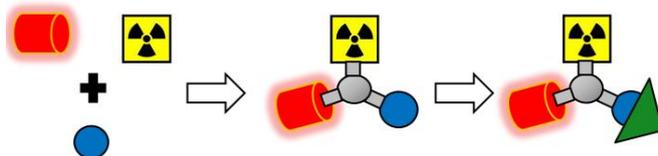


Title Site-specific labelling of proteins by conjugation to tyrosine residues

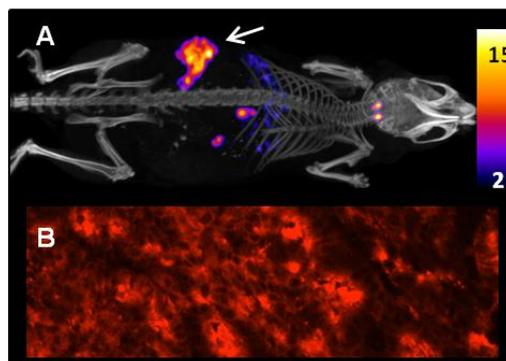
Supervisor Dr Erik Årstad (UCL Chemistry)

Project Proteins is the fastest growing class of therapeutic drugs,¹ and there is a considerable interest in methods that enable conjugation of reporter groups to proteins for development of diagnostic imaging agents. Whilst protein conjugation with lysine and cysteine side chains is well established, current methods are unsatisfactory as they typically result in conjugation at multiple sites, provide moderate to low yields, or require excess of reagents for efficient conjugation.

The aim of this project is to develop a novel method for protein conjugation based on covalent bond formation with tyrosine residues. Tyrosine contains a phenol moiety that is routinely exploited for labelling with radioactive iodine, however, the use of tyrosine for conjugation of other reporter groups has only recently been explored. Diazonium salts² and diazodicarboxamides³ have been shown to react with tyrosine residues in proteins; however, the methods are not sufficiently efficient and practical to allow routine insertion of reporter groups into proteins at low concentrations. For this project, you will explore novel conjugation reactions, as well as modifications of previously reported methods for reactions with tyrosine. If successful, the new conjugation method will be used to insert dual optical and nuclear reporter groups – which recently have been developed by the group⁴ – into antibodies and proteins for imaging studies in collaboration with Centre for Advanced Biomedical Imaging (CABI).



In the group we have developed a multi-component reaction for coupling of a fluorescent dye (red), radioactive iodide (yellow) and a bioconjugation group in one step. Subsequent conjugation to proteins and antibodies allow imaging of biological targets across the scales from whole body imaging (A, right) to the cellular level (B, right).



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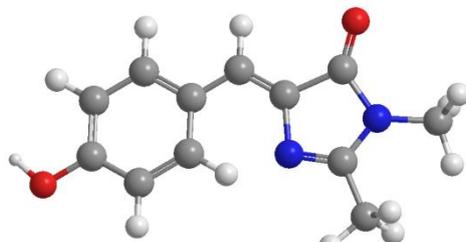
Title	Novel approaches to sensor calibration
Supervisor	Dr Daren Caruana (UCL Chemistry)
Project	<p>There are hundreds of different types of sensors that are used routinely to monitor the environment we live in, medicine and our healthcare. One of the common underlying operational problems that these sensors have is the need to calibrate them, whether they are single use or continuous monitors, the confidence of their measurement can only be increased by calibration. The aim of this project is to develop a remotely positioned unit capable of releasing a predetermined aliquot of salts or other material that can be used to calibrate a sensing probe. The unit will have no moving parts and will provide a feedback registration of release.</p> <p>A reusable unit charged with a set number of calibration events with the following characteristics: fast release of material into a finite volume of liquid, self reporting to register the complete release of material, pre-programmed to provide a cycle of two or three (or more) calibration points per calibration cycle and controlled remotely.</p> <p>This project will explore conventional and novel solutions using an electrochemical based unit containing a unique dissolvable coating that can be electrolysed to release a known amount of material.</p>
References	

Title	Detection of Sickle cell Haemoglobin
Supervisor	Dr Daren Caruana (UCL Chemistry)
Project	<p>Sickle cell disease (SCD) is a genetic disorder that results in a haemoglobin protein (haemoglobin sickle HbS) with a single amino acid substitution but results in severe clinical manifestations. The mutation in the protein leads to the polymerisation of haemoglobin within the red blood cell (RBC) when the oxygen concentration is low. These fibrous structures result in deformation of the RBC and cause vascular occlusion. Patients with SCD can suffer both from the direct consequences of the disease and from iron overload due to repeated blood transfusions. In addition a wide range of endocrine, metabolic and nutritional abnormalities are found in SCD patients.</p> <p>The current most rapid method that can be used to screen for HbS is based on an <i>in vitro</i> haemoglobin solubility test. The method relies on the chemical deoxygenation of a high ionic strength buffer and the precipitation of the HbS which occurs due to its low solubility.</p> <p>The aim of this work programme is to develop a device capable of detecting sickle cell anaemia for screening and to aid the therapeutic effectiveness of blood transfusions. The approach is to use electrochemical methodology to reduce the dissolved oxygen in the system to mimic physiological conditions. From previous preliminary,¹ it is clear that electrochemical depletion of oxygen is likely to be a very successful approach of simulating the low partial pressure of oxygen present in blood capillaries.</p>
References	1. Z. Iqbal et al, <i>Analyst</i> , 132 (2007) 27-33

Title Fluorescent protein mimics

Supervisor Professor Helen Fielding (UCL Chemistry)

Project



Model GFP chromophore

The realization that the Green Fluorescent Protein (GFP) could be expressed in living organisms has brought about a revolution in the life sciences. GFP and its derivatives can be fused to other proteins without interfering with their function or their location and thus it has become a much sought-after, non-invasive tag

that makes it possible to follow dynamic events in cells by illuminating them with ultraviolet light and monitoring the subsequent fluorescence. Fluorescent proteins are used widely as imaging tools for *in vivo* detection of proteins in a variety of biological processes, including growth and mobility of tumour cells, neuron activity, and chromosomal dynamics. There is interest in developing mimics of the GFP chromophore that are fluorescent when bound to DNA or RNA so they can be used as imaging tools to gain better understanding of DNA and RNA biology and advance DNA and RNA applications. Surprisingly, many of the fundamental physical constants that control the photoactivity of these important chromophores are still unknown.

The aim of this project will be to characterise the absorption and fluorescence properties of a number of model fluorescent protein chromophores and to determine the electron affinities of their anions, using photoelectron spectroscopy to measure the photodetachment energy, *i.e.* the binding energy of the electron to the anion. Electronic structure calculations can also be performed to assist with the analysis of the spectroscopic data (using commercial quantum chemistry software).

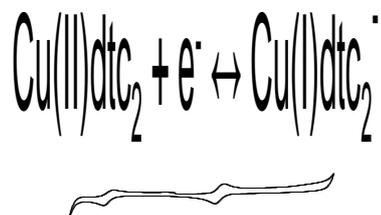
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Title Copper complexes for the detection and treatment of cancer: the role of redox chemistry

Supervisor Dr Katherine Holt and Dr Graeme Hogarth (UCL Chemistry)

Project A common feature of solid tumours is tissue hypoxia – where the oxygen concentration is lower than surrounding tissue. This can be probed by using radiopharmaceuticals that accumulate in regions of low oxygen concentration by virtue of their redox chemistry. Recently Cu radionuclides have been identified as potential targets for PET imaging. Cu has very versatile coordination chemistry allowing molecules with advantageous properties for cellular uptake to be designed and synthesised. Copper also has extensive redox chemistry which means that these complexes will be very sensitive to the redox environment (i.e. oxygen concentrations) within tissues. This project will focus on the redox chemistry of Cu dithiocarbamate complexes. Cyclic voltammetry and other electrochemical techniques will be used to determine the redox states of the Cu complexes and their relative stabilities. This will enable the rapid screening the identification of molecules suitable for uptake and redox trapping by cells.



References J.P. Holland et al, Eur. J. Inorg. Chem., 2008, 3549 – 3560.

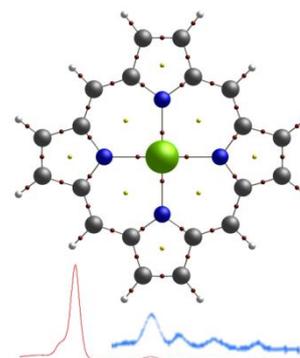
Title	Studying the redox chemistry of keratin using electrochemical methods
Supervisor	Dr Katherine Holt (UCL Chemistry)
Project	<p>Keratin is a protein that is an important structural component of skin, hair and nails. Its structural integrity is attributed to the strong disulphide (S-S) bonds that hold the protein structure together. Very little is currently known about the mechanism of disulphide bond breakage and repair and the role of this chemistry in diseases of the skin and nails. In collaboration with Dr Stuart Jones, Dept of Pharmacy, King's College we have been investigating the role of redox chemistry (i.e. electrochemical reactions) in the mechanisms of nail and skin disease development, especially with respect to attack on the disulphide bonds.</p> <p>In this project different methods for preparing keratin samples from hair and nails will be explored. The electrochemical response of the keratin will be investigated using cyclic voltammetry and other electrochemical techniques. The electrochemical response of the keratin after treatment with different oxidising and reducing agents will be compared. Electrochemical responses will be related to disulphide bond integrity using Raman spectroscopy to detect the number of disulphide bonds and any changes in their structure. Conclusions will be drawn about the role of redox chemistry in damage and repair of tissues such as skin and nails to enable more effective drug delivery and treatment strategies to be developed</p>
References	R.H. Khengar et. at., Free Radical Biology and Medicine, 2010, 49, 5, 865.

Title Tuning porphyrins: quantum chemical studies of the effect of structural modification on absorption properties

Supervisor Dr Andy Kerridge (UCL Chemistry)

Project Porphyrins play a fundamental role in nature, being critical components in both cardiovascular oxygen transport and photosynthesis. This has led them to be described as the 'pigments of life', and their photophysical properties are resulting in an increasingly important technological role. One of the most important porphyrin applications are their use as photosensitisers in photodynamic cancer therapy (PDT). In this application the position and intensity of optical absorption bands is of critical importance, and this project seeks to investigate the dependence of these absorption bands on molecular structure.

The project will use a quantum chemical methodology known as Density Functional Theory (DFT) in order to calculate the ground state molecular and electronic structures of porphyrins. Time-dependent (TD)DFT will be used to calculate excited state electronic structures and absorption spectra. Analysis of the resulting electronic structures will be performed using the quantum theory of atoms in molecules (QTAIM) and the electron localisation function (ELF). The project will consist of three main components:



i) Characterisation of free base and metalloporphyrins. Ground and excited electronic states will be calculated and compared with literature values.

ii) The effect of substitution. The dependence of molecular & electronic structure and absorption properties on peripheral- and skeletal-substitution will be investigated.

ii) Tuning porphyrins. The results of i) and ii) will be used to clarify how a porphyrin complex can be 'tuned' to suit a specific technological requirement.

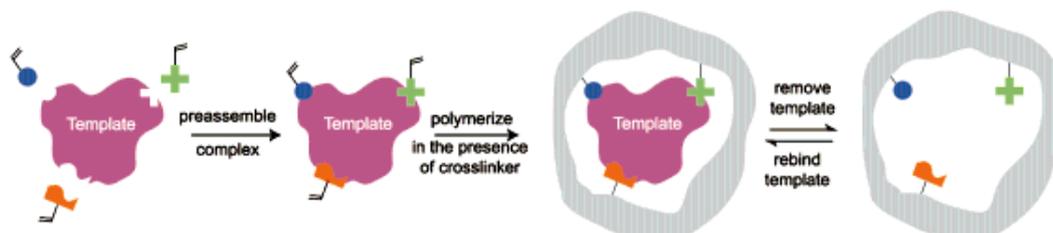
Work involved: Molecular simulations using the TURBOMOLE quantum chemistry code will be performed in a Linux environment. Topological analysis of calculated electron densities will be performed using the existing dgrid (Linux) and multiwfn (Window/Linux) programs. Numerical and graphical data will be critically assessed in order to establish criteria for inducing variation in absorption properties.

References

Title **Molecularly Imprinted Polymers – potentially “synthetic antibodies” or “just not good enough”?**

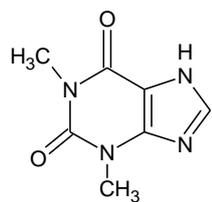
Supervisor Dr Dewi Lewis (UCL Chemistry)

Project Molecular imprinting¹ has for the past 20 or so years been developed as a means of “designing” materials for high selectivity catalysis, separation and more recently for drug delivery. The principle (outlined below) is simple: insert the molecule you wish to be selective for (or a mimic of it) into a polymerisation reaction and you will create imprints in the resulting polymer which will host that molecule.

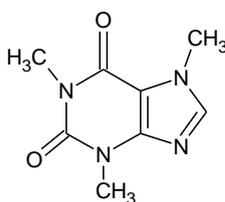


Synthesis of a MIP: from M. J. Whitcombe, E. N. Vulfson, *Adv Materials*, 2001, **13**, 467

The reality is that many of these imprints are not as perfect as we would wish (since we cannot control the polymerisation) or that they are inaccessible to the molecule when it comes to use. Nevertheless, such materials have, huge potential in many fields from biomedicine to airport security. However, to be successful they must



theophylline



caffeine

demonstrate very high levels of selectivity. The aim of this project is to computationally design “optimal” imprints for a variety of applications – starting with the test case of separating caffeine and theophylline.

The overall aim, is to determine the “best possible” imprints and to

determine if they are capable of the separation performance required in, for example, pharmaceutical preparations or in the detection of drugs or explosives. If these idealised materials aren’t “good enough” will a real material be useful?

You will rationally design both “by hand” and using an automated *de novo* molecular design programme (ZEBEDDE²) idealised cavities in a series of cross-linked co-polymers. You will then evaluate the imprint surfaces for their selectivity for the various target molecules using a combination of molecular dynamics and quantum mechanical methods.

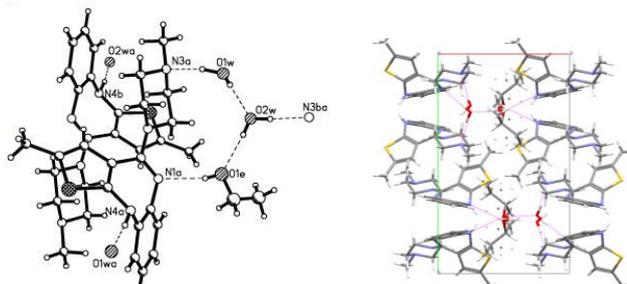
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Title Predicting promiscuous solvate formation as an aid to pharmaceutical development

Supervisor Professor Sally Price (UCL Chemistry)

Project



Olanzapine butanol hydrate: disordered solvate molecules in channels.

Pharmaceutical products usually have the active ingredient as a crystalline solid, almost all will go through a crystallization process in production, and it is highly desirable that they can be stored anywhere in the world, through great changes in temperature and relative humidity without change. Hence, it is a major disadvantage if the crystal structure is likely to absorb water or other solvent molecules during processing and storage.¹ The search for the range of solid forms of some pharmaceuticals, using automated systems to use a wide range of solvents, has shown that some molecules form a large number of solvates, including some mixed solvates where water and the solvent are both included in the crystal structure. This is a problem for developing this drug molecule, so it would be very useful to be able to predict which molecules are promiscuous solvate formers.

We have calculated the crystal energy landscape,² the range of low energy crystal structures for over 150 molecules, including recently a few pharmaceuticals³ where our collaborators in Strathclyde have found many solvates. This has led to the hypothesis that molecules which are promiscuous solvate formers are those which cannot pack densely with themselves, but have a significant fraction of void space in any crystal structure of the pure molecule. This project is to test this hypothesis, by analysing the available experimental crystal structures (using the Cambridge Structural Database and its analysis programs⁴) for the molecules in our database of computed crystal structures, and calculating and correlating the packing coefficients with the range of solvates known.

The project is mainly developing informatics, the extraction and analysis of data from databases, to test hypotheses, and so requires good organisational and spreadsheet skills, and logical thinking.

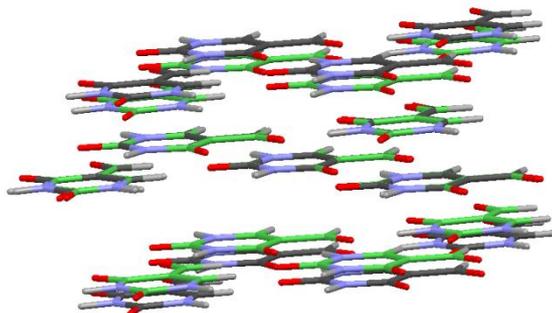
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3. Johnston A. et al. *CrystEngComm* **2008**, *10*, 23-25
4. Macrae, C. F. *J. Appl. Crystallogr.* **2008**, *41*, 466-470

Title Exploring electronic level modelling of organic polymorphs

Supervisor Professor Sally Price and Dr Jörg Saßmannshausen (UCL Chemistry)

Project



The development of new drugs depends on knowing the relative stability of their crystal structures (polymorphs). It can be difficult to find all the polymorphs, let alone determine their relative stability by calorimetry if they decompose prior to melting.

Hence a computational method of predicting all possible crystal structures (polymorphs) and their relative thermodynamic stability is needed for developing new pharmaceuticals and other speciality chemicals.² Accurate evaluation of the relative energies of different crystal structures of organic molecule is very demanding, as the molecular conformation can change to improve the intermolecular interactions, of which the dispersion (van der Waals) interactions are an important component. Standard periodic density functional (DFT) methods are inadequate, as the poor modelling of the dispersion affects some structures more than others. A commercial company has shown that by adding an empirically fitted damped $-C_6/R^6$ model for the dispersion to a specific DFT energy (a DFT+d model), provides reasonable relative lattice energies for a wide range of small organic molecules.³ However, a recent study of two different dispersion corrected models gives rather surprising results for the energy differences between many pharmaceutical polymorphs.⁴

This project is to use the two DFT+d models currently implemented in CASTEP to explore their ability to reproduce the structures and relative energies of polymorphs, of small pharmaceuticals and model molecules. This project will provide training in using a widely used computational chemistry code CASTEP for an important new area of application. Some background in computational chemistry and crystallography background would be useful but not essential.

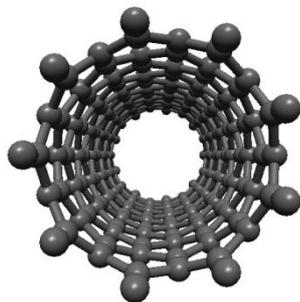
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Title Interaction of pharmaceutically active molecules with chemically modified carbon tubes and graphenes

Supervisor Dr Christoph Salzmann (UCL Chemistry)

Project



Carbon nanotubes and graphene are the vanguard materials of the emerging nanosciences. Consisting solely of sp^2 hybridised carbon atoms these materials display very large conjugated pi-systems. A wide range of pharmaceutically active molecules (*e.g.* antiphlogistics, antiepileptics, betablockers and lipid-regulating agents) contain conjugated groups as well, and they are therefore expected to interact with the carbon nanomaterials through pi-stacking interactions

resulting in the immobilisation of the molecules from solution onto the insoluble carbon materials.

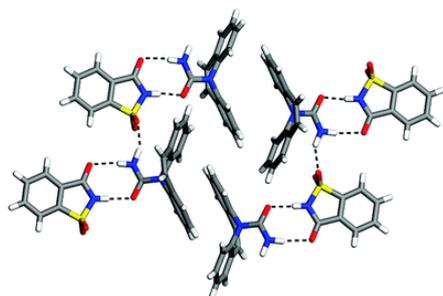
The aim of this project is to follow the adsorption and interaction of a range of pharmaceutically active molecules with carbon nanotube and graphene materials. This will require the preparation and design of carbon materials with large specific surface areas. The adsorption processes will be followed mainly by using X-ray photoelectron, Raman, FTIR and fluorescence spectroscopy. Furthermore, it will be investigated if the presence of functional groups on the carbon materials (*e.g.* carboxylic acids, amines *etc.*) can change and allow tuning the adsorption characteristics. Potential applications resulting from this work are in new sensor technologies, water purification and drug release / delivery systems.

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Title Computational and systematic experimental studies on the solid forms of saccharin

Supervisor Professor Derek Tocher and Professor Sally Price (UCL Chemistry)

Project The small organic molecule saccharin is ubiquitous as an artificial sweetener with effectively no food energy. However it also has other potential uses related to the human condition where its role may be more actively beneficial. In particular in the pharmaceutical industry a key concern is to discover ways to improve the physicochemical properties of active pharmaceutical ingredients (APIs). The solubility, dissolution rates, melting point and moisture sorption tendency of APIs all affect the bioavailability, manufacture and stability of the form of the drug placed on the market. The pharmaceutical industry may seek to manipulate these properties by formulating the drug as either a co-crystal or as a salt, rather than taking it to the market in its 'pure' form (e.g. as the free acid, free base or neutral molecule). In principle saccharin may be combined with an API to form either a salt or co-crystal.



For example, it has been shown that saccharin will co-crystallize with indomethacin (a non-steroidal anti-inflammatory) and carbamazepine (an anti-convulsant) to form 1:1 adducts and will form saccharinate salts with a wide range of APIs e.g. quinine (anti-malarial), haloperidol (anti-psychotic) and mirtazapine (anti-depressant).

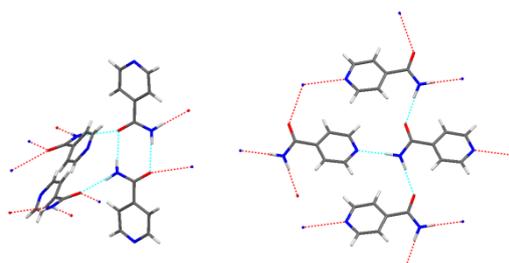
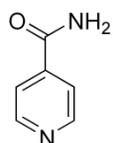
There are two strands to this project. The computational strand¹ will focus on the question as to whether we could predict the known crystal structure⁴ of saccharin, asking the question 'do we expect this molecule to exhibit polymorphism (i.e. should it have more than one crystal structure)? The experimental strand will focus on a systematic study to investigate the factors which determine the propensity of saccharin to co-crystallise.² Are there functional groups, common in pharmaceuticals, which are likely to bind to saccharin to form a co-crystal? This will involve simple mechanochemistry experiments (liquid assisted grinding) to detect co-crystal or salt formation between model molecules related to the groups interacting with saccharin in known co-crystals. Samples generated will be analysed and assessed using spectroscopic and crystallographic techniques.

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Title Crystallising isonicotinamide

Supervisor Professor Derek Tocher and Professor Sally Price (UCL Chemistry)

Project



Isonicotinamide Form 1 – EHOWIH01¹ Form 2 – EHOWIH02¹

Isonicotinamide has been investigated as a potential anti-inflammatory and is widely used in cocrystallisation studies, as the physical properties, such as solubility, of a crystal containing two different molecules may be more suitable for development of a pharmaceutical product. Isonicotinamide is polymorphic, adopting more than one crystal structure, with different physical properties. The two polymorphs shown above have different hydrogen bonding motifs. It also forms co-crystals with a variety of carboxylic acids.¹ Recent investigations into producing cocrystals of 3-arylbutanoic acids found two new polymorphs crystallising together.² Other investigators have shown a clear link between the solvent and the polymorph found, relating this to the hydrogen bonding association of the molecules in a range of non-polar, alcoholic and other solvents.³

This project will examine both experimentally and computationally the variety of ways that isonicotinamide can crystallise. Computer modelling will be used to generate the low energy crystal structures of isonicotinamide to see the range of ways the molecule can pack with itself⁴ and how this relates to the known polymorphs and motifs within cocrystals. Experimentally, a range of crystallisation and cocrystallisation experiments⁵ will be performed, to see how series of molecules (e.g. alcohols) that range from being solvents to solids at ambient conditions affect the polymorph or cocrystal formed. Such experiments range from solution crystallisation, thermal microscopy and grinding experiments. This project will aim to rationalise the formation of polymorphs and cocrystals with the competition between different hydrogen bonding preferences.

The project will involve using a range of crystallisation techniques, examining the product by IR, and characterising any new structures by X-ray diffraction, as well as generating and analysing the computed structures.

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Title	Atmospheric free radical reactions, solar UV radiation and health implications
Supervisor	Dr David Rowley (UCL Chemistry)
Project	<p>Ozone (O₃) is a crucial component in the Earth's atmosphere, as it acts as a filter of dangerous Solar UV radiation, it initiates the oxidation and therefore removal of many toxic pollutants, it contributes (both positively and negatively) to the greenhouse effect and it is a toxic gas that affects human health directly. Consequently, understanding the factors that control the abundance of atmospheric ozone is a key goal to understanding the extent of these environmental issues, as is understanding the effective toxicology of this molecule in these direct and indirect processes. On account of its reactivity, many trace species interact with ozone in the air, either producing or destroying it. The aims of this project are therefore to study such reactions under controlled conditions in the laboratory, but also to address the effects of ozone production or loss on human health, other ecosystems and the built environment.</p>
References	

Title	Engineering better MRI contrast agents
Supervisor	Dr Andrew Wills (UCL Chemistry)
Project	MRI is rapidly becoming a standard tool in medicine with over 75 million scans being performed each year. Contrast agents improve the ability to discern features in MRI images. Currently used materials are typically based on gadolinium which is toxic and requires encapsulation. This project aims to produce new contrast agents with reduced risks and involves research in synthesis and fundamental magnetism.
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