ScotChem Computational Chemistry Symposium

20th June 2024
University of St Andrews

Plenary speaker

Dr Cristina Trujillo
University of Manchester
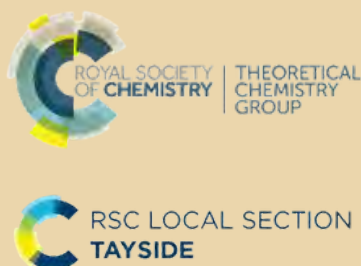
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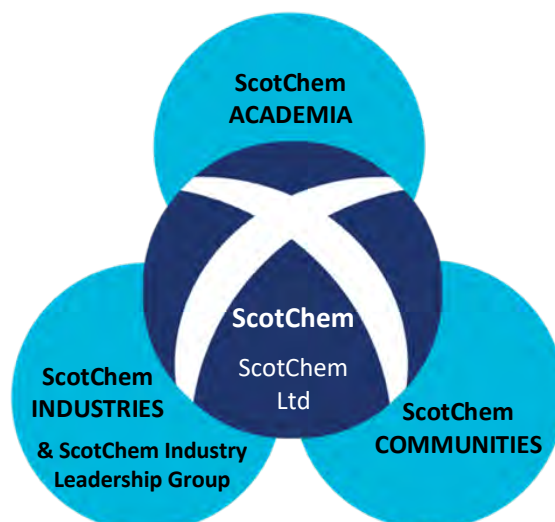
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ScotChem COMMUNITIES connects with individuals, schools and whole communities, nurturing a more meaningful, holistic relationship with the public and growing their trust in and support for the sector. The focus is on enabling access and equity from primary school to university, maximising inclusion in the chemical sciences and STEM subjects more broadly, at all stages of education journeys. ScotCHEM COMMUNITIES promotes the value of chemistry, chemistry research and the chemical industries to the public and ensures that all citizens benefit from the strength and growth of Scotland's chemistry research and industry sectors.

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The **Theoretical Chemistry Group** is one of the RSC's Interest Groups. The aims of the group are to promote the interests of theoretical and computational chemists and ensure that the interests of its members are adequately represented in the activities of the RSC and other bodies.

RSC members can join the Theoretical Chemistry Group by updating their details in the "My communities and subscriptions" tab of the online RSC membership area.

Upcoming event

Theoretical Chemistry Group Graduate Student Meeting 2024

13 September 2024

University of Warwick

The Theoretical Chemistry Group Graduate Student Meeting is an early career event that showcases the work of graduate students in computational and theoretical chemistry.

It will take place at the University of Warwick on Friday, September 13th, 2024, in the afternoon, directly following the 7th Computational Molecular Science (CMS) meeting.

Registration for the Graduate Student meeting is free.

Contributions of talks and posters by graduate students are encouraged. Non-presenters and all interested are most welcome to register as well.
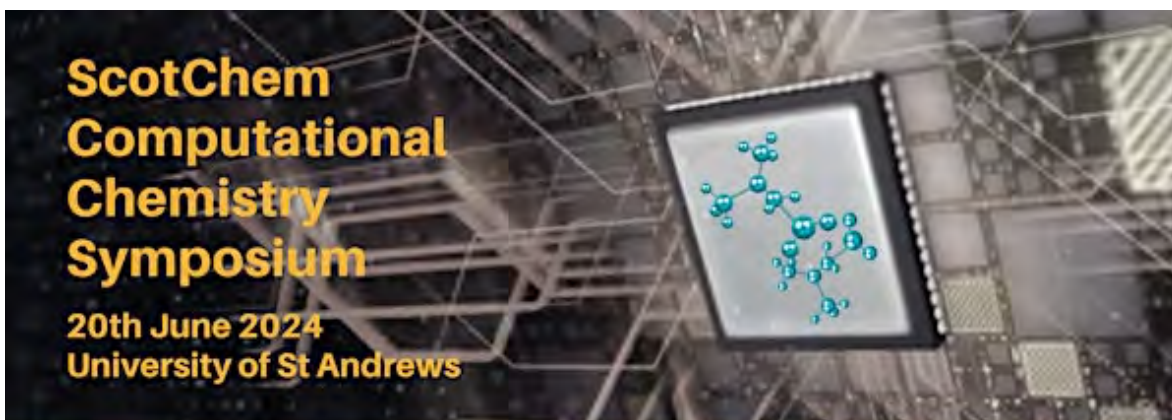
Titles and abstracts (for talks) should be submitted by 15 July 2024. Oral presenters will have their travel expenses reimbursed.

Please submit your abstract and register by July 15th at the following link:

warwick.ac.uk/fac/sci/chemistry/chemevents/events/cms2024/abstract-gsm/

Welcome to the

ScotChem Computational Chemistry Symposium 2024

Since the dawn of ScotChem as the strategic alliance for chemical sciences in Scotland, the annual Computational Chemistry Symposia under its auspices have been prominent events to showcase the multifaceted activities in this field around Scotland. The first of the series was held in 2007 in St Andrews, and the symposia have been rotating around the institutions of the founding members ever since (see https://www.scotchem.ac.uk/computational-chemistry-symposia).

The symposia are one-day events (occasionally broadened by dedicated workshop activities) consisting of invited plenary lectures and contributed talks, as well as a poster session from all areas of Computational Chemistry. They provide a platform for PhD students, postdoctoral researchers and newly appointed academics in the field to present their own research, get inspired by the work of others and for networking.

As with previous meetings, attendance is free, thanks to generous sponsorship by:

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Organising Committee

School of Chemistry St Andrews

Michael Bühl
Herbert Früchtl
Stuart Macgregor
John Mitchell
Tanja van Mourik

ScotChem

Suzanne Halden
Alan Wiles

Directions

St Andrews can be reached by car (free parking indicated on the map below) and by public transport via bus (https://www.travelinescotland.com/). There are frequent bus connections from Leuchars railway station (journey approx. 10-12 minutes; buses every 5-10 minutes).

The Chemistry (Purdie) Building is located on the North Haugh at the western entrance to the town. **Lectures will take place in Purdie Lecture Theatre B** (on level 2, the main entrance level; LT B exits also to level 1), coffee, lunch will be served, and **the poster session will take place in the Common Room** on level 1.

Map of the North Haugh Campus

ScotChem Computational Chemistry Symposium 2024 Programme

Thursday 20 June 2024, Purdie Lecture Theatre B	
9:30 - 1020	Registration
10:25	Welcome and announcements – *Michael Büehl*
Session I - Chair: John B. O. Mitchell	
10:30	*L1:* **Carlos Martin Fernandez** (University of St Andrews) *Energy decompositions of ion-pair interactions: how important is dispersion for the stability of σ-alkane complexes?*
10:55	*L2:* **Alexander van Teijlingen** (University of Strathclyde) *Protein controlled biomineralization for enamel regeneration*
11:20	*L3:* **Alex De Matos Loja** (Heriot-Watt University) *Carbonyl Sulfide following electron ionisation: excited state potential energy surfaces of OCS^+ and OCS^{2+}*
11:45	*L4:* **Ambre Carpentier** (Heriot-Watt University) *Computational Modelling of Ruthenium Catalysed C–H Alkylation of Heteroarenes*
12:10	**BioAscent** presentation
12:20 – 13:30	Lunch (Common Room)
Session II - Chair: Tanja van Mourik	
13:30	*L5:* **Cate Anstöter** (University of Edinburgh) *Developing a computational toolkit: from anions to aromaticity*
13:55	*L6:* **Joelle Mergola-Greef** (University of Aberdeen) *Heavy-atom modulation of electronic and optical properties in 1-dimensional oligomeric derivatives of Telomestatin*
14:20	*L7:* **Nicholas Johnson** (University of Aberdeen) *Design of cyclic peptide inhibitors to SARS-CoV-2 spike interaction with GRP78*
14:45	Coffee/tea
Session III - Chair: Stuart Macgregor	
15:15	*L8:* **Rochelle Ferns** (University of St Andrews) *Exploring addition reactions of magnesium(I) complexes using Density Functional Theory*
15:40	*L9:* **Ivan Yankov** (University of Strathclyde) *A multitask model for predicting the thermal stability of double stranded nucleic acid*
16:05	*PL10:* Plenary lecture: **Cristina Trujillo** (University of Manchester) *Computationally-led Catalyst Design*
16:40-18:00	Poster session (Common Room)

Lecture Abstracts

Energy decompositions of ion-pair interactions: how important is dispersion for the stability of σ-alkane complexes?

C. Martín-Fernández,* M. A. Sajjad and S. A. Macgregor

School of Chemistry, University of St Andrews, St Andrews, Scotland, U.K.

London dispersion, despite being a lot weaker than other interaction forces, has been increasingly recognized, in the past decade or so, as a key player in the stability of many chemical systems.[1] However, its accurate quantification is not always straightforward, especially when other forces (electrostatics, polarization) can be more important. Our previous work on σ-alkane cationic complexes in the crystalline solid state hinted at the important stabilization brought by the anionic environment, and while the interactions between these ion-pairs are largely Coulombic, London dispersion can be an additionally relevant stabilizing component.[2,3]

In order to analyse these observations further, we have compared the local energy decomposition analysis (LED) based on DLPNO-CCSD(T)[4] with the quantification of dispersion *via* simple pairwise additive corrections (e.g. D3, XDM) and a more detailed partition of the interaction using EDA-NCI,[5] a density-based partition that provides SAPT-quality results. Due to the large size of the systems, together with the large computational cost of the DLPNO-CCSD(T) calculations, extensive calculations have been carried out in model systems to ensure the robustness of our computational approach. Furthermore, comparison with computationally cost-effective approaches like EDA-NCI can prove useful to extend our protocol to other systems.

We have found that around 65-70% of the interaction energy for the studied ion-pairs is already well described at the Hartree-Fock level, since it accounts for most of the electrostatic interaction arising from the charge separation. Interestingly, over 90% of the remaining correlation interaction energy corresponds to London dispersion, highlighting its importance as a stabilizing factor in these systems. Additional insight into the interactions is obtained from Dispersion Interaction Density (DID) plots, which we can compare to our previous Independent Gradient Model (IGM) results.[3] Overall, there is a good correlation between the dispersion-corrected DFT and DLPNO-CCSD(T) results, but the dispersion correction on its own is not necessarily an accurate measure of the absolute dispersion contribution.

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Protein controlled biomineralization for enamel regeneration

Alexander van Teijlingen

University of Strathclyde

Traditional enamel repair methods focus on precipitating mineral deposits onto teeth without replicating the nanoscale architecture or functionality of healthy enamel. Our bioinspired approach addresses these limitations, avoiding mechanical property deficiencies and toxic chemicals.

Here, we engineered an elastin-like recombinamer based supramolecular matrix that imitates the structure and function of the enamel-developing matrix. This matrix can trigger epitaxial growth of apatite nanocrystals, recreating the microarchitecture of enamel and restoring its mechanical properties.

To this end, we perform multiscale simulations of this protein system from all-atomic crystal face binding studies to protofilament *via* protein self-assembly in the presence of Ca^{2+} ions to the formation of the supramolecular fibrals. Additionally, we explore membrane formation through protein cross-linking, enabling nucleation and growth of enamel with controllable morphology.

Our approach emulates the amelogenin matrix, facilitating the transition from intrinsically disordered proteins to beta-sheet-rich forms and promoting the epitaxial growth of mineralized layers on eroded teeth.

Carbonyl Sulfide following electron ionisation: excited state potential energy surfaces of OCS$^+$ and OCS^{2+}.

Alex De Matos Loja

Heriot-Watt University

Electron ionisation methods have been employed on gas-phase carbonyl sulfide (OCS) for the purpose of understanding atmospheric processes where high-energy electron collisions are prevalent.[1] In order to interpret experimental results, high accuracy potential energy surfaces (PES) are required. For the cation and dication species, which are the product ions observed experimentally, there are few previously published PESs and generally these are limited in scope[2-5].

We present excited state potential energy surfaces along the bond breaking degrees of freedom for both the cation and dication species of OCS in multiple spin states using the equation-of-motion coupled cluster (EOM-CCSD) method. The opposing bond length has been fixed along the PES cuts to that of the neutral OCS equilibrium length. T1 diagnostic for all points has also been calculated and comparisons drawn with results using multiconfigurational methods to discuss the suitability of the method used. The main purpose of the surfaces was to understand the channels which lead to the dominant fragments seen experimentally.

References:

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Computational Modelling of Ruthenium Catalysed C–H Alkylation of Heteroarenes

Ambre Carpentier[1], Igor Larrosa[2] and Stuart A. Macgregor[2]

[1]Institute of Chemical Sciences, Heriot-Watt University, Edinburgh, EH14 4AS, U.K.
[2]School of Chemistry, University of Manchester, Manchester M13 9PL
[2]EaStCHEM, School of Chemistry, University of St Andrews, St Andrews

Ruthenium-based catalysts featuring the *p*-cymene ligand have been used to promote C–H alkylation of arenes and heteroarenes, although requiring elevated temperatures.[1,2] Recently, the Larrosa group has developed a highly active Ru(II) catalyst (**Int1**) that is proposed to react through a bis-cyclometallated intermediate, (**Int2**).[3,4] This species is thought to be sufficiently electron-rich to perform alkyl halide oxidative addition at a Ru(II) metal centre at room temperature (**Int2 → Int3**).

Here we present a mechanistic study using density functional theory calculations on the C–H alkylation of heteroarenes using this system. This allowed us to identify, after cyclometallation, the oxidative addition mechanism of primary, secondary and tertiary alkyl halides by comparing possible concerted, S_N2 and radical pathways, followed by either reductive elimination or deprotonation / rearomatisation.
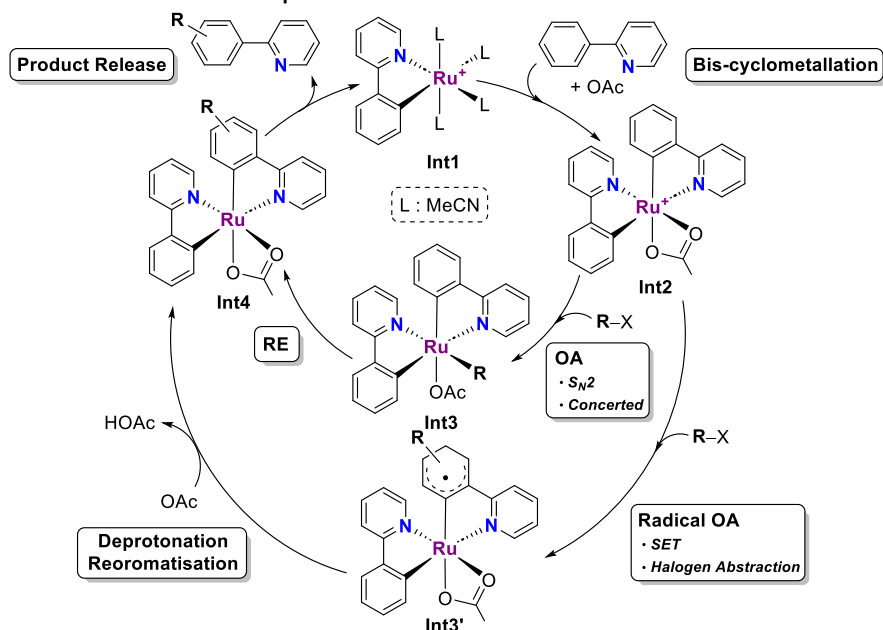
Figure 1: Possible mechanisms for the Ru-catalysed alkylation of 2-ppy with alkyl halides.

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Developing a computational toolkit: from anions to aromaticity

Cate Anstöter

University of Edinburgh

This talk explores the application of electronic structure methods to electron dominated phenomena, focussing on anions and aromatic systems. Both anions and aromaticity are ubiquitous throughout life, and yet remain poorly understood.

Anions still represent a challenge for conventional electronic structure methods and experimental investigations. Gaining an understanding of the intrinsic structure and dynamics of these underexplored species requires novel applications of quantum chemistry, which will be illustrated alongside complementary experimental investigations.

Aromaticity provides different challenges, with a robust definition still a highly contentious quest. This talk will demonstrate how using a spectroscopic ring-current model can provide new rational design principles for novel redox active aromatic materials.

Heavy-atom modulation of electronic and optical properties in 1-dimensional oligomeric derivatives of Telomestatin

Joëlle Mérgola-Greef[1] and Bruce F. Milne[1]

1. Marine Biodiscovery Centre, Department of Chemistry, University of Aberdeen

Real-space self-interaction corrected (time-dependent) density functional theory has been used to investigate the ground-state electronic structure and optical absorption profiles of a series of linear oligomers (with n = 1-10) inspired by the macrocyclic natural product Telomestatin.[1] In this study, the scope has been expanded from oligomers containing oxygen to those incorporating heavier atoms such as sulphur, selenium, and tellurium (Figure 1).
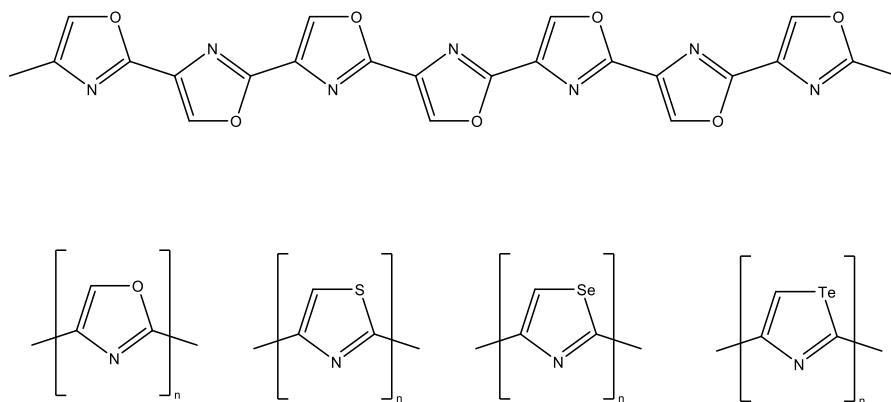

Figure 1. Linear all-trans model based on Telomestatin (top) and general schematic of the methyl-capped linear oligomers studied in this work (bottom).

The inclusion of these heavier atoms significantly impacts the electronic properties and absorption characteristics of the oligomers. These modifications allow for a broader investigation into the tunability of the properties of the materials, providing insights into how different atomic substitutions can influence the overall behaviour of the oligomers. Length-dependent development of plasmonic excitations in the UV region is seen in the neutral species which is augmented by polaron-type absorption in the IR when the chains are doped with an additional electron/hole. Combined with the tuneable absorption in the visible region this suggests these oligomers as good candidates for applications such as transparent antennae in dye-sensitised solar energy collection materials.

References

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Design of cyclic peptide inhibitors to SARS-CoV-2 spike interaction with GRP78

Nicholas Johnson

University of Aberdeen

The Covid-19 pandemic has caused huge disruption over the last four years. Vaccines have had a significant impact on the number and severity of cases, yet the number of deaths has now risen to over 7 million and the total number of confirmed cases continues to rise. New broad-spectrum antivirals are, thus, very much needed to combat the threat of new variants of the virus. Glucose Regulating Protein 78 (GRP78) is a molecular chaperone that typically resides within the endoplasmic reticulum but when cells are under stress it is over-expressed and can be translocated to the cell surface. Molecular docking studies have found that a loop structure within the SARS-CoV-2 spike protein's receptor binding domain (RBD) had favourable binding affinities with cell surface GRP78, suggesting another route for the viral entry into the cells. In this work, we have designed, using an ensemble docking approach, cyclic peptides derived from the loop structure of the SARS-CoV-2 spike protein from both the Wild-type and Omicron variants. Experimentally, both peptides were synthesised and found to be able to bind to GRP78, with the Omicron variant showing slower dissociation from the target protein. This result was consistent with the greater transmissibility of the Omicron variant. Our results open the door for further development of these motifs, paving the way to novel anti-SARS-CoV-2 drugs.

Exploring addition reactions of magnesium(I) complexes using Density Functional Theory

Rochelle Ferns[a], Andreas Stasch[a], Tanja van Mourik[a]

[a]School of Chemistry, University of St Andrews

Main group compounds are the most abundant elements in the earth's crust. They are less toxic as well as less expensive than transition elements and can function as excellent catalyst.[1-5] This study uses Density Functional Theory to study addition reactions of magnesium(I) compounds. Mg(I) compounds have good thermal stability, they are soluble in apolar solvents and act as safe and highly selective reducing agents. Two sets of reactions will be discussed. The first between hydrogen and [{(^{iPrDip}NacNac)Mg}$_2$(μ-O)], where Dip = 2,6-iPr$_2$-C$_6$H$_5$ and the second between diphenylacetylene and [(^{Dep}nacnacMg)$_2$] (nacnac=HC(MeCNAr)$_2$ Dep=C$_6$H$_3$Et$_2$-2,6). Both the systems have first been studied using cut back models and then the study has been replicated using full models. We will focus on the study of the reaction pathway, solvent effect, and effect of bulky groups on the ligands.
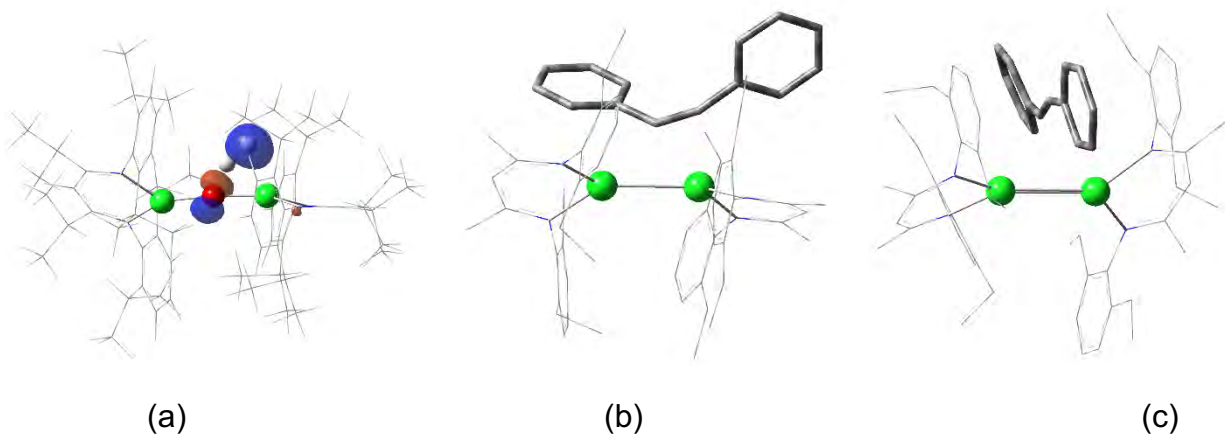
(a)   (b)   (c)

Figure: (a) HOMO for the transition state in the reaction of H$_2$ with [{(^{iPrDip}NacNac)Mg}$_2$(μ-O)], orientation of the diphenylacetylene group parallel (b) and antiparallel (c) to the Mg dimer in the reaction between diphenylacetylene and [(^{Dep}nacnacMg)$_2$] resulting in the formation of different isomers.

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A multitask model for predicting the thermal stability of double stranded nucleic acid

Ivan Y. Yankov, Prof Glenn Burley and Dr David Palmer

Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow, UK

Oligonucleotides have applications in targeted therapy, biosensor technology, molecular biology, and biotechnology.[1] Their design is governed by careful consideration of the thermodynamic properties and melting temperature which describe the thermal stability of oligonucleotides. Machine learning models are fast, accurate and simple to use alternatives to physics-based simulation techniques which have a high barrier to entry due to domain expertise to carefully select simulation parameters.

The aim of this work is to design an AI system that can simultaneously predict reported thermodynamic properties and melting temperature which informs the design of oligonucleotides.

We propose a multitask machine learning model to predict thermodynamic properties - enthalpy (ΔH), entropy (ΔS), and Gibbs free energy change (ΔG), and melting temperature (T_m) from an input sequence of an oligonucleotide. [2]

The multitask model predictions on native fully complementary duplexes of oligodeoxyribonucleotides in Monte Carlo sampling cross-validation achieve a coefficient of determination of [0.97, 0.95, 0.94 and 0.92] and root mean squared error of [0.64 kcal·mol^{-1}, 4.86 kcal·mol^{-1} and 4.56 kcal·mol^{-1}] and [3.82 ºC] for ΔG, ΔH, $T\Delta S$ and T_m, respectively. The results are benchmarked against the widely accepted modelling approaches in the field such as the nearest neighbor model and molecular dynamic simulations.[3,4] The impact of sequence engineered features, model architecture and hyper parameters are discussed.

The multitask model provides a unified approach to predicting the thermal stability of oligodeoxyribonucleotides. Analysis of engineered features and model architecture, reveal useful encoding insights about future work with chemically modified nucleotides, RNA and DNA-ligand complexes.

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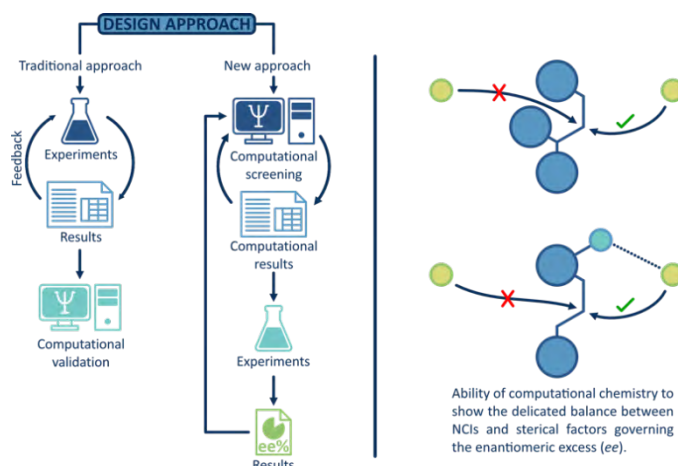
Computationally-led Catalyst Design

Cristina Trujillo

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Organocatalysis remains one of the most challenging topics in contemporary organic chemistry. While the organocatalysis fields is currently growing exponentially, an understanding of the mechanistic details involved in most of these reactions has often lagged far behind the pace of catalyst development, which retards catalyst design.

However, over the last two decades, computational methods have become a cost-effective treatment of large chemical systems with reasonable accuracy to provide a rationale for the experimental outcome. In this talk, different works on the in silico design of catalysts will be presented. The delicate balance between steric and attractive Non-Covalent Interactions (NCIs), as the main controlling factors, in organocatalysis will be examined.

Ability of computational chemistry to show the delicated balance between NCIs and sterical factors governing the enantiomeric excess (*ee*).

Keywords: *computational chemistry, organocatalysis, noncovalent interactions*

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List of Posters

Poster no.	Title	Presenter
P1	Virtual high throughput screening (vHTS) approach to identify novel binders for designing oral PROTACs	S. Chakraborti (University of Dundee)
P2	Propane: A Comparison of Selected Configuration Interaction Approaches	A. W. Prentice (Heriot-Watt University)
P3	Neural Network Potentials for pK_a Prediction	R. J. Urquhart (University of Strathclyde)
P4	Computational Modelling of Organocatalysis	A. S. Goodfellow (University of St Andrews)
P5	Computational Study of Methane Activation at an Iridium Cyclometallated PONOP Complex in the Solid State	Daniel Storm (University of St Andrews)
P6	Development of Solvation-Based Molecular Descriptors for Retention Time Predictions	M. Taylor (University of Strathclyde)
P7	Insights into Na insertion in organic carboxylate anodes using solid-state NMR spectroscopy and DFT calculations	H. S. Seleghini (University of St Andrews)
P8	Designing Artificial Metalloenzymes using Computational Approaches	I. Tolu (University of Strathclyde)
P9	Computational Study on Self-Assembled Monolayers on an Ag Surface	L. P. Muthaiah (University of St Andrews)
P10	Insights from DFT modelling into the catalytic activity of a manganese-pincer complex towards a range of organic substrates	Aniekan E. Owen (University of St Andrews)
P11	SERS Activity of Pyridine on Different Single Atom Sites on a Gold Slab	A. Singh (University of Strathclyde)
P12	Enhancing IDP Conformational Ensemble Analysis Through Torsional Clustering	M. Mattia (University of Edinburgh)
P13	A Protocol Language for Automated Peptide Chemistry	N. Morris (University of Glasgow)
P14	In Search of Enzyme Activation: A Computational Workflow for Evaluating Allosteric Drug Candidates	Frederick G. Powell (Heriot-Watt University)

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| Poster no.	Title	Presenter
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P16	Arabinoxylan Polymer Flexibility and Interactions with GLYCAM06j and CHARMM36m	Peter Starrs (University of St Andrews)
P17	Molecular Modelling to Study a Marine Viral Halogenase	B. A. J. Connaughton (University of St Andrews)
P18	Mechanistic Insights into Phosphirenium Ions as Masked Sources for Divalent Phosphenium Cations in Lewis Acid Catalysis	Patrick McClenaghan (University of St Andrews)

Poster Abstracts

Virtual high throughput screening (vHTS) approach to identify novel binders for designing oral PROTACs

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Strategic combination of the components in a PROTAC (target ligand, E3 ligase ligand and the linker) is crucial to achieve the desired physicochemical properties for oral bioavailability, which is challenging as PROTACs generally fall outside Rule-of-five (Ro5) space. In this work, we virtually screened ~7×10^6 diverse compounds to identify easily synthesisable (1-2 steps) novel chemical scaffolds with favourable properties for developing oral PROTACs. Our vHTS approach involved three independent workflows combining ligand-based (shape- and pharmacophore-centric) and structure-based (molecular docking) techniques. Interaction fingerprint of known binders with the target protein was leveraged to minimize potential false positives. A subset of the filtered hits
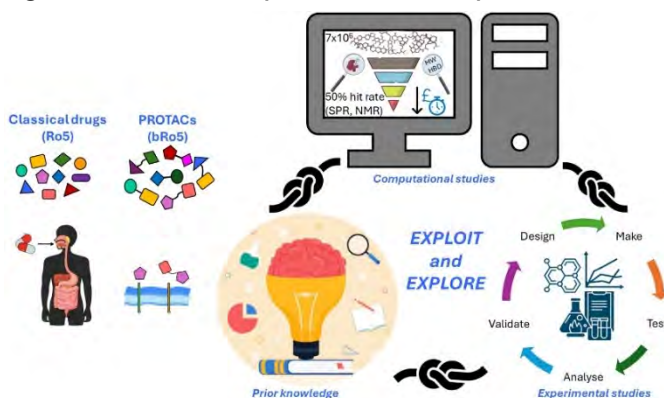
from each workflow was carefully selected for testing by visual inspection of docked poses, assessment of exit vector for linker attachment, novelty and sociability of the scaffolds, and physicochemical properties (like HBD, MW) influenced from our experiences and reported studies[1,2].

We tested 38 of the virtual hit compounds in orthogonal biophysical assays, SPR and NMR. SPR results show that 10.5% of these compounds bind to the protein with good ligand efficiency and Kd between 20µM and 100µM. 39.5% of the compounds are weak binders (Kd >100µM). These hits were confirmed to bind at the desired site by ^{19}F-reporter displacement NMR experiments. Currently, we aim to understand the structure-activity relationship (SAR) of the best hits through rigorous Design-Make-Test-Analyse (DMTA) cycles. These efforts are computationally guided and have already led to more potent analogues. Promising new binders will be developed into PROTACs and taken forward based on cellular degradation assay outcomes.

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Propane: A Comparison of Selected Configuration Interaction Approaches

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Selected configuration interaction (SCI) aims to take advantage of the sparsity of the full configuration interaction (FCI) Hamiltonian by iteratively building up a variational wave function via a method-dependent selection protocol, allowing the generation of compact, yet highly accurate, approximate wave functions when compared to FCI. Many different flavours of SCI algorithms exist, such as energy-, coefficient-, integral- or error-driven approaches.[1-5] Additionally, the way they explore the first-order interacting space may be purely deterministic or stochastic in nature.

In light of the recently proposed FCI energy of propane,[6] which corresponds to a FCI space of 26 electrons dispersed across 23 orbitals and contains over 1 trillion determinants in C_1 symmetry, the applicability of different SCI methods and implementations were compared with one another, building upon the work done by Loos et al.[7] The methods were compared not only by the energy difference with respect to FCI but also by the size of the variational wavefunction. In addition, the bond breaking potential energy surface was investigated allowing the dissociation energy to be approximated. In conjunction with previous work,[8] the error-driven selection protocol appears to generate the most compact approximate wave functions, reaching chemical accuracy despite only containing 33,000 SDs in the canonical Hartree-Fock molecular orbital basis.

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Neural Network Potentials for pK$_a$ Prediction

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Measurement of acidity/basicity (pK$_a$) is crucial to many disciplines of chemistry including pharmacology, drug discovery and theoretical chemistry. Traditionally, methods like titration, NMR and spectroscopy are used, but they are costly and time consuming. Theoretical techniques such as DFT and recently machine learning (ML) is increasingly being used to predict pKa values much faster and at lower cost.

Machine learning potentials blend empirical and high-level methods like DFT, offering a balance between computational speed and accuracy. Specifically, neural network potentials (NNPs) excel in converting molecular structures into Potential Energy Surfaces for swift and precise energy forecasts. ANAKIN-ME (ANI),[1] a leading NNP, achieves sub-kcal/mol precision on test datasets and was the first NNP to show transferability to systems beyond its initial training.

We show for the first time that ANI-architecture NNPs can be extended to different phases and charge states which we use to calculate the pKa of imidazole's with a pK$_a$ range of 22-34. Using thermodynamic cycles to calculate the free energy change of the aqueous phase requires different models to work in tandem with each other to perform the calculation, a process that is very sensitive to minor changes in energy, which has led to traditionally high errors in pK$_a$ calculation. Twinned with low-energy conformer searches *via* CREST,[2] our method allows for molecules to be modelled beyond the global minima, providing a more realistic model of the molecules in solution and, which gives a higher prediction accuracy of pK$_a$ with a RMSE value of 2.02 pK$_a$ units.

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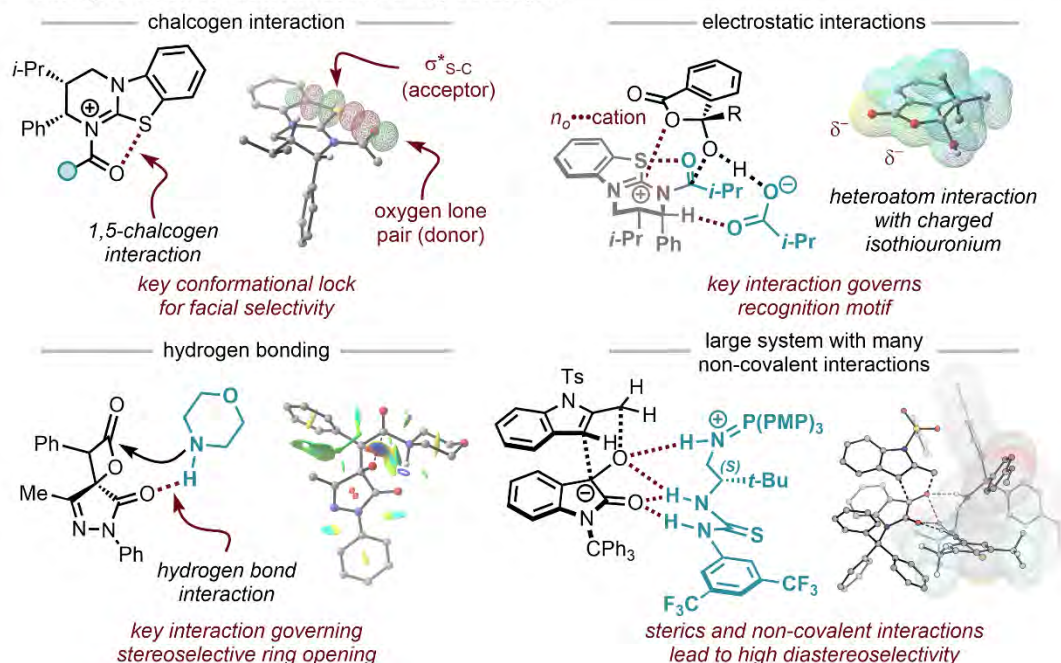
Computational Modelling of Organocatalysis

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Non-covalent interactions are widely prevalent throughout catalysis and encompass a wide range of interactions, such as hydrogen bonding, chalcogen, sigma-hole and dispersive interactions. These govern reaction outcomes and are crucial towards stereoselective reactions. Computationally, organocatalysis can be challenging to explore due to the trend towards large systems and the conformational flexibility that this can afford, alongside subtle energetic differences in the stereodetermining transition states. DFT becomes very expensive for some systems due to size, number of conformations to consider or both. This work will discuss approaches towards modelling systems dominated by key non-covalent interactions in the context of reactivity from the Smith group.[1-4]

Examples of non-covalent interactions in organocatalysis

chalcogen interaction

σ*$_{S-C}$ (acceptor)

oxygen lone pair (donor)

1,5-chalcogen interaction

key conformational lock for facial selectivity

electrostatic interactions

n_o•••cation

heteroatom interaction with charged isothiouronium

key interaction governs recognition motif

hydrogen bonding

hydrogen bond interaction

key interaction governing stereoselective ring opening

large system with many non-covalent interactions

sterics and non-covalent interactions lead to high diastereoselectivity

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Computational Study of Methane Activation at an Iridium Cyclometallated PONOP Complex in the Solid State

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Metal complexes with supporting pincer ligands have been used extensively in the study of hydrocarbon C-H bond activation in solution.[1] In 2009 the first example of a σ-methane complex in solution was characterised spectroscopically at a neutral Rh-PONOP complex.[2] An alternative approach to study σ-alkane complexes is through Solid-state Molecular OrganoMetallic (SMOM) Chemistry developed by the Weller group.[3] A recent example involves methane activation at the cyclometallated iridium PONOP complex, **1⁺** that has been characterised directly in the solid state (Figure 1).
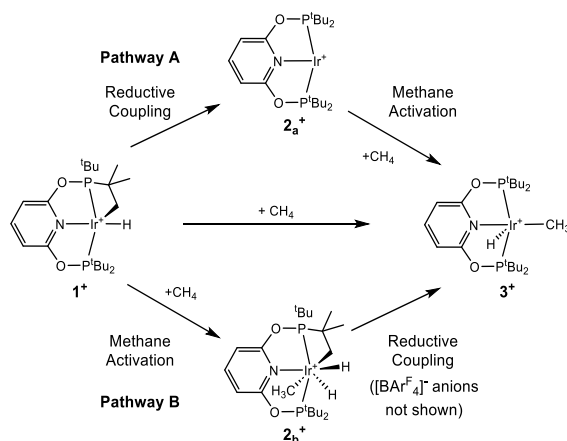

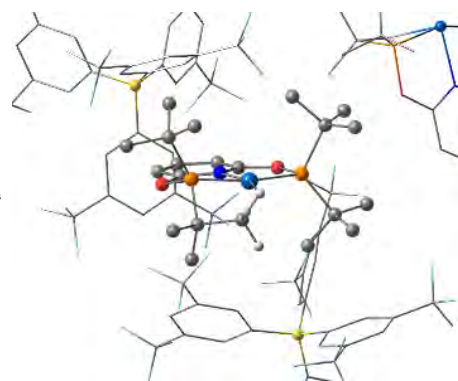**Figure 1:** Possible pathways for the addition of methane to cyclometallated iridium PONOP complex **1⁺**

Figure 2: Computed structure of **TS(1⁺-2ₐ⁺)** along **Pathway A**. Non-participating H atom are omitted for clarity

This poster will describe the results of periodic density functional theory investigating this methane activation process. **Pathway A** involves rate-limiting C-H reductive coupling via **TS(1⁺-2ₐ⁺)** (Figure 2) to form 14e⁻ [Ir(PONOP)]⁺ (**2ₐ⁺**), followed by methane activation to obtain [Ir(PONOP)(H)Me]⁺ (**3⁺**). Alternative mechanisms all involve initial CH_4 addition followed by C-H bond formation at the cyclometallated arm. The most accessible (**Pathway B**) involves an Ir(V) intermediate (**2ᵦ⁺**). **Pathway A** is computed to be the most stable with an overall barrier of 31.1 kcal/mol. This work will compare these different reaction mechanisms in both the solid-state and in the gas-phase.

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Development of Solvation-Based Molecular Descriptors for Retention Time Predictions

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QSRR models are widely used in the pharmaceutical industry to help identify unknown compounds in HPLC screening experiments[1]. These models rely on high quality, relevant descriptors. Traditional descriptors are focused on solute features, but chromatographic retention is a phenomenon defined by solvation and partition interactions. Therefore, new molecular descriptors are developed that describe solvation structure around a solute using the reference interaction site model (RISM). The usefulness of these descriptors has been proven previously for predictions of hydration free energy[2]. Novel solvation descriptors, bespoke to chromatography, have been developed and validated using 6 HPLC retention time datasets, with different chromatographic conditions, provided by Pfizer. Various methods of accounting for the chemical environment of the columns have been tested, including modelling the chromatographic solvents, mobile phase additives and solute charge. 1D RISM equations were solved for the analyte molecules in various systems with pyRISM solver software[3]. The Kovalenko-Hirata solvation free energy density functional was used to derive molecular descriptors. Compared to a benchmark using Mordred[4] descriptors, the addition of novel solvation descriptors improved retention time (RT) predictions. An example is shown in figure 1A and 1B. RMSE was reduced and R^2 was increased by the addition of RISM descriptors for solutes in water. A small but consistent improvement in predictive accuracy was achieved for all 6 datasets (figure 1C) by incorporating descriptors for solvation in either water or organic solvent. Together, the descriptors display synergy which suggests that the information provided by RISM descriptors is complementary to that provided by the standard 2D descriptors.
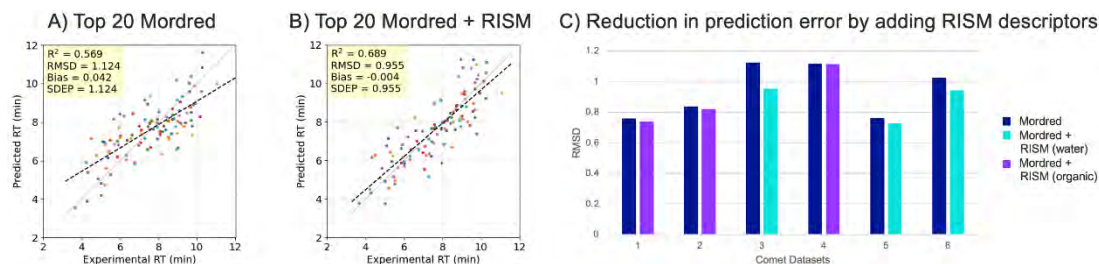

Figure 2: Predicted vs Experimental RT for a PLS model using A) Mordred descriptors and B) Mordred descriptors plus RISM descriptors. Bar chart C) compares Mordred benchmarks to models with addition of RISM descriptors. Models with water solvation descriptors are shown in blue and organic solvation descriptors in purple. Reported results for datasets 3, 5 and 6 are PLS models and results for datasets 1, 2, and 4 are random forest regression models.

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Insights into Na insertion in organic carboxylate anodes using solid-state NMR spectroscopy and DFT calculations

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The growing demand and cost increase of lithium-ion batteries (LIBs) has prompted intense research on the development of similar technologies based on more abundant and cheaper elements, with one of the alternatives being the use of Na as a replacement for Li.[1] Many of the materials used in LIBs are not suitable for sodium-ion batteries (NIBs), posing a particularly significant problem for anode materials, as Na intercalation is often unfavourable and materials can suffer from significant volume changes and mechanical stress as a result.[1] One class of possible anode materials for NIBs are conjugated carboxylate-based coordination compounds, which do not exhibit large volume changes or significant modifications to the long-range structure upon Na intercalation.[1,2]

Aiming to understand the Na insertion, together with the structural changes resulting from multiple charge and discharge cycles of the sodium benzenedicarboxylate (Na_2BDC) NIB anode, an *ex-situ* study of the electrochemical charging and discharging process has been performed. This has been combined with a study of the chemically sodiated anode material synthesised using a radical mediator. This work was carried out using multinuclear and multidimensional solid-state NMR spectroscopy, alongside *ab initio* random structure searching (AIRSS) and DFT calculations to help understand the structural changes taking place. From such techniques, it was possible to study the dynamic of sodium ions in the material, the identification of different sodiated polymorphs, and the structural changes caused by the insertion and removal of sodium upon cycling on the Na_2BDC anode.
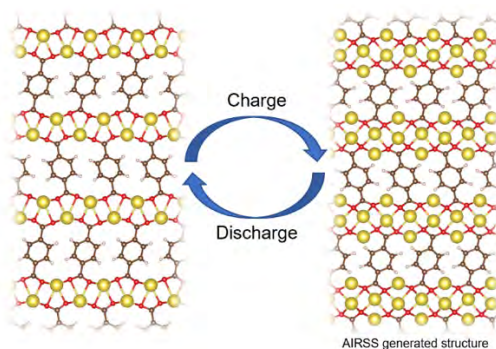

Figure 1. Schematic showing the sodiation process in sodium benzenedicarboxylate, with the sodiated structure generated using *ab initio* random structure search (AIRSS).

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Designing Artificial Metalloenzymes using Computational Approaches

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Artificial Metalloenzymes are biocatalysts that can be designed and optimised for new-to-nature reactions. They provide the usage of broad range of substrates, different types of reactions with improved catalytic activity and compatibility with in vivo systems. Multidrug resistance regulator protein LmrR is a dimeric transcription factor which has a hydrophobic binding pocket between its dimers. The residues around this pocket are important for different features like providing dimer stability and binding to hydrophobic substances by π-stacking. Even though this protein lacks natural catalytic activity, it is involved in comprehensive studies in enzyme design due to its unique structure and evolvability[1-3].
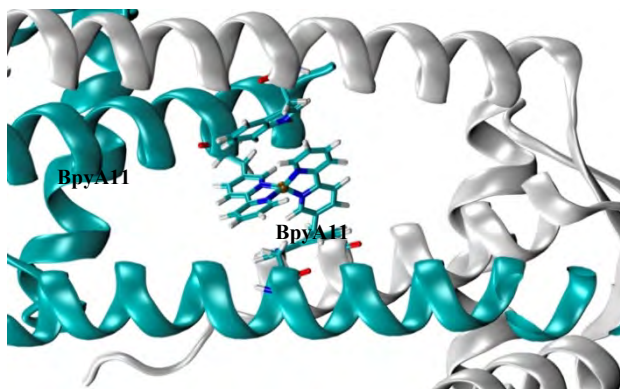
Here we incorporated a non-canonical amino acid, bipyridine alanine (BpyA), into A11 position in both dimers. Cobalt (II) is coordinated to the BpyA residues to catalyse atom transfer radical cyclisation (ATRC) reactions. These reactions are useful for synthesising functional 4-10 membered ring systems. Since the 3D structure of this complex is not known, our study demonstrates the structural difference between the WT LmrR and Cobalt containing biocatalyst LmrR by molecular dynamic studies. The MD simulations show that the presence of the Cobalt (II) bipyridine complex decreases the volume of hydrophobic pocket of the protein. Further MD and QM/MM studies will be undertaken to explore the ATRC reaction to optimise the catalytic activity of this engineered enzyme.

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Computational Study on Self-Assembled Monolayers on an Ag Surface

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In this project, periodic DFT calculations were carried out on self-assembled monolayers consisting of [1,1'-biphenyl]-2,2',4,6,6'-pentacarboxylic acid (BPPCA) on an Ag surface using VASP. Self-assembled monolayers (SAMs) (picture 1) are molecular layers adsorbed (chemisorbed or physisorbed) on a surface. They have unique surface properties and various applications in fields such as surface chemistry, biosensors, electronics, and nanotechnology. The two phenyl rings of BPPCA are found to be oriented perpendicular to each other with two COOH groups in the upper ring and three COOH groups in the lower ring. The carboxylic group in the lower phenyl ring at position 4 (picture 2) acts as the anchoring group and binds to the surface through coordination bonding. The main objective of the project is to investigate the H-bonding interaction when molecules are placed adjacent to each other on the surface.

The current study explores the arrangement of the molecules and the H bonding interaction with different orientations of the molecules on the surface. The different orientations of the molecule lead to different patterns/arrangements for example square, hexagonal and orthorhombic, with pores of different sizes. These pores potentially offer the opportunity to adsorb additional and different molecules following regular patterns. This opens the possibility to functionalize the surface for new applications.
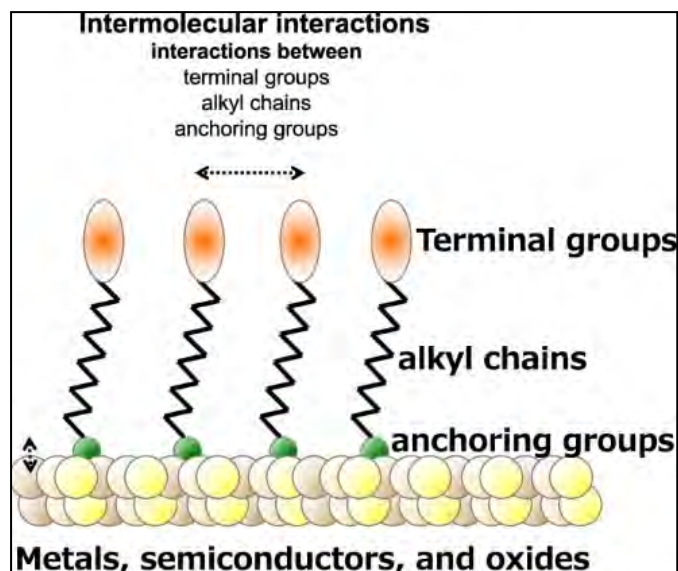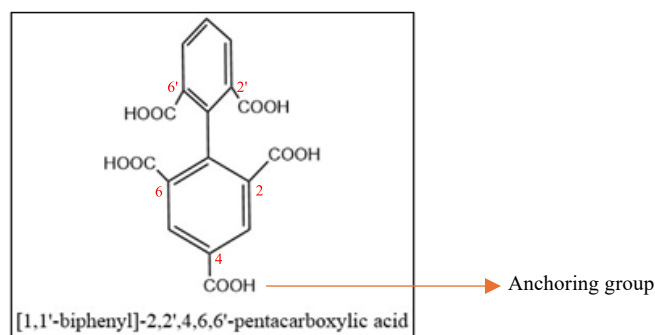

Figure 4 Schematic image of Self-Assembled Monolayer[1]

Figure 3 Biphenylpentacarboxylic acid

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Insights from DFT modelling into the catalytic activity of a manganese-pincer complex towards a range of organic substrates

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Earth-abundant manganese-based catalyst provides a more sustainable alternative for the synthesis of important chemical substances when compared to precious metal-based catalyst. In the Kumar group, a Mn-PNP macho pincer catalyst **1** has been employed for the synthesis of urea derivatives, polyureas and polyethyleneimines (PEI) from simple feedstocks like methanol, amines, ethylene glycol and ethanolamine through a range of chemical process involving coupling and direct synthesis.[1,2] The mechanistic studies of the catalytic pathways are supported by DFT calculations at the PBE0-D3/def2-TZVP/PCM//RI-BP86/def2-SVP/PCM level of theory.[3] The key catalytic steps involve the (de)hydrogenation, (de)hydration, coupling, and polymer chain growth of intermediates. The rate limiting step is computed to be the regeneration of the active catalyst by transfer hydrogenation or by release of dihydrogen. For ethanolamine as substrate (bottom of Fig. 1), it is difficult to distinguish between a chain-growth and a step-growth polymerisation mechanism.[4]
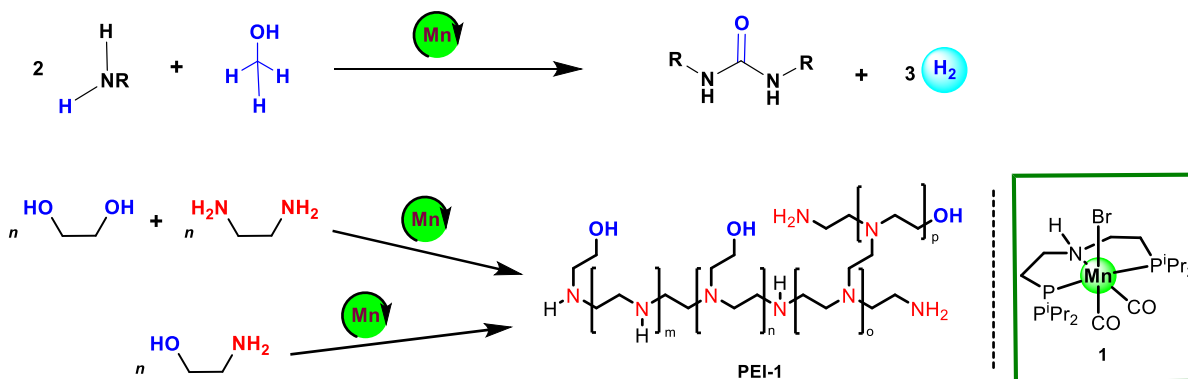
Scheme 1: Top: Dehydrogenative synthesis of urea derivatives using the Mn-pincer complex, **1**. Bottom: Synthesis of PEI from the catalytic coupling of bifunctional alcohols and amines using 1.

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SERS Activity of Pyridine on Different Single Atom Sites on a Gold Slab

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Surface enhanced Raman scattering (SERS) has significant advantages for sensitive analysis combining high enhancement factors, and positive *in situ* analyte identification with relatively simple experimental techniques [1-3]. However, although much has been discovered about the mechanism behind the enhancement, it is still not fully understood inhibiting development [4]. Changes in Raman scattering intensity caused by the position of a chemisorbed pyridine on a gold slab was characterised using self-consistent charge tight-binding density functional theory (SSC-DFTB) calculations using two interaction potentials [5,6]. This approach enables the local sites which give SERS to be characterised with the effect of the flexible metal charge distribution included. As well as the pyridine and bonded gold atom, nearest neighbour gold atoms have significantly changed charges which differ depending on position on the slab. This affects the absolute and relative intensity of the predicted SERS at each position. Investigation of an atom displaced from the face and an associated vacancy showed an asymmetric charge distribution on the nearest neighbour gold atoms which affects intensities. Relative intensity changes analogous to those obtained in electrochemical SERS on varying potential and an increase in absolute intensity by a factor of 8 between the face of the slab and a high energy corner site were found. These sites are modelled pre plasmonic enhancement and hence the changes reflect the Chemical or Charge transfer (CT) contribution to enhancement. An increase of about 20 is expected for pyridine but the application of a plasmonic field will cause further changes to the nearest neighbour atom charges and affect the CT contribution so a factor of 8 is reasonable for the static site.

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Enhancing IDP Conformational Ensemble Analysis Through Torsional Clustering

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Proteins are flexible biopolymers essential to all biological processes, with their collective conformational ensemble dictating their biological function. This dynamic nature is particularly pronounced in intrinsically disordered proteins (IDPs), which, despite exhibiting a higher degree of conformational variability compared to folded proteins, play crucial roles as promiscuous binders. This capacity allows them to participate in a wide range of cellular interactions, making them central to the molecular mechanisms of various diseases, including cancers and neurodegenerative disorders. Given the challenges associated with direct experimental observation of these dynamics, utilizing experimentally determined structures as starting points for molecular dynamics (MD) simulations has become a standard approach [1]. Nevertheless, with the current state of the art computational power and unbiased MD algorithms, achieving sampling on biological timescales remains challenging in atomistic simulations conducted in explicit solvent environments, this is particularly true for IDPs.

Our aim is to combine molecular simulations and generative neural networks (GNNs), a machine learning method, to predict the conformations of IDPs. We use molearn [2], a framework for training GNN on protein conformational spaces to achieve this. To this end, we have generated 1.4 µs of molecular dynamics data of α-synuclein, an IDP. Training molearn with the α-synuclein dataset using the standard GNN architecture performs worse than using MD data of globular proteins such as MurD [3]. We show that the model performance is lower when trying to reconstruct extended conformations compared to ones that are more compact. An avenue we are currently exploring to improve the model's ability to learn, is looking at a different protein's representation. In this context, we are exploring ways to cluster torsional angles in toroidal space, which we hope can serve as a set of internal coordinates to enhance the learning algorithm's interpretation of protein conformations.

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A Protocol Language for Automated Peptide Chemistry

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The assembly of peptide chains by solid phase peptide synthesis (SPPS) is already well automated. However, many peptide chemistry protocols that relate to post-translational modifications are not. They are based in prose and informal, making them difficult to reason about and automate. We aim to develop protocol languages for peptide chemistry that enables both automation and formal reasoning, in the same way a programming language captures the domains specifics of a problem.
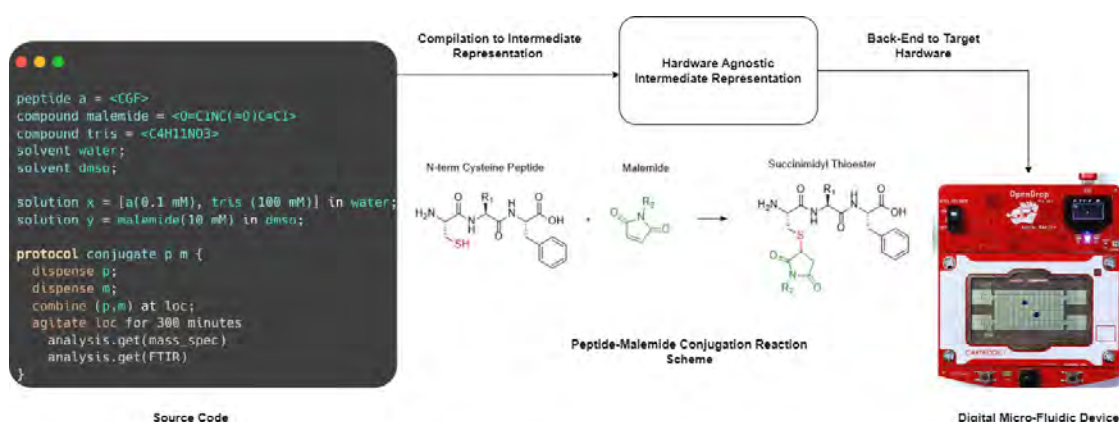

Figure 1: a scheme outlining the compilation of source code to executable hardware. Pictured Device is a digital microfluidic board: OpenDrop V4.

We aim to develop rich type systems that encode useful information about the chemistry, which will allow the filtering of badly formed programs and increase reliability, reproducibility and safety.

Source code is compiled into a hardware-agnostic, intermediate representation. Different back-ends can be developed to target a range of hardware, such as digital microfluidic boards (DMFBs), increasing the portability of the language.

DMFBs use electro-wetting technology to manipulate discrete droplets of fluid over an array of electrodes. DMFBs are fully programmable and are seeing increasing use for automated bio-protocols (such as PCR testing). There are ongoing academic efforts to develop DMFBs directly, such as with BioScript [1]

The final goal is to enable dynamic feedback, to allow programs to make decisions based on analytical data. This would allow for fully autonomous systems, that could greatly enhance process optimisation and throughput. This can be achieved by the incorporation of *probabilistic semantics*, as previously demonstrated in another language that was developed for optimising biology protocols[2].

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In Search of Enzyme Activation: A Computational Workflow for Evaluating Allosteric Drug Candidates

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We have developed a computational workflow using steered molecular dynamics (sMD) and Markov state models (MSMs) to assess the allosteric potential of small-molecule modulators of enzyme activity (see ***Figure 1***).[1] Our workflow uses sMD to explore the conformational space of the target system. By employing sMD, we can sample conformational space that is inaccessible under routine MD timescales. Subsequently, we utilise intermediate conformations arrived at *via* sMD as the starting point for multiple short, equilibrium MD simulations. The resulting data is pooled and used to construct MSMs,[2] affording us insight into the metastable conformational states of the target protein, as well as the probability of the protein occupying such states with and without an allosteric modulator *in situ*.
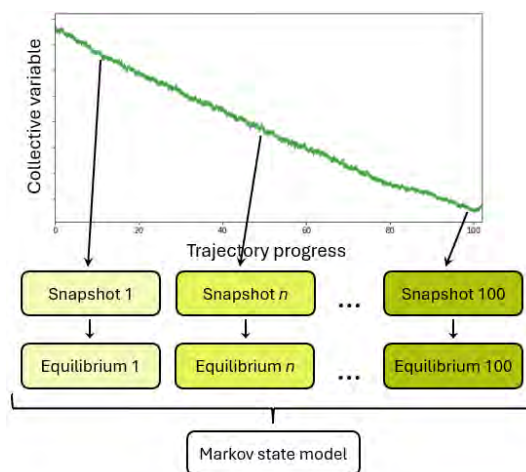

Figure 1 – A schematic overview of our sMD/MSM workflow.

We have applied our workflow to investigate small-molecule activators of the cell-signalling enzyme, Epac1. Epac1 is endogenously activated by the ubiquitous secondary messenger, cyclic AMP (cAMP).[3] whereupon it plays a key role in regulating inflammation response in cardiovascular and pulmonary endothelial cells.[4] As such, it was identified as a key target for pharmaceutical intervention and a drug discovery project has ensued. To date, we have successfully modelled Epac1 with cAMP, as well as our hit compound, I942 (a partial Epac1 activator).[5] We are now modelling a selection of candidates first arrived at *via* a protein-ligand docking assay.

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Digichem: Computational Chemistry For Everyone

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The accuracy, speed, and breadth of problems that can be addressed by computational chemistry has steadily expanded, yet, arguably, comparatively little has been done to improve the usability, accessibility, or productivity of the field. Most quantum chemistry (QC) calculations are still too slow to be executed on personal machines, relegating them to the domain of large, distributed, super-computing clusters, invariably running a flavor of Linux that does not provide a graphical-user interface (GUI). While the experienced theoretician may feel perfectly at home here, the average user can become quickly overwhelmed by the unfamiliar operating system and the nuances of correctly setting up a quantum chemistry calculation.

Choice of interface   Automated orbital plots   Simulated spectra
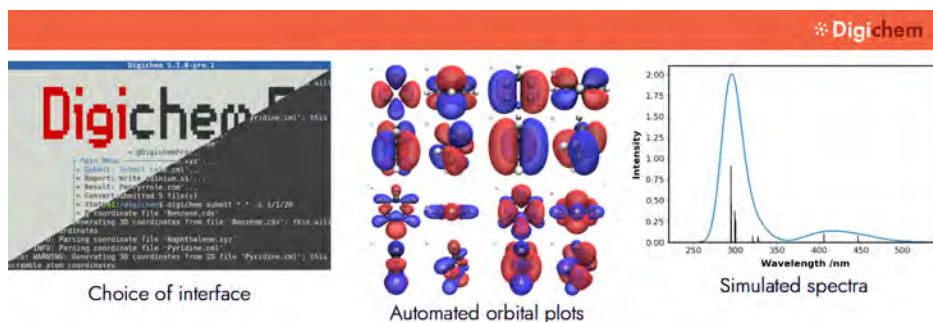
This unruly jigsaw puzzle is hard to learn and ultimately negatively affects work efficiency, especially for novices. To solve this, we have developed a program that manages and automates all parts of the computational process, from the submission of new calculations to the analysis of results. Digichem provides a user-friendly interface that is much more familiar to non-expert without sacrificing functionality. Digichem supports simultaneous submission of thousands of molecules and interfaces to popular batch submission systems (SLURM,[1] PBS[2]) and QC programs (Gaussian,[3,4] Orca,[5] Turbomole[6]). Digichem automatically parses and formats the calculation output, generates 3D molecular orbital plots and 2D graphs, provides databases for querying, and more, all designed to make computational chemistry accessible for everyone.

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Arabinoxylan Polymer Flexibility and Interactions with GLYCAM06j and CHARMM36m

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Arabinoxylan (AX) hydrogels hold potential in the food and drug delivery applications due to their physical properties.[1,2] AX found in the seed husk of certain species, such as *Plantago ovata*, forms gels via hydrogen bonding, with different extractable fractions producing gels with varying physical properties.[3] The specific structure and decoration pattern of side chains are believed to influence gel properties. We have used replica exchange molecular dynamics (REMD) simulations to study the effect of single-unit L-arabinose substitutions on xylan chain flexibility. These systems correspond to AX found in wheat endosperm and serve as an accessible test case with which to evaluate force fields before they are turned to the more complex *p. ovata* AX. Simulations of small AX oligomers comprising different arabinose substitutions have been conducted and used the results used to build ensembles of large static chains in the unperturbed state. With these we can determine properties such as radius of gyration and persistence length as a function of any arbitrary arabinose substitution. We find differences in results between the GLYCAM06 and CHARMM36 carbohydrate forcefields, with CHARMM36 generally indicating stiffer chains. Meanwhile, GLYCAM06 also predicts the inverted chair form of the xylopyranose units to be far too stable. Both models appear to overestimate persistence lengths relative to experiment, although there is disagreement amongst experimental results. [4] We also make some comparison between both forcefields and density function theory (DFT) for the disaccharide xylobiose.
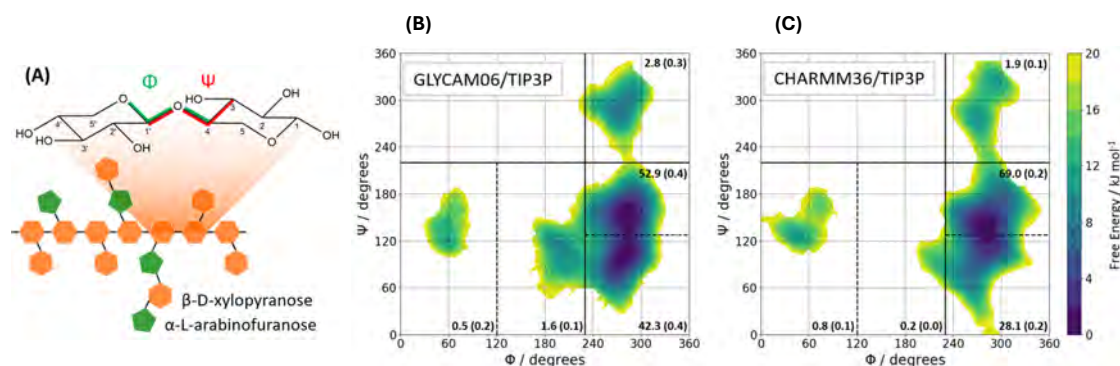

Figure 1: (A) Schematic of a generic AX structure with xylobiose highlighted as a simple model system for the backbone. (B) Free energy Ramachandran plot for the xylobiose β-1,4 glycosidic linkage obtained from REMD using GLYCAM06. (C) The same using CHARMM36m.

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Molecular Modelling to Study a Marine Viral Halogenase

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In 2019, members of the Goss Lab discovered VirX1,[1] a flavin-dependent halogenase with a 3-D structure similar to that of PrnA, a well-studied 7-chlorohalogenase.[2] VirX1 is thought to facilitate the halogenation of aromatic ligands such as tryptophan *via* the *chloramine mechanism*.[1] In the first step, the ligand sources a halogen from a pre-halogenated active site lysine residue to form a Wheland intermediate, which is then deprotonated by an active site glutamine residue in the second step to form the halogenated product. However, PrnA is known to facilitate the same overall transformation *via* the so-called *hypohalous acid mechanism*,[2] which differs from the *chloramine mechanism* in the first step. In the *hypohalous acid mechanism*, the ligand sources a halogen from a hypohalous acid molecule which in turn deprotonates the active site lysine residue to form a Wheland intermediate.

This computational study first seeks to build a reaction energy profile of the *chloramine mechanism* with VirX1, using hybrid quantum mechanical/molecular mechanical calculations. Ultimately, the study seeks to compare the two possible mechanisms and investigate substrate scope.
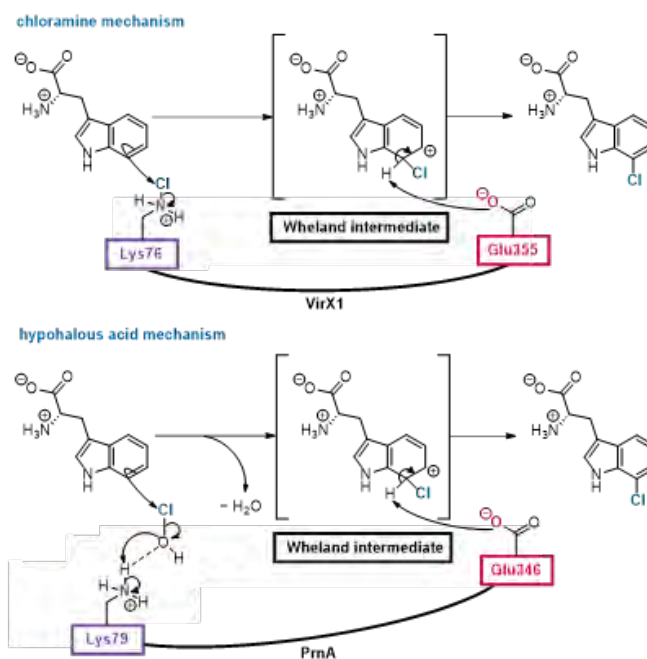
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Mechanistic Insights into Phosphirenium Ions as Masked Sources for Divalent Phosphenium Cations in Lewis Acid Catalysis

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Recent years have seen increased interest in the use of phosphorus in main-group catalysis.[1] As part of this, the chemistry of diazaphosphenium cations, isoelectronic with *N*-heterocyclic carbenes, has been developed. Diazaphosphenium cations have become a popular ligand of choice in coordination chemistry and have also emerged as successful hydride acceptors and hydride transfer reagents in catalysis.[2] However, examples where the divalent P centre is not stabilised by heteroatom substituents are far less common.

In this study we use computational modelling to investigate the role of phosphirenium ions, (**I**, Figure 1) as a source reactive phosphenium cations, PAr_2^+ (**II**) without heteroatom substituents. The PAr_2^+ species can then initiate Lewis Acid catalysis, for example the hydrosilylation of ketones.[3] This involves the nucleophilic attack of benzophenone on the phosphenium catalyst to give **III$_P$**, followed by hydride transfer and silyl group migration to give **V$_P$**. This work presents a benchmarking study using various density functionals from Jacob's Ladder. Additionally, the electronic effects of substituents on the reaction pathway are explored and their effect on various side-reactions are discussed.
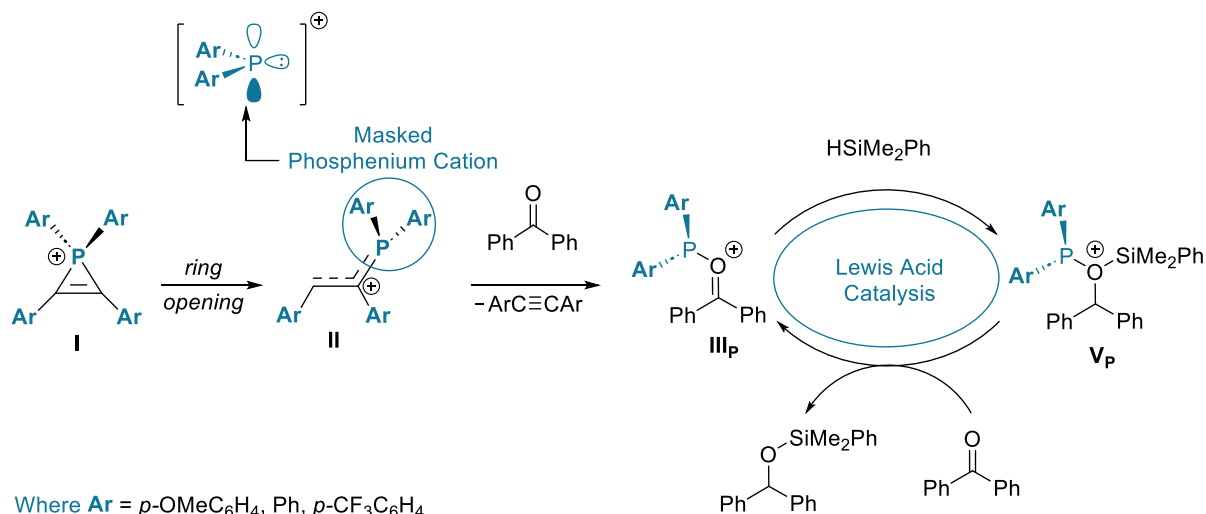

Where **Ar** = *p*-OMeC$_6$H$_4$, Ph, *p*-CF$_3$C$_6$H$_4$

Figure 1. Proposed Catalytic Cycle for the Hydrosilylation of Benzophenone

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