

# Young Modellers Forum – 1st December 2006

## Abstracts for Oral Presentations

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### The Computational Photochemistry of Conjugated Organic Radical Cations

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Through studying conjugated carbocations, we aim to model the dynamics of electron hole transport in organic materials. This has important applications in both materials chemistry (conducting polymers) and chemical biology (photosynthesis, respiration). Currently, we can accurately model the ground and excited electronic states of small conjugated  $\pi$ -systems (up to 16 active electrons) using expensive ab-initio methods, such as CASSCF. However, a faster, cheaper treatment is required to investigate larger systems and their dynamics. We are developing a parameterised QM/MM hybrid method: MM-VB (molecular mechanics–valence bond) [1], designed to replicate CASSCF results at a fraction of the computational cost. Our current work involves extending MM-VB to treat cations. In this work, we performed an extensive ab-initio study of the naphthalene radical cation ( $N^{+\bullet}$ ). These new results provide a mechanism for the photostability of  $N^{+\bullet}$  as well as a test bed for developing the new MM-VB parameters.

Based on a CASSCF//CASPT2 study of the ground and excited state potential energy surfaces of  $N^{+\bullet}$ , we propose a mechanism for its ultra-fast non-radiative relaxation from the second excited state down to the ground state, via two consecutive, sloped conical intersections, which explains the experimentally observed photostability [2]. This has important applications for astrophysics, where  $N^{+\bullet}$  is one of a group of cations extensively studied as the leading candidates for the diffuse interstellar bands.

MM-VB embeds a QM treatment of the active electrons into an MM2 force field via a parameterised Heisenberg Hamiltonian, cheaply providing accurate energies and geometries for several electronic states of neutral conjugated hydrocarbons with up to 28 active MOs and enabling the use of direct dynamics modelling. The original MM-VB parameter set was benchmarked against CASSCF results on small conjugated hydrocarbons. However, minimal modifications to the neutral parameter set were required to accurately reproduce CASSCF energies and geometries for minima and crossings between ground and first excited states of  $N^{+\bullet}$ , as well as the cations of benzene, anthracene and phenanthrene.

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- [1] Bernardi, F., Olivucci, M., Robb, M. A., *J. Am. Chem. Soc.* (1992) **114**, 1606-1616.
- [2] Zhao, L., Lian, R., Shkrob I. A., Crowell, R. A., Pommeret, S., Chronister, E. L., Liu, A. D., Trifunac, A. D. *J. Phys. Chem. A.* (2004) **108**, 25.
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### **A computational study of the fluorescence of 2-aminourine and pyrrolocytosine in nucleic acids.**

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2-Aminopurine and pyrrolocytosine are fluorescent nucleobase analogues; they are used as fluorescent markers in nucleic acids. When 2-aminopurine or pyrrolocytosine is incorporated into a DNA/RNA strand the fluorescence is quenched. When the single strand nucleic acid goes to double strand, both hydrogen bonding and ordered base stacking occur, and the fluorescence is quenched further. These effects on the fluorescence can be used to monitor the position of neighbouring bases.

In this work we have examined the effects of the four major bases, guanine, thymine, cytosine and adenine, on the fluorescence of 2-aminopurine and pyrrolocytosine using *ab initio* methods (the Configuration Interaction Singles, CIS, method). The results suggest that hydrogen-bonding does not have a major influence on the fluorescence transition. In contrast, base stacking is predicted to dramatically alter the nature of the fluorescence (and absorption) transition. These findings have been interpreted in light of experimental evidence.

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### **Understanding Stereoselectivity – Molecular Modelling to Inform Organic Synthesis**

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Around half of the drugs currently in clinical use are of natural product origin. Cancer chemotherapy, in particular, presents an ideal challenge for the discovery and development of natural product-inspired drugs. Unfortunately, many promising natural lead compounds are available only in extremely small quantities and so organic synthesis is a key option in sourcing these important drug candidates. At the heart of this challenge lies the strategic and efficient transformation of simple starting materials into highly complex targets. Using elaborate synthetic intermediates however, the stereochemical

outcome of reactions is often unpredictable and the cost of failure at the late stages of a synthetic effort is very high. The purpose of our research is to enhance the efficiency of organic chemistry with the development of a widely applicable predictive model able to aid and inform synthesis planning.

We have performed high-level *ab initio* calculations to model the competing transition structures for a key synthetic transformation, the boron aldol reaction. This work has shown that in certain cases the course of these reactions are determined by a boat-shaped transition structure, which overturns the long held dogma that chair like transition structures are formed. Our calculations are in excellent agreement with experimentally observed values and we have reduced this high-level analysis into a useful pictorial model, to explain the factors that control the stereoselectivity.

The complexity of reactions involving highly elaborate molecular building blocks not only rules out the use of simple stereochemical models, but also rules out high-level calculations due to the immense computational time and expense involved. Our *ab initio* data were used to derive a computationally cheap molecular mechanics model which makes a full conformational analysis possible. The parameterization of our force field is a fully automated process, optimized using a multi-objective genetic algorithm. This new model can be run on large reaction systems in hours, where high level calculations would be unfeasible, to give a quantitative prediction of product selectivity. The model is truly predictive since no experimental data has gone into its construction and it has performed well in validation against experimental results.

#### References

Paton, R. S.; Goodman, J. M. Understanding the Origins of Remote Asymmetric Induction in the Boron Aldol Reactions of  $\beta$ -Alkoxy Methyl Ketones, *Org. Lett* (2006) **8**, 4299-4302.

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### **The Mechanism of Induction of the Tetracycline Repressor Protein**

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The tetracycline repressor (TetR) is in many ways the archetypical signal-transduction system. It is not only clinically important because it regulates the main resistance mechanism of Gram-negative bacteria to the tetracycline class of antibiotics, but also in modern microbiological research as a “gene switch” that allows genes to be turned on and off using tetracycline derivatives. TetR binds to two operons that regulate both its own expression and that of the tetracycline antiporter (TetA), a membrane-bound protein that actively transports tetracyclines out of the bacterium. We<sup>1</sup> have used long time-scale molecular dynamics (MD) simulations to determine the mechanism of the allosteric

change in TetR that leads to induction and to identify the binding interactions that provoke this change.<sup>2</sup>

Low-frequency normal mode (LFNM) analyses reveal that a loop region that is not resolved in the TetR X-ray structures is mainly responsible for the allosteric change, which is the result of a reorganization of salt bridges that is initiated by the tetracycline displacing an aspartate from the active-site magnesium ion. The receptor cavity of TetR shrinks by about 40% of its volume on binding the antibiotic and becomes far more hydrophobic than in the non-induced form. The roles of mobile residues in the receptor site will be discussed.

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1. *Molecular Dynamics Simulations of the Tetracycline-Repressor Protein: The Mechanism of Induction*, H. Lanig, O. G. Othersen, F. R. Beierlein, U. Seidel and T. Clark *J. Mol. Biol.*, **2006**, 359 1125-1136.
2. *Structural Changes and Binding Characteristics of the Tetracycline-Repressor Binding Site on Induction*, H. Lanig, O. G. Othersen, U. Seidel, F. R. Beierlein, T. E. Exner and T. Clark *J. Med. Chem.*, **2006**, 49, 3444-3447.

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### **Ensemble molecular dynamics simulations of wildtype and mutant HIV-1 proteases reveal novel conformations of the inhibitor saquinavir**

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Inhibitors of HIV-1 protease have been a long standing example of "structure guided drug design". Unfortunately, proliferation of characteristic drug resistant mutations has severely limited the success of clinical therapy. In particular the G48V and L90M mutations of HIV-1 protease are commonly associated with resistance to saquinavir. We investigated the molecular basis through which these mutations confer drug resistance.

We conducted ensembles of fully atomistic molecular dynamics simulations of HIV-1 protease wildtype, G48V and L90M single mutants and the G48V/L90M double mutant complexed with the inhibitor saquinavir. Each simulation had a duration of 1.3 ns and employed equilibration protocols to allow conformation sampling of the drug in the active site of the protease. One simulation in each ensemble was extended to 25 ns to study the differential dynamics of saquinavir in the enzyme active site over a longer timescale.

We demonstrated the existence of four stable conformations of the P2 subsite of saquinavir with differing frequencies of adoption in each protease system. The P2

subsite favoured hydrogen bonding with the catalytic aspartic acid dyad in the wildtype, whilst preferring to bind with the flaps of the protease in all three mutants. Changes in the conformation of the P2 subsite also altered the hydrogen bond network between the drug and different regions of the protease active site (1).

Longer simulations revealed that the drug remained stably bound to the wildtype protease, whilst the effect of increased coupling to the flaps in all mutants resulted in significant drug motion away from the active site centre.

Both the protease backbone and the catalytic residues were most flexible in the L90M mutant, whereas G48V, in combination with L90M, restored the rigidity of the enzyme whilst continuing to expel the drug.

The primary mutation associated with saquinavir therapy, L90M, increases the flexibility of HIV-1 protease, leading to increased drug resistance, whilst G48V compensates L90M through restoration of structural rigidity.

Furthermore, HIV takes advantage of both these mutations to increase the likelihood of adoption of a kinetic mechanism of drug expulsion that involves increased coupling to the highly mobile flaps of the protease.

References:

[1] Sadiq S. K., Zasada S. J., and Coveney P. V. Grid Assisted Ensemble Molecular Dynamics Simulations of HIV-1 Proteases Reveal Novel Conformations of the Inhibitor Saquinavir, *LNBI* 4216, Berthold, MR, Glen, R & Fischer I (eds.) *CompLife* 2006, Springer-Verlag, pp.150-161

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## **Modeling MM polarization in hybrid QM/MM calculations**

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We present a method for modeling polarization in hybrid QM/MM calculations. The method, which expresses the induced dipoles as a set of "induced" charges, is based on the induced dipole approach and methodology for calculating potential-derived point charges from distributed multipole series. The method has the advantage that the same methodology can be used to determine the induced charges and the potential derived charges and so both sets of charges are rigorously defined within the same framework. Here we assess the importance of explicit polarization in the classical part of a QM/MM system with regard to improving the classical description and the consequent effects on the quantum description. Results from the application of the induced charges method to ligand docking and to the analysis of transition state structures are discussed.

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## **Hybrid QM/MM Modeling of the Arg90Cit Mutant of *Bacillus Subtilis* Chorismate Mutase Reveals Unexpected Complexity of Catalytic Effects**

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A more detailed understanding of factors influencing enzymatic binding and activation-energy lowering will provide fundamental insights into biological function, inhibitor design and novel biocatalyst engineering. Discerning the relative contributions of different catalytic effects, such as preferential electrostatic transition state (TS) stabilization and ground state (GS) substrate destabilization, among others, is very difficult in practice. Site-directed mutation of catalytically implicated residues, however, potentially allows the investigation of activity when just one of these effects is perturbed.

Chorismate mutase (CM) is an ideal and widely used system for testing theories of enzymatic function. In this work, detailed hybrid QM/MM simulations have revealed the complexity of structural alterations and active-site charge effects in an Arg90Cit CM mutant. A cationic arginine (Arg90), strongly implicated in stabilization of negative charge developing in the TS,<sup>1</sup> is replaced by an isosteric but neutral citrulline. The experimental  $10^4$ -fold reduction in  $k_{\text{cat}}$ , or 5.9 kcal/mol increase in reaction free-energy barrier, with only a 2.7-fold increase in  $K_{\text{m}}$ , has been interpreted as evidence that unfavourable TS stabilization, with relatively small ground-state complex perturbation accounts for the reduced activity.<sup>2</sup>

SCCDFTB/MM dynamics and adaptive umbrella sampling have been used to produce useful multidimensional free energy surfaces for the mutant ground-state complex. Consistent minima are observed for two distinct citrulline conformations (and associated interaction patterns), one being only slightly, and one more significantly distorted from the WT Arg90 local environment. The free energy barriers for conformational transitions demonstrate that they are highly unlikely. Multiple B3LYP/6-31G(d)-MM reaction pathways from each of the stable GS conformations with the QM region consisting of either the substrate alone, or the substrate and citrulline residue, have produced accurate and consistent potential energy profiles.

The reaction profiles and barrier heights from the distorted structure pathways reproduce experimental results for the mutant well. Those corresponding to the other citrulline arrangement are not significantly different from analogous WT calculations. These results suggest that Arg90Cit ground-state effects may be important, and that a new, more distorted (but perhaps more stable) arrangement should be considered. The cationic nature of the residue 90, considered essential for activity, seems to have little catalytic effect. Combining these types of experimental results and computational techniques appears to be a powerful tool for investigating enzyme functionality.

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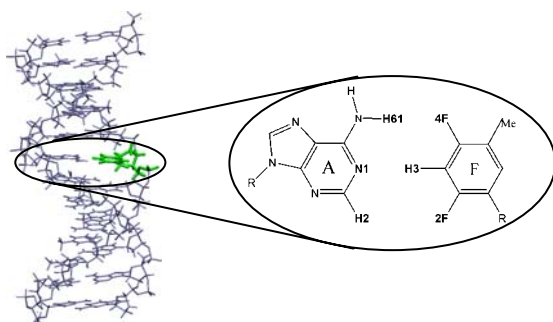
## Simulations of B-DNA under Torsional Stress Reveal Enhanced Base Breathing

Angelo Pugliese and *Charles A Laughton*

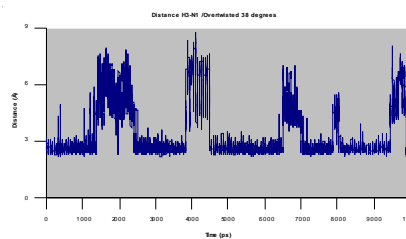
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An analysis of the structure of the DNA in a variety of repair protein complexes that share the common feature of ‘flipping’ the damaged base out of the helix into a protein pocket reveals considerable perturbations to the helical twist of the DNA around the lesion site, though no common pattern of distortion is evident. We hypothesised that repair proteins might induce helical stress into the DNA as part of their strategy for reducing the energy penalty associated with the base flipping process, which is generally costly. We performed molecular dynamics simulations on the DNA dodecamer 5'-CTTTCFTTCTT, where F is the non-natural base difluorotoluene (Fig. 1A), while the DNA was constrained to have a variety of helical twists ranging from 30-40 degrees per base step. We have previously shown that (unconstrained) simulations of DNA containing F show spontaneous base breathing events on the timescale accessible to molecular simulation<sup>1</sup>. Surprisingly, we find that both under- and over-twisting of the DNA enhance base breathing (Fig. 1B); breathing events occur more frequently, and are longer-lasting. Energetic analysis of the data suggests that the origins of this phenomenon are multi-factorial: alterations to DNA helical twist perturb base stacking interactions, but also destabilize the hydration of the helix. These result in a) the relative stabilization of the ‘breathed’ state and b) the reduction in the energy barrier between that state and the closed state. We conclude that it is therefore quite feasible that DNA repair proteins induce helical stress into DNA to promote the base flipping process required for their biological activity, and that to this end, either over- or under-twisting of the DNA locally can be a valid strategy.

Figure 1. A



B



References

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## **Graph Theoretic Exploration of RNA Three-dimensional Structures Graph Theoretic Approaches for Exploring and Analyzing RNA 3D Structures**

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RNA function is dependent on its folding into closely packed helices. Hydrogen bond interactions between RNA base residues play a major part in stabilizing these sometimes complex folds. Base triple interactions, particularly those with at least two hydrogen bonds to each base residue, are expected to be highly stable and therefore may have an important role in forming functional RNA tertiary structures. In addition to triples, other clusters of hydrogen bonded interactions may reveal motifs which form core and conserved components of RNA 3D structure. Highly complex structures such as the ribosomal subunits are seen as prime targets for discovering novel interactions of these types. Our laboratory has developed several approaches to enable the rapid searching for such clusters of hydrogen bonded interactions. In addition to conventional formations, the contributions of hydrogen bonding by protonated base pairing interactions have also been investigated. Our program NASSAM, is a pattern matching algorithm using graph theory, that allows fast and efficient searching of databases of nucleic acid structures based on a simplified vectorial representation of the nucleic acid bases (Harrison *et al.* 2003). This method allow searches to be carried out rapidly, efficiently and provides output to easily locate known or novel base triple interactions in RNA structure by using input search patterns consisting of either known or theoretical pattern formations. Filters were then used to further screen NASSAM output. The NASSAM searches yielded a number of novel base triple interactions. An alternative approach which utilizes specific hydrogen bonding interactions as search patterns, COGNAC, was also deployed. The approaches developed here will be a valuable method for studying models and mechanisms of RNA structural interactions formed from smaller subsets of base interactions. Base triples, quartets, quintets and the A-minor motifs are a few examples of such interactions.

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Harrison, A-M, South, D.R., Willett, P., and Artymiuk, P.J. (2003) Representation, searching and discovery of patterns of bases in complex RNA structures. *Journal of Computer-Aided Molecular Design*, **17**, 537-549.

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## **Molecular Basis of Substrate Specificity of the Adenylation Domains of Nonribosomal Peptide Synthetases.**

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Nonribosomal Peptide Synthetases (NRPSs) from bacteria and fungi, synthesise structurally complex biologically active peptide products, including numerous potential antibiotics. As antibiotic resistance is increasing more rapidly than new antibiotics are produced and/or discovered there is a need to exploit enzymes such as NRPSs to generate novel antibiotics. NRPSs are multi domain enzymes and the order in which the amino or hydroxyl acids are combined into the peptide product is normally determined by the arrangement of the Adenylation Domains (A Domains). Currently very little is known about how these A domains select for a specific substrate. Until the molecular basis of substrate specificity of these domains is understood, it is not possible to 'reprogram' A domains, and therefore NRPSs, to produce novel products. In this paper we report work to determine the molecular basis of substrate specificity of the A domains of NRPSs. Using an in-house database of A domain sequences and the only available A domain crystal structure, PheA, bioinformatics sequence and structure analysis methods have been used to predict which amino acid sidechains line the domain active sites. A Principal Component Analysis (PCA) model was built utilising only the predicted binding pocket residues of a set of sequences of biochemically characterised A domains. The dataset used to train the model is representative of a wide range of substrates and genera. The model was tested by predicting the substrate specificity of uncharacterised domains.

To test this model further, molecular dynamics (MD) simulations have been performed with the native ligand and a 'new' ligand, known not to bind in the native pocket. Binding pocket residues were then mutated, guided by the PCA model predictions, and the native and 'new' ligands docked into this new pocket. MD simulations were then performed on these systems. Analysis of these simulations provides insight into the role of these binding pocket residues in the molecular recognition of the substrate.

The implications of this work for designing new NRPSs by informative manipulation of the A domain primary sequence will be discussed.

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## **Driving protein-ligand docking by quantitative chemical shifts perturbations**

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Docking is a convenient computational method for predicting protein-ligand complexes. However, the success of current docking approaches is to a large extent limited to those cases where well-defined binding cavities exist, which limit the search space considerably. In contrast, protein-protein interfaces, an emerging therapeutic opportunity, present large, flat interaction surfaces to which accurate docking solutions are difficult to find[1]. These limitations are now starting to be overcome by so-called data-driven docking approaches. There, the docking objective and/or scoring functions are “tailored” to the target, incorporating as much specific knowledge as available, including experimental measurements. In our approach, DrugScore[2] (DS) potential fields are combined with a chemical shifts perturbations (CSP) term, yielding a hybrid-scoring function. The CSP term accounts for differences between CSP predicted on the protein side at each docking step and the experimentally measured ones from the complex under study[3]. The traditionally restricted use of CSP to a qualitative indication of the binding location is here expanded to a full structure determination scheme. Observed CSP on the protein side after ligand binding are affected also by protein rearrangements. As such, we define those CSP that arise mainly from the direct influence of the ligand as “direct markers CSP” and the rest as “indirect markers”. In our case, direct markers are those that we are able to predict from the native complex within a threshold, if the ligand is considered as the only perturbing source. So far, we have been able to test the approach with 5 complexes for which experimental data was publicly available (BMRB database) and for which DS-only did not work. After running 100 docking experiments on them, in all cases a “good docking solution” (RMSD of the solution vs. the original PDB < 2.00 Å) was found ranked first. The single remaining bottle-neck is then to correctly identify a priori those direct markers. We will discuss how data mining experiments have been applied to overcome this last step.

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## A Fast and Accurate Biomembrane Model

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We have developed a simplified molecular mechanics model for hydrated bilayer membranes composed of DMPC phospholipids. Using non-isotropic potentials, groups of atoms are “coarse-grained” into rigid-bodies of tunable shape: each lipid molecule, that in reality comprises more than a hundred atoms, is represented by only ten macro-particles, covalently bonded via harmonic springs. In particular, each hydrocarbon tail is modelled by a chain of three neutral ellipsoids [1], the glycerol-ester region by two ellipsoids with embedded dipoles, and the head-group by two charged spherical units. Water molecules are described using the soft sticky dipole potential [2], an efficient single-site model. To simulate the system via molecular dynamics, we have implemented BRAHMS, a Biomembrane Reduced-Approach Molecular Simulator: reduced number of interactions, removal of fast degrees of freedom and use of efficient algorithms make our methodology one hundred times less demanding of CPU-time than standard atomic-level modelling. Despite the simplified representation, the use of anisotropic potentials along with full incorporation of electrostatics allows the underlying physics to be accurately captured. Our model correctly reproduces experimental data for DMPC bilayers such as lipid volume and area, membrane thickness, tail order parameters, magnitude and orientation of the head-group dipole, and compressibility moduli. We have also calculated the lateral pressure distribution along the bilayer normal: results are consistent with the existing atomic-level simulation data and several different theoretical predictions. The efficiency of our methodology allows us to reach relatively long simulation times (hundreds of nanoseconds), making it possible to study rare events and slow phenomena. In particular, we have detected occasional permeation of water molecules across the membrane and computed the permeability coefficient: our result is within an order of magnitude of experiment. The self-assembly process has also been simulated: starting from a random solution, lipids spontaneously aggregate in a bilayer.

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