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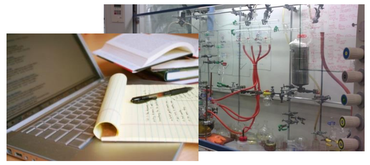
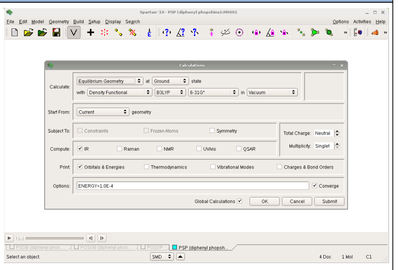
QUANTUM MODELLING OF CHALLENGING CHEMICAL SYSTEMS

Investigating computational approaches to model phosphorus containing compounds and predict their chemistry

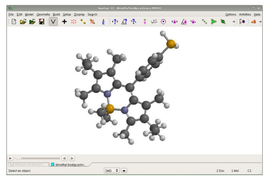
Introduction to Computational Chemistry

Traditional methods of discovering new molecules involves hours of research and laboratory synthesis.





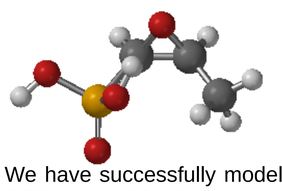
Additionally, if the molecule of interest ignites spontaneously in air, or is thermally sensitive to decomposition (explosive), is biologically active (toxic) or contains a radioactive element, then the research worker must be highly trained and requires sophisticated, expensive apparatus before making the compound.



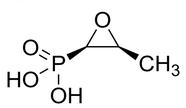
Advances in computing mean that fast and reliable modelling studies now no longer require access to national supercomputers, but can be done on a desktop PC using a program such as Spartan, as long as there aren't too many electrons in the system. In this fashion, it should prove possible to employ Spartan to first model the aforementioned difficult systems before synthesising them for real.

Although Spartan (and other programs) can model many features of a molecule such as its structure, energy and reactivity, it's important to realise that there is a relationship between how long a calculation will take and how accurate it is. As such, quick approximations - often useful starting points - can be carried out at a relatively low level of theory using classical theories about mechanics. However, in this project we sought a higher level of theory - *Density Functional Theory (DFT)* – which uses quantum mechanical methods to determine the properties of a molecule from functionals of the electron density. It is the most commonly used method due to its strength of speed and accuracy. For the molecules in this poster, the structure was built in the window, the level of theory was chosen, and the molecular properties to be modelled were selected.

Can We Successfully Model P-Antibiotics?

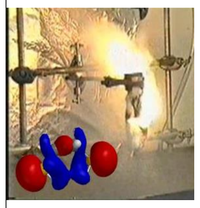


(2*R*,3S)-3-methyloxiran-2-yl]phosphonic acid



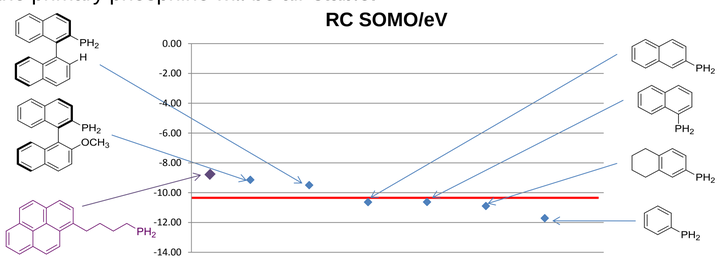
We have successfully modelled one of the most widely used antibiotics, using DFT with a B3LYP functional. The calculated bond angles were found to be accurate within a 0.6% difference from measurements taken from the crystal structure.[1] The bond lengths were found to be accurate within a 1.9% difference. Therefore this shows Spartan is capable of modelling the antibiotic Fosfomycin's structure. Future work will model its interactions with receptors.

Modelling If A Compound Will Be Explosive



Primary phosphines have a reputation for being unstable, toxic, noxious and highly air-sensitive compounds. However, previous research undertaken by the Higham group led to the discovery of certain primary phosphines that had unprecedented air-stability. We then used DFT calculations to establish that increased conjugation in the molecule (more double and single bonds in a sequence) provides resistance to oxidation by air, as shown in the in graph below.[2]

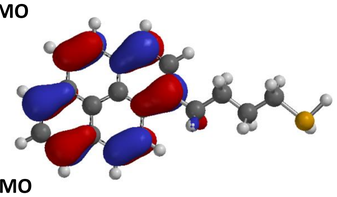
It appears that if the phosphine is air-sensitive then it initially forms a high energy radical – this then reacts with oxygen to eventually form an oxide with the release of a large amount of energy. Those phosphines with a low energy radical do not enter this oxidative process and are stable. **Target:** the group wished to prepare the novel pyrene compound **2** because if stable this would represent the first air-stable alkyl primary phosphine with just C, P and H atoms. So is it stable? Modelling the molecule's radical cation energy gives an E_{SOMO} of -8.64 eV. This can be compared to the graph below, where values of above -10 eV suggests the primary phosphine will be air-stable.



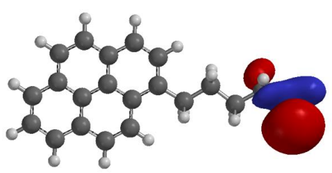
E_{SOMO} values of some primary phosphines with differing degrees of π-conjugation in their carbon backbone.

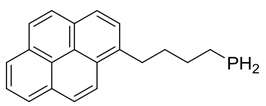
Another trend is observed in the orbitals of these highly conjugated molecules; whereas the neutral HOMO has a strictly π-electron nature with no interference from the phosphorus atom, its radical counterpart has a SOMO which shows the phosphorus atom now contributes the most to the orbital character. Our calculations show primary phosphine **2**, complies with these predictions (**a** and **b**, *below*) and should be air-stable; it was prepared in the lab and tested (below).

a HOMO



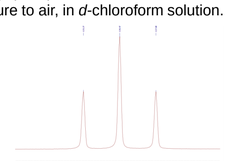
b SOMO





2

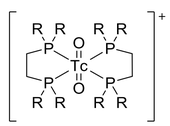
^{31}P NMR spectrum of **2** showing 100% of the primary phosphine remains even after 7 days exposure to air, in *d*-chloroform solution.



Outcome: Compound **2** *is* air-stable

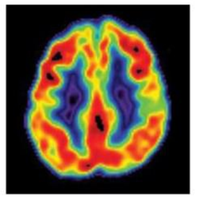
Predicting Properties of Radioactive Imaging Agents

Myoview™ is a metal complex used in over 40 million heart scans worldwide, each year, because of its ability to provide *in vivo* nuclear imaging due to the unstable nature of the technetium metal as a gamma emitter. This radiation can be detected by the clinical imaging technique known as Single Photon Emission Computed Tomography (SPECT), and create images of organs like the heart or brain (see below).



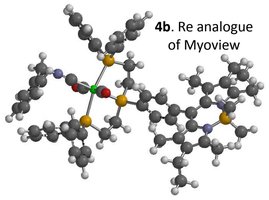
Myoview

4a. SPECT imaging in the diagnosis of Alzheimer's



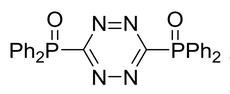
One problem with these agents is that they cannot be easily tracked in actual *cells*. The Higham group is working on sophisticated analogues which are also fluorescent and would allow us to follow them by microscopy. This means we could see their mode of action in cultured cells rather than in an actual patient.

However due to the radioactive nature of ^{99m}Tc this limits experimentalists and hinders more exploratory research. Therefore non-radioactive rhenium is used as a convenient substitute in the lab – this still allows the fluorescence then to be measured in actual cells. However to show these rhenium probes *are* accurate technetium models, the Tc and Re analogues were calculated and compared; the summer studies show they are, within 1%.



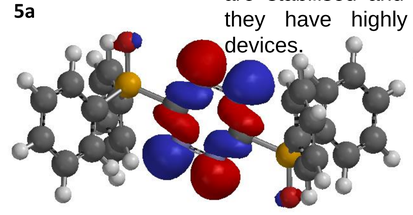
4b. Re analogue of Myoview

Modelling Stability Of Nitrogen-Rich Aromatics



5a

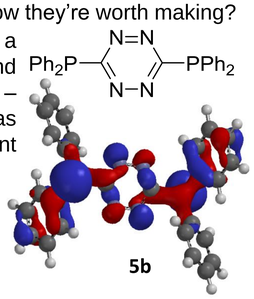
Nitrogen-rich aromatics are often used as explosives and can be highly unstable to work with. This research field is neglected due to this reputation, however rings containing four nitrogen atoms *are* stabilised and can be synthesised. Audebert[3] has shown they have highly favourable optoelectronic properties for devices.



As a phosphorus research group we were approached by Audebert who was keen to know if phosphorus could be incorporated onto a tetrazine – the difficulty here is that only two such compounds have ever been made, which used hazardous reagents. Can modelling show they're worth making?

The calculations show a phosphotetrazine oxide will have a HOMO with an n nature – 'nonbonding' as shown by **5a** and the electron density to be localised on to the tetrazine ring – this renders the molecule fluorescent. Whereas phosphotetrazines are forecast to be non-fluorescent derivatives and will have HOMO's of π nature, shown in **5b**.

Modelling using DFT and B3LYP/6-31G* showed that **5a** and **5b** should act as an on/off fluorescent switch sensitive to oxygen – and so their syntheses is now underway.



5b

References: [1]A. Perales, S. Garcia-Bianco, *Acta Crystallography,* 1978, B34, 238-242. [2]L. J. Higham, *Angewandte Chemie International Edition,* 2012, 51, 1-5. [3]G.Clavier and P. Audebert, *Chemical Reviews*, 2010, 110, 3299-3314.