs by their involvement?

Appendix C: Student surveys

CCE101 start of course survey

Please fill out this form so that we know your experience in this course type and what resources you have or don't have access to. This information will help us plan for the course.

"Remote course" = A normally in-person course that has been adapted to online platforms to ensure teaching continuity during extraordinary circumstances (e.g. COVID-19). As an emergency response, it is recognized that neither students nor instructors may be optimally equipped to attend to all remote course components.

"Online course" = A course carefully designed by a team of experts (e.g., course professor, instructional designer, graphic designer) intended from conception to be offered through online platforms. Professors and students who chose to teach and learn in this format are expected to be optimally equipped to attend to all online course components.

Please enter your RMC email address (preferred) or valid civilian email address.

* Indicates required question

Email*
Your email

Name*
Your answer

Student number*
Your answer

Alternate personal email (we will never use this information unless all other means of communication are disrupted)*
Your answer
I am currently living*

- in RMC barracks
- in Kingston, not at RMC
- in Ontario
- in Canada
- outside Canada

When did you last successfully complete a chemistry course?*

- Last year
- Two years ago
- More than two years ago
- Other:

Was that last chemistry course delivered:*

- Remote or online
- In person
- Hybrid of online and in-person components
- Other:

What is your experience writing in-person tests and exams? (In any course)*

- I have never written an in-person exam
- I have written in-person exams in the past year
- I have written in-person exams in high school but not in the past year
- Other:

Is there anything you'd like to tell us about working in an **classroom** environment and/or in this course? This could be your concerns, suggestions, etc.

Your answer

What is your experience taking remote or online courses?*

- I have never taken a remote or online course
- I have taken 1–3 remote or online courses
- I have taken >3 remote or online courses
- Other:

Is there anything you'd like to tell us about working in an **online** environment and/or in this course? This could be your concerns, suggestions, etc.
Your answer

Please select all the tools you expect to have available during the Fall term*

- A quiet place to work
- Home Internet access (good to excellent)
- Home Internet access (bad to moderate)
- Computer (laptop or desktop)
- Tablet (e.g. iPad)
- Webcam (built into computer/phone/tablet or separate)
- Printer
- Scanner
- Cell phone with working camera
- Scanner app (photo to PDF)
- Microsoft office (Excel, Word, Powerpoint) or equivalent
- Headset with microphone
- External microphone
- Access to Moodle
- Other:

Impressions of chemistry
The following questions seek your ideas and impressions of the roles of chemistry in society. Each question presents two opposing statements, with points between them. Please select the point that best represents your position between the two extremes. For example, if your opinion strongly aligns with the right-most statement, you should select a circle close to that side, but if your opinion is more neutral or ambiguous, you should select a circle closer to the centre.
These questions are optional, but your responses will help us improve the course for this year and in the future.

Overall, I believe that discovery and advances in chemistry...
Impair quality of life 1 2 3 4 5 6 7 Improve quality of life

Overall, I believe that discovery and advances in chemistry...

Impair health and well-being	1 2 3 4 5 6 7	Improve health and well-being

Overall, I believe that discovery and advances in chemistry...

Create environmental problems	1 2 3 4 5 6 7	Solve environmental problems

Overall, I believe that discovery and advances in chemistry...

Have no impact on my military career	1 2 3 4 5 6 7	Are critical to my military career

If you have any other comments or information you would like us to know before classes begin please enter it here:

Your answer

CCE101 end of course survey

On behalf of the entire CCE101 team of instructors, thank you all for a tremendous year!

We are committed to offering the best possible experience for all students, no matter what the next change might be, and as part of that effort we ask that you please complete the following survey openly and honestly. We are asking for your email for continuity and validation purposes: your identity will be anonymized and your email address erased.

Please enter your RMC email address (preferred) or valid civilian email address.

* Indicates required question

Email*

Your email

How effective were the following to assist your learning and retention of the material? *

	1 (not at all)	2	3	4	5 (highly)
Moodle lessons	O	O	O	O	O
Videos	O	O	O	O	O
Self-tests	O	O	O	O	O
Assignments	O	O	O	O	O
Lab assignments	O	O	O	O	O
Open question period (Tuesdays)	O	O	O	O	O

Tutorial session (Lab times)	O	O	O	O	O
Tutorial session (Fridays)	O	O	O	O	O
Assignment feedback	O	O	O	O	O

How effective were the following to encourage your engagement and desire to participate in the course?*

	1 (not at all)	2	3	4	5 (highly)
Moodle lessons	O	O	O	O	O
Videos	O	O	O	O	O
Self-tests	O	O	O	O	O
Assignments	O	O	O	O	O
Lab assignments	O	O	O	O	O
Open question period (Tuesdays)	O	O	O	O	O
Tutorial session (Lab times)	O	O	O	O	O
Tutorial session (Fridays)	O	O	O	O	O
Assignment feedback	O	O	O	O	O

How often did you...*

	Never	Once/ rarely	Sometimes	Often/ regularly	Always/ consistently
use scheduled class time to work on course material (outside of zoom calls)?	O	O	O	O	O
work on course material outside of scheduled class time?	O	O	O	O	O
read the feedback from TAs?	O	O	O	O	O
participate in informal group chats/peer support during the course?	O	O	O	O	O
did group chats help you learn the material?	O	O	O	O	O

did group chats encourage you to participate more in the course?	O	O	O	O	O
miss class due to circumstances beyond your control?	O	O	O	O	O
miss class due to circumstances within your control?	O	O	O	O	O
respond to a propted question	O	O	O	O	O
ask a question or offer an idea unprompted?	O	O	O	O	O

Indicate your agreement with the following statements for the WINTER TERM ONLY:*

	Disagree	Somewhat agree	Mostly agree	Fully agree

I covered all these topics in high school.	O	O	O	O
I remembered all these topics from high school.	O	O	O	O
The course content was too easy.	O	O	O	O
The course content was too difficult.	O	O	O	O
The pace of the course was too fast.	O	O	O	O
The pace of the course was too slow.	O	O	O	O

Do you feel you had enough access the course instructors for help?
Your answer

Would you feel comfortable asking the course instructors for help?
Your answer

What aspects worked particularly well in the course? (i.e. what should we CONTINUE doing)
Your answer

What aspects could have worked better? (i.e. what should be IMPROVED)
Your answer

What do you recommend that we START doing in the course to make it better next time?

Your answer

What aspects of the course did not work well and that we should STOP doing in the future?

Your answer

Impressions of chemistry

The following four questions seek your ideas and impressions of the roles of chemistry in society. Each question presents two opposing statements, with points between them. Please select the point that best represents your position between the two extremes. For example, if your opinion strongly aligns with the right-most statement, you should select a circle close to that side, but if your opinion is more neutral or ambiguous, you should select a circle closer to the centre.

These questions are optional but your responses will help us improve the course for this year and in the future.

Overall, I believe that discovery and advances in chemistry...

Impair quality of life	1 2 3 4 5 6 7	Improve quality of life

Overall, I believe that discovery and advances in chemistry...

Impair health and well-being	1 2 3 4 5 6 7	Improve health and well-being

Overall, I believe that discovery and advances in chemistry...

Create environmental problems	1 2 3 4 5 6 7	Solve environmental problems

Overall, I believe that discovery and advances in chemistry...

Have no impact on my military career	1 2 3 4 5 6 7	Are critical to my military career

Final thoughts

Lastly, if you have any advice you would like to share with future students or other ideas on any aspect of the course, please let us know. Thank you again and have a terrific summer!

What advice would you offer future students to help them succeed in the course?

Your answer

Is there anything else you'd like to share (e.g. suggestions, concerns, etc)?

Your answer