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Computational Chemistry Symposium 2012

ScotCHEM

14 June 2012

University of Glasgow

Kelvin (Physics) Building, Lecture Theatre 312

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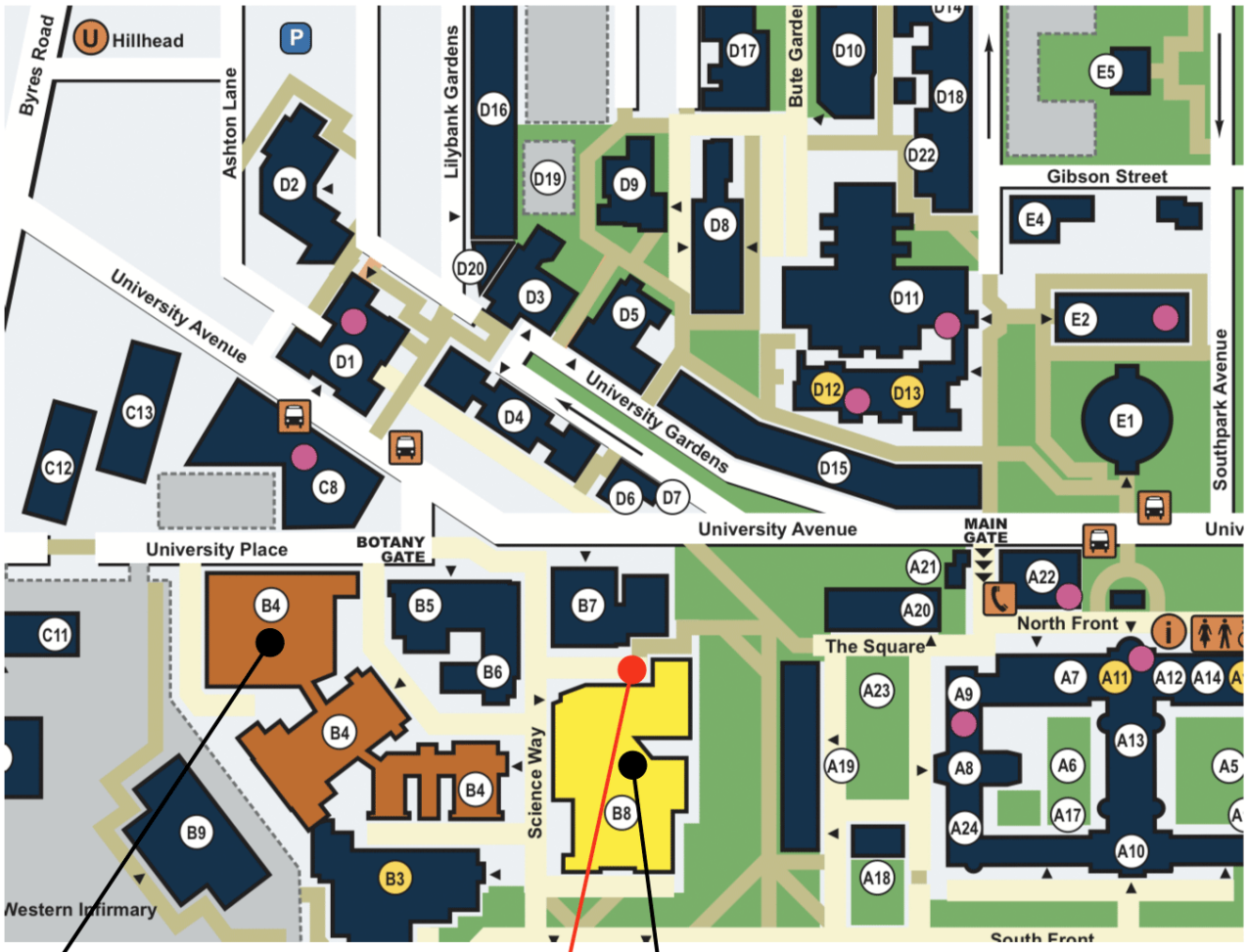

B4: Joseph Black Bldg (Chemistry)

B8: Kelvin Bldg (Physics)

Outside stairs to Kelvin LT 312

Programme

From 9:30 Registration and coffee (Kelvin Building, LT 312)

Session I. Chair: Dr Hans Senn

10:25 Welcome and announcements

10:30 – 11:10 O1: *Prof David J. Tozer (University of Durham)*
Dispersion, static correlation and delocalisation errors in DFT: An electrostatic theorem perspective

11:10 – 11:30 O2: *Dr Jeremy P. Coe (Heriot-Watt University)*
Applications and development of Monte Carlo configuration interaction

11:30 – 11:50 O3: *Martin Hilgemann (Dell HPC)*
Best practices for computational chemistry applications on Dell systems

11:50 – 13:10 Lunch (Joseph Black Building A4-41a, Conference Room)

Session II. Chair: Dr Tell Tuttle

13:10 – 13:40 O4: *Prof Maxim Fedorov (University of Strathclyde)*
Theory of molecular liquids & computational biomolecular design: Predicting the solvation behaviour of *de novo* designed molecules

13:40 – 14:00 O5: *Dr Hernán Ahumada (University of Glasgow)*
Reorientational dynamics in *closo*-carboranes using molecular dynamics and ^{11}B MAS NMR

14:00 – 14:30 O6: *Dr Lev Sarkisov (University of Edinburgh)*
Challenges and opportunities in the computational design of functional porous materials

14:30 – 14:50 O7: *Dr Lazaros Mavridis (University of St Andrews)*
Predicting potential athletic performance-enhancing substances

14:50 – 15:20 Afternoon tea & coffee (Kelvin Building 470, Physics Common Room)

Session III. Chair: Dr Grant Hill

15:20 – 15:50 O8: *Dr Louis Farrugia (University of Glasgow)*
Chemical concepts and QTAIM

15:50 – 16:10 O9: *Dr Andrés G. Algarra (Heriot-Watt University)*
A Natural Bond Orbital analysis of the electronic structure of $L_nM–CH_3$ and $L_nM–CF_3$ complexes

16:10 – 16:30 O10: *Dr Alexandra Simperler (NSCCS, Imperial College)*
The EPSRC UK National Service for Computational Chemistry Software

Poster Session

16:30 – 18:00 Poster session (Joseph Black Building A4-41a, Conference Room)

18:00 Poster prizes

Abstracts of talks

O1

Dispersion, static correlation and delocalisation errors in DFT: An electrostatic theorem perspective

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Dispersion [1, 2], static correlation [3] and delocalisation errors [3] in DFT are considered from the unconventional perspective of the force on a nucleus in a stretched diatomic molecule [4]. The electrostatic theorem of Feynman [5] is used to relate errors in the forces to errors in electron density distortions, which in turn are related to erroneous terms in the Kohn–Sham equations. For H_2, the exact dispersion force arises from a subtle density distortion; the static correlation error leads to an overestimated force due to an exaggerated distortion. For H_2^+, the exact force arises from a delicate balance between attractive and repulsive components; the delocalisation error leads to an underestimated force due to an underestimated distortion. The net force in H_2^+ can become repulsive, giving the characteristic barrier in the potential energy curve. Increasing the fraction of long-range exact orbital exchange increases the distortion, reducing delocalisation error but increasing static correlation error.

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O2

Applications and development of Monte Carlo configuration interaction

Jeremy P. Coe, Martin J. Paterson

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Full configuration interaction (FCI), although the most accurate method for a given basis, is computationally intractable for all but the smallest systems and basis sets. A number of procedures (see, e.g., [1] for a review) have been proposed which essentially attempt to seek out the important configurations and so produce an accurate wavefunction using only a small percentage of the FCI space. One promising method is that of Monte Carlo configuration interaction (MCCI) [2]. This offers the possibility of recovering much of the static and dynamic correlation using only a very small fraction of the configurations required for a full CI. To achieve this an iterative process of a CI calculation within a sample of coupled configurations followed by randomly augmenting the sample at each step is employed. Here configurations whose coefficients are lower than a user-specified value in the MCCI wavefunction are eventually removed from it.
We adapt a version of the MCCI program [3] to demonstrate that accurate potential curves may be calculated, using substantially reduced wavefunctions compared with full CI, for systems that have multi-reference character [4]. We also assess the accuracy of multipole moments, ionisation energies and electron affinities calculated using the method. We investigate approximating the natural orbitals in MCCI and then using these to accelerate the convergence of an MCCI calculation. Finally, we consider combining a second-order perturbation scheme [5] with MCCI to try to account for more of any neglected dynamic correlation.

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4. J. P. Coe, D. J. Taylor, M. J. Paterson, **2012**, submitted.
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O3

Best practices for computational chemistry applications on Dell systems

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In this presentation the computational workload characteristics for several popular computational chemistry applications using orbital methods and density functional theory will be discussed. An in-depth investigation of common pitfalls and general performance problems will be shown. Some workarounds and best practices are described that can help a scientist to get the best performance out of his computational resources.

O4

Theory of molecular liquids & computational biomolecular design: Predicting the solvation behaviour of *de novo* designed molecules

David S. Palmer, Maxim V. Fedorov

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Understanding the solvation behaviour of bioactive molecules is a fundamental step in biomolecular design: from predicting the bioavailability of novel pharmaceuticals, to assessing the environment fate of potential pollutants. The Integral equation theory (IET) of molecular liquids is a powerful method for the description of structural and thermodynamical parameters of molecules in solutions. Although IET has been an active topic of academic research for many years, in its common form the theory does not permit accurate calculations of solvation thermodynamics across multiple classes of molecules, which has prevented it from being widely used in many practical applications such as computational drug design. We have developed a free energy functional (3D RISM/UC), which allows accurate calculations of hydration free energies for molecules ranging from simple alkanes to pharmaceuticals. It is shown that this method can be used to calculate the intrinsic aqueous solubility of crystalline druglike molecules. Our approach is easily implemented using existing computational software & commodity-scale HPC facilities, which makes it immediately suitable for use in a wide range of industrial and academic applications.

O5

Reorientational dynamics in *closo*-carboranes using molecular dynamics and ^{11}B MAS NMR

Hernán Ahumada, Teresa Kurkiewicz, Michael J. Thrippleton, Stephen Wimperis

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The carboranes are clusters of carbon, boron, and hydrogen. They have been widely studied on account of their exhibiting a range of physico-chemical properties. A large number of derivatives with different chemical properties has been synthesized; for example, some metallocarboranes act as a potent and specific inhibitor of the HIV protease.[1] One of the most studied groups of carboranes are the *closo*-carboranes, $C_2B_{10}H_{12}$. These compounds consist of a slightly distorted icosahedron, with CH and BH units. There are three structural isomers called *ortho-*, *meta-* and *para*-carborane. At temperatures higher than 275 K for the *ortho-*, 285 K for *meta-*, and 300 K for *para-* isomers, in this phase the molecules interact weakly and reorient rapidly and isotropically. Below this transition temperature, the rapid molecular reorientation continues but the reorientation becomes anisotropic. Diffraction studies indicate that this different reorientation behaviour is associated with a change in space group, from face-centred cubic (isotropic reorientation) to orthorhombic (anisotropic reorientation).
This work explores the dynamic behaviour of the three *closo*-carborane isomers using molecular dynamics (MD), and relates the theoretical results to experimental MAS NMR measurements.[2,3] We have simulated 100 ns of trajectory for a cubic box with 216 molecules of each isomer at different temperatures. Next, we have calculated the rotational correlation time (τ_c) from the correlation function for the BH and CH bonds in all simulations. From τ_c, we have then calculated the longitudinal ^{11}B and ^{13}C relaxation times (T_1). Agreement between the experimental and theoretical values is found, and the theoretical values reproduce the experimental trends. To visualize the phase change in the mobility with respect to temperature, we have performed three simulated annealing runs of 100 ns each where the temperature was increased from 150 to 350 K. The observed changes in mobility can be related to the phase transitions, but the MD overestimates the transition temperature. Dynamic shift, energy distributions, and angles distributions in time were also calculated.

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O6

Challenges and opportunities in the computational design of functional porous materials

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Adsorption in porous materials has been considered as an energy efficient alternative to distillation in large scale chemical engineering processes. Removal of carbon dioxide from industrial flue gases is one example of a large scale process where energy efficiency is crucial. Other applications of porous materials include catalysis, energy storage, sensing and drug delivery. Recent advances in the chemistry of new porous materials, such as metal organic frameworks, make it possible to develop materials with properties highly tailored for specific applications.
Given a large number and complexity of porous materials it becomes vital to develop systematic approaches to characterize them, and to screen them for promising performance with as little experimental effort as possible. It is also important to gain fundamental understanding of the adsorption processes on molecular level. This is where molecular simulation of adsorption becomes an indispensable research tool.
In this presentation, I will introduce the subject of molecular simulation of adsorption and draw examples from the research in my group on how to use this technique to improve our understanding of adsorption phenomena and to streamline the discovery of new porous materials.

O7
Predicting potential athletic performance-enhancing substances

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The World Anti-Doping Agency (WADA) is pursuing an anti-doping program to combat the use of performance-enhancing substances in sport, so protecting the athlete's fundamental right to participate in doping-free sport [1]. In order to ensure fairness and protect the athletes from using substances that can threaten their health, WADA has published the Prohibited List [2]. The prohibited list is an international standard for identifying substances and methods prohibited in-competition, out-of-competition and in particular sports. The List groups methods and substances into categories: anabolic agents (S1), peptide hormones, growth factors & related substances (S2), β-2 agonists (S3), hormone antagonists and modulators (S4), diuretics and other masking agents (S5), stimulants (S6), narcotics (S7), cannabinoids (S8), glucocorticoids (S9) and β-blockers (P2).
Ideally, one would like to identify all substances that have one or more of the above pharmacological actions in a fast and cost effective way. There are a large number of high throughput virtual screening (HTVS) algorithms that use various molecular representation techniques and have already been tested, with varying success, on a number of difficult cheminformatics problems [3–6]. Recently, a comparison study on the directory of useful decoys (DUD) has shown that 2D fingerprint-based methods still give better virtual screening performance than the more sophisticated 3D shape-based approaches [6].
Here, we introduce our novel molecular representation technique, the bio-activity fingerprints (BioActFP). BioActFP is based on experimental data derived from the ChEMBL database (~7,000,000 activity records for 1,300,000 compounds). ChEMBL was screened and eight well populated categories of activities were used for the fingerprint creation (K_i, K_d, EC50, ED50, activity, potency, inhibition and IC50), for each experimental value a label "active" or "inactive" was placed according to a number of criteria. Ideally, we would like to use those fingerprints to calculate the probability of a given molecule being a member of a family of molecules that are known to interact with a specific target or have a similar pharmacological action. In order to do so, we calculate the Tanimoto similarity scores between a query molecule to all the members of a family which we then fit to a Gaussian distribution in order to transform them to probabilities. Finally the Parzen–Rosenblatt window method [8–9] is used to estimate the probability that the query molecule is a member of the given family.
We evaluate our method and compare it with the more traditional and well known 2D circular fingerprints (CFP) [7] on some of the WADA prohibited classes. As expected the top-ranking compounds based on BioActFP have more diverse scaffolds, compared to CFP, and our method has proven itself able to make correct blind predictions of pharmacological activity on the targets identified.

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O8
Chemical concepts and QTAIM

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The methodology of Richard Bader's Quantum Theory of Atoms in Molecules (QTAIM) provides a means of obtaining chemical information directly from the electron density. Since this method may be equally applied to densities from quantum calculations and those obtained by experiment from high-resolution X-ray diffraction data, it has become very popular. In many cases, the "standard" chemical structure can be unambiguously recovered from the density, in terms of the network of critical points in the density and their associated bond paths. However, the relationship between QTAIM parameters and chemical bonding is not a straight forward one. The connection is heuristic and not derived from any fundamental theory. This talk will focus on a few examples, where the QTAIM interpretation requires careful consideration. These examples often involve the so called catastrophe structures, where the atomic geometry lies on a cusp between two or more distinct topological structures.

O9

A Natural Bond Orbital analysis of the electronic structure of $L_nM–CH_3$ and $L_nM–CF_3$ complexes

Andrés G. Algarra, Vladimir V. Grushin, Stuart A. Macgregor

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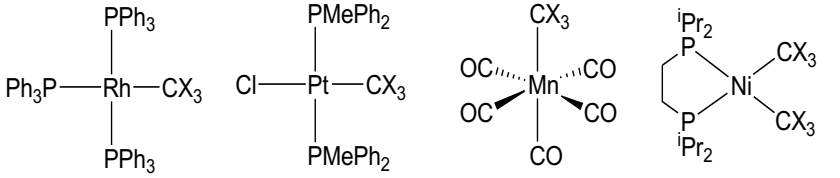
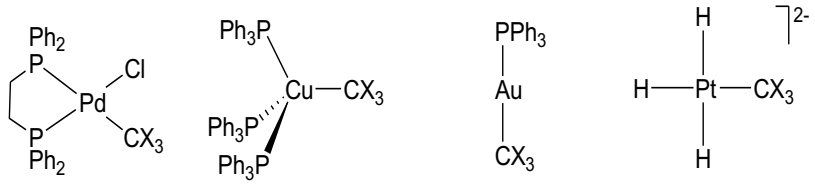
An analysis of the DFT-computed geometries of the $[L_nM(CX_3)]$ species (**1**–**8**, X = H, F) has been performed. This shows that L_nM-CF_3 bonds can be up to 0.1 Å shorter than the equivalent L_nM-CH_3 bonds as well as a higher *trans* influence of the CF_3 ligand, in contradiction to the idea that CF_3 might be expected to be an electron withdrawing group.





A natural bonding orbital (NBO) analysis on pairs **1**, **2**, **3** and **8** indicate that the computed charge at the metal center is usually slightly more negative (or less positive) in the $[L_nM(CF_3)]$ species compared to its CH_3 congener. NBO analysis shows that CH_3/CF_3 replacement has two significant and apparently counter-directing effects, in that it both maintains and indeed can increase the electron density at the metal center, while at the same time causing a stabilization of the metal-based d-orbitals. These effects account for the enhanced reactivity of $[L_nM(CF_3)]$ species towards nucleophiles and form a basis for understanding the reactivity of $[L_nM(CF_3)]$ species in the literature.

O10
The EPSRC UK National Service for Computational Chemistry Software

Alexandra Simperler

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The EPSRC UK National Service for Computational Chemistry Software (NSCCS) at Imperial College London provides access to software, specialist consultation, computing resources and software training to support UK academics working across all fields of chemistry.
The NSCCS hardware is based and managed by our partner at the Rutherford Appleton Laboratory (RAL) of the Science and Technology Facilities Council (STFC). The NSCCS Cluster is called Columbus. Columbus is a 512-cores Silicon Graphics Altix UV 1000 and has a memory of 2 TB with 10 Gb network. CPU: 64 x Intel E7-8837, 2.66 GHz, 24 MB cache, 8 cores per CPU. The cluster hosts a variety of software packages.
Training is an important aspect of the Service. We provide both one-to one training and group training sessions on our software packages (web-based and classroom). In addition to these, we also have a consultation service where users can receive advice on how to tackle specific chemical problems and the most appropriate software to use.
Specialist consultation and support are available to users of our Service. Our service can provide a complete service for experimentalists, including an initial scientific consultation to recommend appropriate methods and software packages for their problem, training on these packages and finally providing them with hardware resources on which to run their calculations.

P1

Hunting for hydrogen in Wadsleyite: Multinuclear solid-state NMR and first-principles calculations

Sharon E. Ashbrook,[1] John M. Griffin,[1] Andrew J. Berry,[2] Stephen Wimperis[3]

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It is thought that the inner Earth contains a vast amount of water in the form of hydrogen bound at defect sites within the nominally anhydrous silicate minerals present in the mantle. Structural studies of silicates, therefore, play an important role in our understanding of the physical and chemical properties of the Earth's interior. However, the high-pressure synthesis conditions typically result in small sample volumes (~1–10 mg), compromising sensitivity. Here we present experimental solid-state NMR results and first-principles calculations that provide insight into local structure and disorder in hydrous wadsleyite (β-Mg_2SiO_4). This deep-Earth mineral has received widespread attention due to its high capacity for the incorporation of water. ^{17}O MAS and STMAS spectra recorded at 20.0 T enable the identification of hydroxyl oxygen sites in samples with different hydration levels. This is consistent with a model structure previously proposed in the literature; however, considerable broadening is also observed, indicating that the structure is not fully ordered. $^{1}H/^{2}H$ MAS and two-dimensional ^{1}H dipolar correlation spectra reveal multiple proton environments in both samples, including some with chemical shifts that are higher than expected for Mg-OH environments. Indeed, DFT calculations carried out for different model structures derived from disordered supercells suggest that some of the observed resonances correspond Si-OH protons. Predictions made from these DFT calculations are confirmed by ^{1}H-^{29}Si and ^{1}H-^{17}O CPMAS and heteronuclear correlation spectra, confirming the presence of both Mg-OH and Si-OH groups in the structure. The DFT calculations additionally reveal it is an Mg3, not an Mg2, vacancy that charge balances the structure.
The combination of multinuclear solid-state NMR and DFT calculations enables the most complete study to date of this extremely important mantle mineral, providing new insight into the mechanism of water storage.

P2

Computational modelling of the photochemical steps involved in photodynamic therapy

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The importance of a deeper understanding of light-induced processes is evident when considering a topical example like Photodynamic Therapy, (PDT). In PDT a photosensitiser chromophore is excited to subsequently, through an energy transfer process, generate the reactive and cytotoxic singlet oxygen species, $O_2(a^1\Delta_g)$. The photosensitisation pathway taking place within a diseased target cell is illustrated in the modified Jablonski diagram in Figure 1.[1]
We present how linear and quadratic density functional response theory can be used to predict the one-photon absorption (OPA) or two-photon absorption (TPA) qualities of new photosensitiser chromophores. We predict that a small change in the structure of the chromophore, whilst having little effect on the OPA spectrum, can have surprising consequences for the TPA spectrum.[2] We also show an example of the use of mutliconfigurational methods to characterise the excited states and to model the non-adiabatic pathways available to these systems, involving the coupling of many potential energy surfaces.

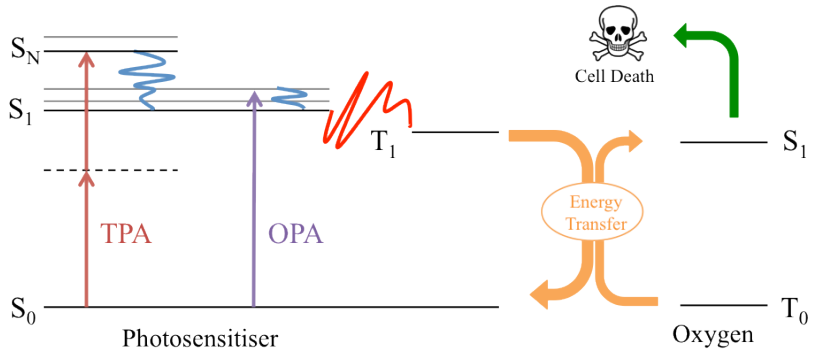

Figure 1. Modified Jablonski diagram indicating the energy flow from the exited photosensitiser species, leading to the generation of singlet oxygen and subsequent cell death of the diseased cell.

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P3

Weak Te…Te bonding through the looking glass of NMR spin-spin coupling

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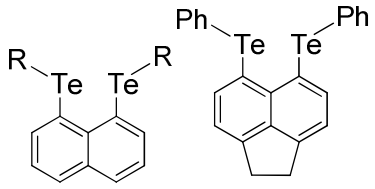
NMR spin-spin coupling between two nuclei can be a probe for the chemical bonding between them. The "through-space" coupling between formally nonbonded atoms can be assessed computationally.[1] Pnictogen and chalgocen substituents, placed in peri-positions on a naphthalene scaffold (Chart I), show onset of multicentre bonding.[2] To explore possible relationships between these two aspects, we now report a joint DFT and experimental study of *J*(Te,Te) couplings in peri-napthalene ditellurides.



N1 (R=Ph)
N1a (R=Me) **A1**

Chart I

Huge “across-the bay” Te,Te couplings in the kHz range have been predicted computationally at appropriate levels of DFT (ZORA-SO), and have been confirmed experimentally for N1 and A1. These couplings turn out to be strongly dependent on the molecular conformation and can be related to the spatial overlap of lone-pair orbitals (assessed through the coupling deformation density pathway[1]) and the onset of multicentre bonding (through natural bond orbital analysis). *J*(Te,Te) couplings can thus be a sensitive probe (“looking glass”) into electronic and geometrical structure of ditellurides.

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P4

Monte Carlo and molecular dynamics approches to compute changes in entropy

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In drug discovery, the early stages of research focus on the identification and optimization of a biomolecular target thought to be involved in a specific disease. Drug molecules able to modulate the biological functions of the biomolecular target with a positive effect in terms of treating an illness, are subsequently designed and synthesised.
An important factor used to characterize the affinity between target and drug is achieved by quantifying the changes in free energy of binding and its entropy and enthalpy components between the thermodynamics state where the drug and the target are solvated in water, and the state where the drug and the target form a complex in an aqueous environment.
In the first stage of this research project, efforts have been focused on the calculation of the entropy change of hydration related to drug-like molecules. The calculation has been performed by applying the thermodynamic integration method, and evolving the system using the *Metropolis Monte Carlo (MMC)* algorithm. Results have shown that the uncertainties in the calculations are of the same order of magnitude as the calculated entropy changes and they can be reduced by increasing the length of the simulations. However, this also increases computational time.
In order to overcome this issue, an extension to the piece of software used to perform *MMC* simulations is in progress. The main idea is to implement a hybrid *MMC/ Molecular Dynamics (MD)* simulation to better guide the *MMC* algorithm to convergence, thereby significantly reducing the computational time of the entire process. The *MD* simulation stage is executed using a specific Application Program Interface (API) known as *OpenMM*. These *APIs* are able to perform *MD* simulations using the modern parallel architectures present on the latest Graphic Processor Units (GPUs).
The computation of the free energy of hydration is only the first part of the whole calculation process to characterize the complex. Indeed the main goal of the research project is the determination of the free energy of binding of the whole complex.

P5
Computational study of minimal amidolytic peptides

Daniel Cannon

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The amide bond is remarkably stable under physiological conditions, yet living systems critically rely on its rapid formation and hydrolysis to assemble and disassemble proteins and peptides, a task carried out by highly efficient enzymes. The *de novo* design of mimics of enzymes that enable effective amidolysis without relying on cofactors has been a longstanding challenge. We have developed methodology that enables the self-selection of amidolytic oligopeptides from sequence libraries based on their function (i.e. catalytic turnover). This is achieved using phage display in combination with precursors that, upon catalytic amide condensation, form powerful gelators that encapsulate amidolytic catalysts, enabling their facile removal by centrifugation. We have demonstrated, that the resulting highly flexible oligopeptides have the ability to spontaneously fold into catalytic triads that enable catalytic hydrolysis of proteins. It is remarkable that the peptides selected from our *in vitro* experiments, which do not rely on a rigid binding framework, give rise to the same catalytic solution that resulted from evolution, yet with a much simpler molecular architecture and an emphasis on creating a catalytic, rather than a binding system. Our results provide new insights into enzymatic catalysis and present a new approach to discovery of catalysts. Moreover, the simplicity of the systems presented, may point to a role of minimal amidolytic peptides in the emergence of life at the molecular level.

P6

The impact of small molecule binding on the energy landscape of the intrinsically disordered protein c-Myc

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Intrinsically disordered proteins are attractive therapeutic targets owing to their prevalence in several diseases. Yet their lack of well-defined structure renders ligand discovery a challenging task. An intriguing example is provided by the oncoprotein c-Myc, a transcription factor that is over expressed in a broad range of cancers. Transcriptional activity of c-Myc is dependent on heterodimerization with partner protein Max. This protein-protein interaction is disrupted by the small molecule 10058-F4 (**1**), that binds to monomeric and disordered c-Myc. To rationalize the mechanism of inhibition, structural ensembles for the segment of the c-Myc domain that binds to **1** were computed in the absence and presence of the ligand using classical force fields and explicit solvent metadynamics molecular simulations. The accuracy of the computed structural ensembles was assessed by comparison of predicted and measured NMR chemical shifts. The small molecule **1** was found to dramatically perturb the composition of the apo equilibrium ensemble and to bind to multiple distinct c-Myc conformations. Comparison of the apo and holo equilibrium ensembles reveals that the c-Myc conformations binding **1** are already partially formed in the apo ensemble, suggesting that **1** inhibits c-Myc/Max formation through an extended conformational selection mechanism. In combination with protein disorder predictions algorithms, the present results suggest that structure-based computational strategies may be applicable to rationally design small molecule inhibitors of intrinsically disordered proteins function.

P7

Probing isotope shifts in ^{195}Pt NMR spectra with DFT

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The ^{195}Pt nucleus is a useful NMR probe, with a broad range of chemical shift values, spanning ca. 13 000 ppm [1]. Modern high-resolution NMR spectrometers are able to detect fine structures on the order of 1 ppm attributed to ligand isotope effects [2], see the figure below.

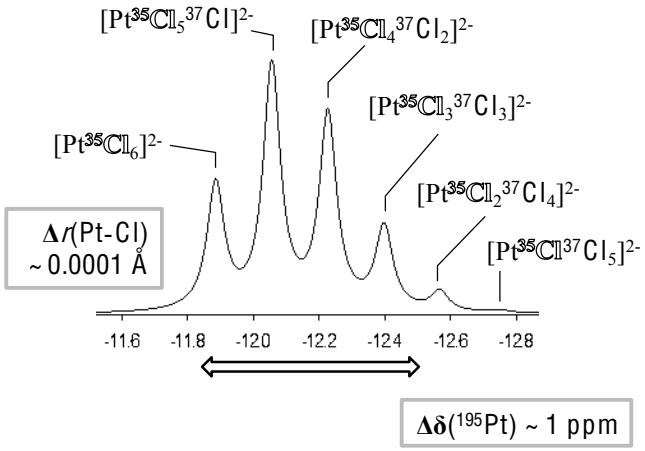

Figure. Fine structure of the ^{195}Pt NMR signal of $[PtCl_6]^{2-}$, arising from the different isotopic substitution with ^{35}Cl and ^{37}Cl.

We now present a study on the origin of these isotope shifts [3]. To this end, zero-point vibrationally averaged (r_g^0) structures were computed at the PBE0/SDD/6-31G* level for $[Pt^{35}Cl_6]^{2-}$ and $[Pt^{37}Cl_6]^{2-}$, for the $[Pt^{35}Cl_n{}^{37}Cl_{5-n}(H_2O)]^-$ (n = 0–5), *cis*-$[Pt^{35}Cl_n{}^{37}Cl_{4-n}(H_2O)_2]$ (n = 0–4), and *fac*-$[Pt^{35}Cl_n{}^{37}Cl_{3-n}(H_2O)_3]^+$ (n = 0–3) isotopologues and isotopomers. Magnetic ^{195}Pt shielding constants, computed at the ZORA-SO/PW91/QZ4P/TZ2P level, were used to evaluate the corresponding $^{35/37}$Cl isotope shifts in the experimental Pt NMR spectra.
The observed trends and the order of magnitude of the effects are captured reasonably well with this approach, although proper description of solvation remains a challenge. The computations confirm that only small changes in Pt–Cl and Pt–O bond lengths upon isotopic substitution, on the order of femtometres, are necessary to produce the observed isotope shifts.

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P8
Hydration thermodynamics of proteins and model systems

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Cell theory calculations were implemented to characterize the hydration thermodynamics around model systems cyclohexane and magnesium ion as well as proteins including BPTI (bovine pancreatic trypsin inhibitor 5PTI), a monomer of Barnase (1BRI), HSP90 (apo 1YES) and HSP90 (holo 3RLR). A structure activity relationship of the 3RR ligand binding to HSP90 is also analysed. Cell theory uses the average energies, forces and torques of each water molecule measured in a frame of reference to parameterise a harmonic potential. From this harmonic potential analytical expressions for entropies and enthalpies are derived. In order to spatially visualize these thermodynamic parameters grid points are used to store the forces, torques, and energies of nearby waters. This allows one to monitor hydration thermodynamics at heterogeneous environments such as that of a protein surface. An understanding of the hydration thermodynamics in binding sites is important in rational drug design. It allows identification of stable waters which could be retained because they are harder to displace while less stable waters can be displaced with chemical groups added designed on the ligand which will create a favourable entropic contribution once the unstable water enters bulk. This results in a ligand with higher affinity to the target.

P9
Superelectrophilic amidine dications: Nucleophilic substitutions of amine C–N bonds by triflate anion

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Methyl and primary alkyl groups attached to amine nitrogen are substituted by extremely weak nucleophiles when the amine is incorporated into a superelectrophilic amidine dication. Even the "non-nucleophilic" triflate (trifluoromethansulphonate) ion quantitatively cleaves $H_3C–N(sp^3)$ bonds to form alkyl triflates under these circumstances. This superelectrophilic activation of C–$N(sp^3)$ bonds provides the first example of triflate acting as a nucleophile in S_N2 reactions.

P10
Gas-phase structures of carboranes

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Gas electron diffraction (GED) is a one of few techniques for determining gas-phase structure. Determining the gas-phase structure is important as molecules are free from the intermolecular interactions experienced in the solid state. In this work we study the structures of three carboranes: *closo*-1,2-$(SH)_2$-1,2-$C_2B_{10}H_{10}$, *closo*-9,12-$(SH)_2$-1,2-$C_2B_{10}H_{10}$ and *closo*-9,12-I_2-1,2-$C_2B_{10}H_{10}$, all of which are derived from the same parent carborane 1,2-$C_2B_{10}H_{10}$.[1]
Experimental measurements were recorded after interacting a 40 keV electron beam with a stream of gaseous molecules. Analysis of the diffraction pattern obtained allows a least-squares refinement between the data and a theoretical model. The use of additional sources of data such as *ab* initio and DFT computational methods allowed the structure to be determined using the SARACEN method.[2] The additional information they provided allowed the application of restraints to differences in bond lengths and angles. The reliability of the experimental structure was tested by calculating the shielding tensors for each NMR active nucleus and comparing these to experimental values.

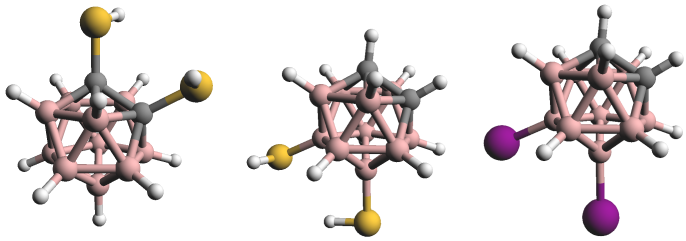

Figure 1. The molecular structures of *closo*-1,2-$(SH)_2$-1,2-$C_2B_{10}H_{10}$ (left), *closo*-9,12-$(SH)_2$-1,2-$C_2B_{10}H_{10}$ (centre) and *closo*-9,12-I_2-1,2-$C_2B_{10}H_{10}$ (right).

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P11

Computing intrinsic aqueous solubility of crystalline drug-like molecules

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We demonstrate methods to predict the intrinsic solubility of 25 crystalline drug-like molecules to reasonable accuracy, via a thermodynamic cycle. We do this by calculating the sublimation free energy using crystal lattice simulations, followed by calculating the hydration free energy by the 3D-Reference interaction Site Model (3D-RISM). Our results (R = 0.85 and RMSE = 1.45 $\log_{10} S$ units when compared to experiment) show considerable improvement over results obtained when using continuum solvation models to predict the hydration free energy (SMD(HF) R = 0.84 and RMSE = 2.03 $\log_{10} S$ units when compared to experiment).

P12

The Jahn–Teller effect in the ultrafast photodissociation of $Mn_2(CO)_{10}$

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Transition metal carbonyl complexes are important species in chemical research and in industry where they exhibit a rich depth of photochemistry that is not so well understood, where state of the art multiconfigurational methods are needed for theoretical study of such photochemistry.
It has been shown that binary carbonyls dissociate on an ultrafast timescale after photoexcitation, with the vibrationally hot initial photoproduct relaxing through one or more Jahn-Teller conical intersections [1-4].
We present our on-going efforts to theoretically model this initial relaxation process through theoretical study of the vibronically coupled potential energy surfaces (figure 1) of one such binary carbonyl, $Mn_2(CO)_{10}$, for both metal-metal and metal-ligand bond dissociation pathways.

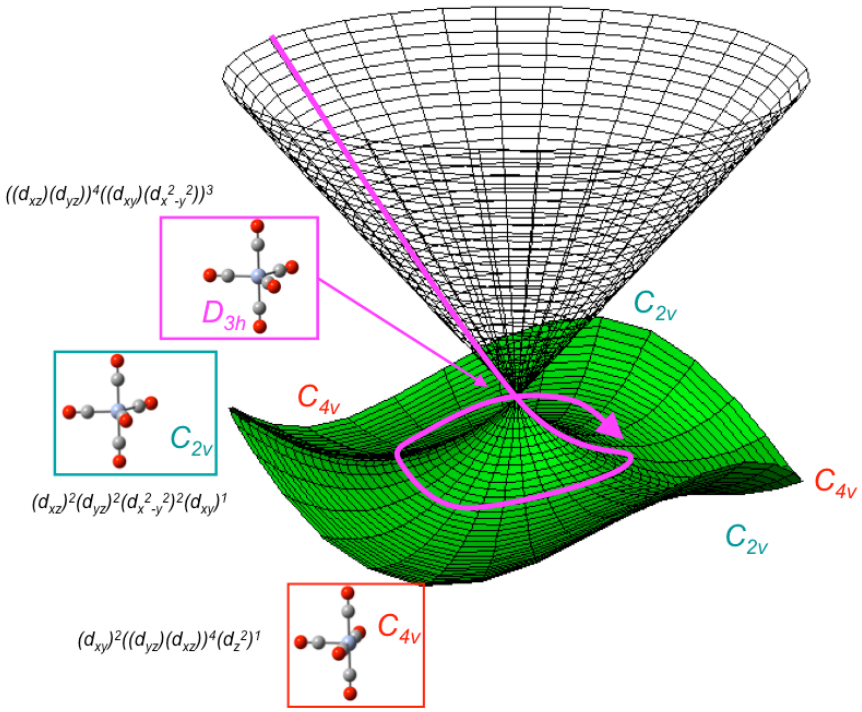

Figure 1. Potential energy surface for relaxation of $^2Mn(CO)_5$ initial photoproduct from Mn-Mn dissociation pathway.

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P13
Surfactant self-assemblies to reinforce nanotubes networks

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Using computer simulations we show that in a random network of nanotubes, surfactant self-assembling on the tube crossings improve the materials stiffness without compromising its porosity. This is important for applications ranging from scaffolds to electrodes to composites.

Individual carbon nanotubes are promising candidates for a range of applications due to their bespoke record properties, such as high strength and stiffness. Yet, for a network of nanotubes these values drop by several orders of magnitude because the forces between the nanotubes are rather low. We propose that surfactant micelles can act as "glue" holding the tubes together and thereby stabilizing the whole network. In this presentation we demonstrate this using computer simulations.

At small tube-tube separations a surfactant aggregate self-assembles at the crossing and encapsulates the junction. This produces a net attraction between the tubes. While the magnitude of the force depends on the angle between the tubes it is generally attractive.

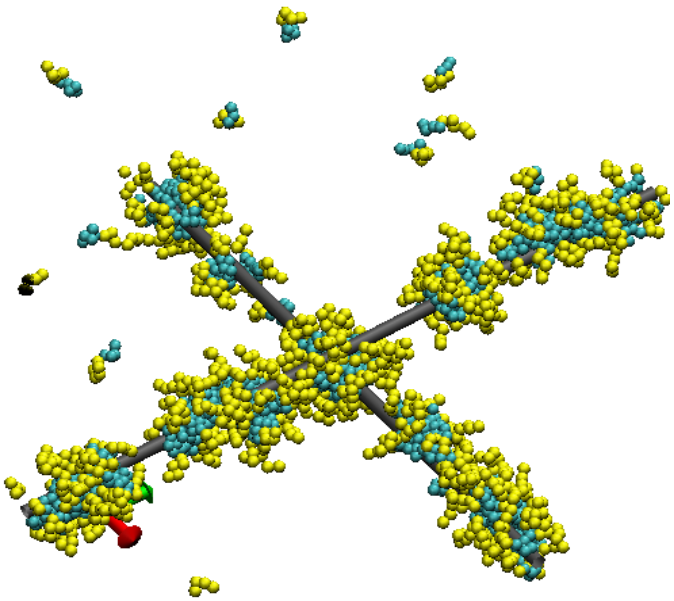

Figure. Adsorbed surfactant micelles on a nanotube junction.

P14

In silico screening of bioactive solutes using molecular integral equation theory

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Understanding the solvation behaviour of bioactive molecules is a fundamental step in biomolecular design: from predicting the bioavailability of novel pharmaceuticals, to assessing the environment fate of potential pollutants. The integral equation theory (IET) of molecular liquids is a powerful method for the description of structural and thermodynamical parameters of molecules in solutions. Although IET has been an active topic of academic research for many years, in its common form the theory does not permit accurate calculations of solvation thermodynamics across multiple classes of molecules, which has prevented it from being widely used in many practical applications such as computational drug design. We have developed a free energy functional (3D RISM/UC), which allows hydration free energies to be calculated accurately for molecules ranging from simple alkanes to pharmaceuticals. Our approach is easily implemented using existing computational software, which makes it immediately suitable for use in a wide range of industrial and academic applications.

P15
Computational chemistry for time-resolved electron diffraction

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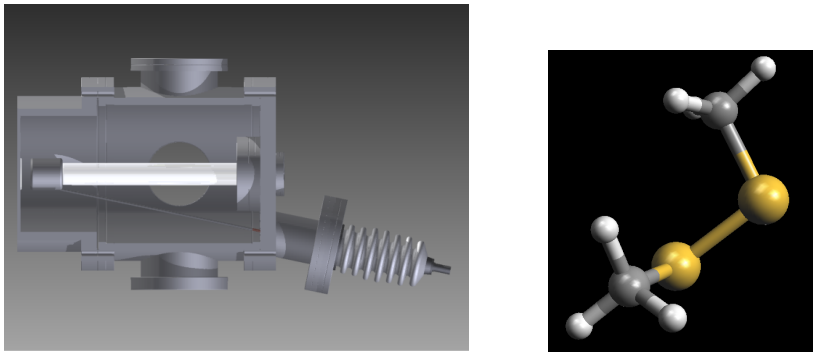
The most fundamental idea of chemistry is to better understand the processes that take place within molecules and the reactions that they undergo. Most of the knowledge that we have about chemistry is *inferred* from experiments; we record how much energy is given off, what wavelengths of light are absorbed or emitted, or how long a reaction takes to complete. Whilst these techniques have allowed us to understand a vast amount about the world around us, none of them really allow us to *see* the atoms involved and how they behave in real time.

Already, standard diffraction techniques allow us to determine the structure of molecules and the bond lengths between atoms to sub-Ångström levels. However, with the development of ultrafast diffraction techniques[1] it will be possible not only to characterise a molecule's structure, but be able to see how this structure changes as a result of external stimulation.

In order to accurately interpret the diffraction data we must first have a good understanding of what the expected ground-state and excited-state structures are. The best way to do this is with the use of computational chemistry methods. Using density functional theory (DFT) and complete active space (CAS) calculations[2] we are able to predict the structures of our molecules. From this we can produce theoretical scattering patterns of the molecules and compare these predictions to experimentally obtained results.

We will present plans and simulations for a novel apparatus that will allow for time-resolved gas electron diffraction (TRGED) experiments. This will enable the structures of gas-phase molecules to be determined and any changes observed upon laser excitation, with sub-picosecond time resolution. We will briefly discuss the theory behind TRGED and consider some of the candidates for study.



(a) (b)

Figure 1. (a) the electron gun that will be used to produce electron pulses of femtosecond duration, and (b) dimethyl disulfide, a potential candidate we could analyse with the new apparatus.

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P16

Computational study of photochemistry and spectroscopy of benzene-water clusters of relevance to insterstellar ice structures

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It has been realized that cold dusty regions play a key role in the chemical evolution of the universe. Icy mantles are accreted on dust grains at low temperatures (≤10 K) where the rich chemical complexity due to physical and chemical processes occurring at the surfaces of interstellar dust grains in such regions makes them sites of star and planet formation. Polycyclic aromatic hydrocarbons (PAHs) are a particularly important class of aromatic molecule, which account for up to 20% of the galactic carbon and are likely to exist in the presence of water ice as either a part of the carbonaceous component of dust grain itself or as a component of icy mantles. UV irradiation of water ice containing polycyclic aromatic hydrocarbons (PAHs) may play an important role in the formation of complex organic species such as alcohols, quinones, ethers, *etc*.
Benzene may be thought of as a prototypical PAH compound and water ice is a good representation of icy mantles on grains. Therefore, the computational study of ground and excited state properties of benzene with water clusters is of astrophysical relevance. Charge transfer (CT) states and diffuse Rydberg-type states play an important role in such complex systems. DFT benchmarking is performed on Benzene-$(H_2O)_6$ clusters to calculate ground state properties such as binding energies. Time dependent DFT inclusive of long range corrected functionals is used to obtain UV spectral results for Bz-W_6 clusters.

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P17

Challenges in estimating the relative stability of polymorphic materials in charge density studies

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Investigating compounds which exhibit polymorphism or phase transitions in order to understand or predict their formation is of great importance in fields such as pharmaceuticals. The aim of this work is to use high resolution structural studies, with energy calculations carried out using these, to predict the relative energies of polymorphs, and the underlying intermolecular interactions.
The crystal structure for a range of organic and transition metals complexes compounds have been obtained at the highest level of accuracy through X-ray high resolution methodology. More precise hydrogen atom positions were obtained by neutron diffraction experiments in cases where suitable size crystals were grown.
The experimental charge density (ECD) analysis, which requires a high level of data accuracy, has become a widespread tool to study problems of chemical and physical interest. Our particular aim is to investigate intermolecular interaction energies in different polymorphs or phase transition materials and to estimate their relative stability provided by lattice energy calculations based on the accurate electron density. In order to validate the results obtained with experimental charge density analysis, theoretical calculations were also performed using different approaches and programs. However, a reliable and affordable calculation method is a prerequisite to analyse and rank polymorph stability, which are known to present very small energy differences such as 1 kJ/mol or even less.
One of the organic compounds studied is sulfathiazole, known to crystallize in five polymorphic forms.[1] Four of the forms were characterized using the high resolution X-ray diffraction technique; the single crystal of form V was difficult to obtain in good quality. The lattice energy calculation results using XD software[2] based on ECD showed a high dependence on the refinement strategy applied to the multipole model. On the other hand, challenges arise also in estimating the lattice energy using theoretical calculation programs. Variation in the trend of relative polymorph stability could be observed when the results for different theoretical calculation programs were compared. The precise estimation of lattice energy seems to be difficult and further investigations are necessary.

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P18

Design, synthesis and testing of ligands for platinum group mineral collection

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Froth flotation is a physicochemical process used in industry to separate mine output by the relative water wettabilities (hydrophobicity) of the finely ground mineral components. It is widely used to recover high value minerals from the high volume of waste generated in the mining process. Flotation is carried out in tanks equipped with an air inlet and agitator. The process involves adding small organic surfactants ('collectors') which selectively impart hydrophobicity to the desired mineral, facilitating the attachment of that mineral to the bubbles. The mineral-bubble aggregates rise to the top of the tank and are collected in a thick froth, which can be easily separated. We present a Density Functional Theory study of collector binding interactions to Sperrylite, an ore of platinum arsenide, and demonstrate both methodology and preliminary results for surface energy, hydration enthalpy and ligand binding strengths. Calculated hydration enthalpies show mixed concordance with literature, in some cases ([1 0 0]) showing close agreement and in other cases ([1 1 0]) no agreement at all. Similarly for our surface energies we show very good concordance with the [1 0 0] face but much poorer concordance with other faces. Some binding strengths for sodium ethyl xanthate on the [1 0 0] face are presented.

P19

Combining calculations and gas electron diffraction data to determine the structures of weakly associated species

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Apparatus has been built at the University of Edinburgh for collecting electron diffraction data using a continuous 35 kV electron source and a phosphor/CCD camera detector. Heated effusive nozzles, as well as gas handling systems for seeding samples into carrier gases for use with pulsed nozzles have been designed, to increase the variety of species that can be studied. With the supersonic expansion we will be capable of producing vibrationally cooled gas molecules, allowing both known starting points for laser excitation and reducing the amplitudes of vibration between pairs of atoms. These amplitudes of vibration define the widths of the Gaussian-shaped peaks in our experimental radial-distribution curves. Large amplitudes of vibration between weakly associated species make them difficult to study. Vibrational cooling will allow species such as carboxylic acid dimers and DNA base-pair mimics to be studies in the gas phase.

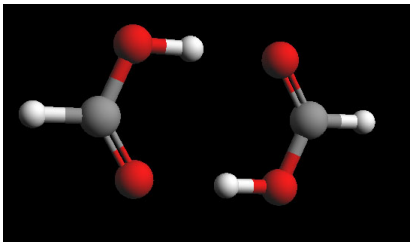

Figure. Formic acid dimer from B3LYP 6-311++G** calculation.

Potential candidates for these vibrationally cooled studies have been identified and counterpoise calculations[1] carried out to determine the interaction energies. These calculations were carried out at the B3LYP level using the 6-311++G** basis set.
Dimers of formic acid and other hydrogen-bonded species are found to have amplitudes of vibration that lie well within the expected range of the observation. However, silyl halide derivatives, which associate through van der Waals interactions, are shown to lie near to the limit of observation when calculated using harmonic approximations.[2] For this reason force constants have also been calculated using anharmonic potentials[3] to fully ascertain their suitability.

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P20
One- and two-photon absorption spectra of s-tetrazine

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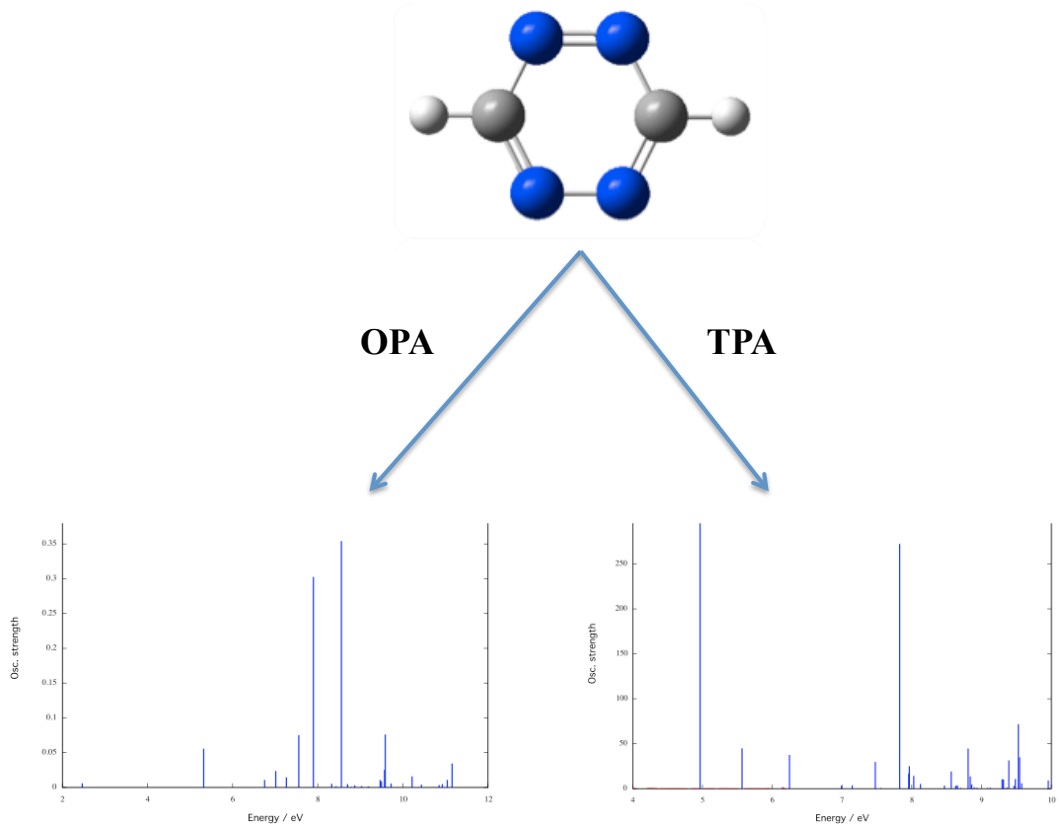
We present a study of the one- and two-photon electronic spectrum of s-tetrazine using a variety of coupled cluster response and density functional methods.
S-tetrazine is a paradigm organic system known and used extensively for many years in a variety of roles such as a model complex for structure and reactivity and as a useful reagent in Diels-Alder reactions, especially in its substituted forms.
While its reactive ground state chemistry is reasonably well known, its electronic spectroscopy is less so. Organic systems have been shown in recent years to possess rich ultrafast photochemistry including vibronic coupling induced features on their excited state potential energy surfaces such as conical intersections and avoided crossings. So a fuller understanding of the excitation energies and character of the vertical electronic excited states of s-tetrazine would be very useful.
Both the one- and two-photon absorption spectra have been calculated as the different selection rules between the two methods means that different electronic states and therefore different photochemical pathways are potentially available meaning a small difference in the excitation method could mean a large difference in the resulting photochemistry.
Highly correlated methods have been used for this study including a range of coupled cluster response methods, CC2, CCSD and CC3, along with the long-range corrected density functional CAM-B3LYP with large all-electron basis sets. A study of the Rydberg states using Kauffman model has also been included.



P21

Accurate spin-state orderings for an Fe(IV)=O active-site model

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During its catalytic cycle, the active site non-haem iron complex of the halogenase SyrB2 adopts a number of high-spin intermediates with low-lying excited spin states. With a view to computational reaction modelling, the capability of both density functional theory and coupled-cluster theory to accurately calculate the relative energies of the spin-states of an Fe(IV)=O active-site model was assessed.

P22
Conformational landscapes of potential HIV-1 reverse transcriptase inhibitors

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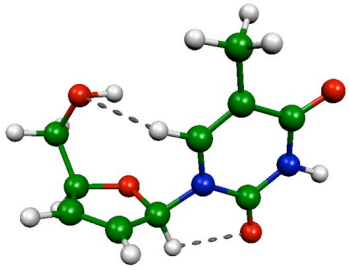
The intracellular activity of human immunodeficiency virus type 1 (HIV-1), which causes acquired immunodeficiency syndrome (AIDS), relies on the functioning of the enzyme reverse transcriptase (RT). Due to its paramount role in the HIV-1 life cycle, RT has been the main target in the fight against this virus. One known RT inhibitor is 2′,3′-didehydro-2′,3′-dideoxythymidine (stavudine, d4T), a patented drug, which often constitutes an essential part of combined antiretroviral therapy. The other 2′,3′-didehydro-2′,3′-dideoxy nucleosides (d4C, d4U, d4G and d4A) are also potential RT inhibitors, but the detailed mechanisms of their biological effect still remain unresolved. As the structural properties of these nucleosides, particularly those governed by intramolecular interactions, determine to a great extent their potential therapeutic efficiency, an extensive conformational analysis is a first step in the design of nucleoside analogues as anti-HIV drugs.



d4T

We determined the complete conformational landscapes of the different 2′,3′-didehydro-2′,3′-dideoxy nucleosides. The results confirm the current belief that the biological activity of d4T is connected with termination of the DNA chain synthesis in the 5′-3′ direction. It is found that there are no energetic or conformational obstacles to the incorporation of d4C, d4U, d4A and d4G into double-helical DNA. This supports the suggestion that the biological activity of 2′,3′-didehydro-2′,3′-dideoxy analogues is directly related to the lack of a hydroxyl group at the C3′-position of the sugar moiety. As a result, these nucleosides act as competitive reverse transcriptase inhibitors through termination of the DNA biosynthesis in the 5′-3′ direction.

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P23

A theoretical investigation into azophenine: A remarkable molecular switch for nano-electronics

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The Schaub group have been working on a system comprising an azophenine molecule on a copper 110 surface which could potentially be used as a molecular switch for nano-electronics as it has been found by STM that it can be interconverted between two stable states via tautomerisation. This investigation has been focussed on providing theoretical support for the STM research by using DFT to model various structures of azophenine and a proton substituted analogue thereof. In each case gas phase calculations were performed using the M06-2X functional, while the M06 functional was also used on systems which involved copper. The para geometry was found to be the most stable tautomer in the absence of copper but the ortho tautomer was most stable in the presence of copper. The azophenine molecule and its analogue behaved similarly in the case of each functional and also in neutral vs. monocationic gas phase systems involving copper. Periodic calculations were performed on the analogous molecule using the PBE functional with added terms for dispersion interactions and correction for unphysical dipole. These calculations also showed that the para tautomer was the most stable structure in the absence of copper, but also showed the para tautomer to remain the most stable on a copper 110 surface, albeit by a dramatically reduced margin. The ortho tautomer was shown to have the greatest adsorption energy on the copper surface.

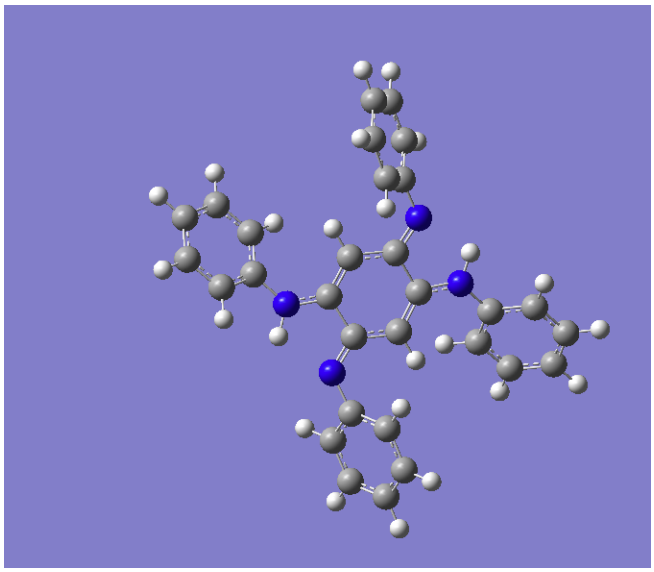

Figure. Structure of azophenine

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Covalent and H-bond networks on metal surfaces

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Molecules interact with metal surfaces in a variety of ways: They may cover the surface as a covalent, H-bonded or Van der Waals network, attached to the surface covalently or just using it as a planar scaffold. They may even change the structure of the surface. I will present three examples of joint experimental / computational projects carried out in St Andrews:

1. Graphene on rhodium [111]:
   A single sheet of graphene was grown on a Rh-[111] surface and found to show large-scale periodic features. We found that, due to the lattice mismatch between the substrate and graphene, there are regions of covalent binding between the constituents, alternating with non-interacting regions, which leads to a buckling of the graphene sheet.
2. Oligomers of melamine on gold [111]
   Melamine and some of its oligomers form ordered structures on Au. It was found that their geometry can be predicted by optimising planar, H-bonded networks of molecules, without explicit consideration of the substrate.
3. Melamine on gold [111]
   At room temperature and above, surface metal atoms are fairly mobile and the shape of step edges changes easily. It was found that in the presence of melamine, Au layers grow "fingers" along unusual directions. The direction of these fingers coincides with the closest packing of lysine dimers on the Au surface.

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