

Mod:organic

From ChemWiki

See also: 1C comp-lab startup, 1C Timetable, Laptop use, Programs, **Module 1C Script**, Module 1C Toolbox, Writing up, Don't panic.

Synthesis and computational lab: 1C

This is a two-week duration modelling module, part of an eight week chemical synthesis laboratory involving four experiments in total. **1C** is "twinned" with a synthetic component **1S** involving the asymmetric epoxidation of an alkene and its characterisation by NMR spectroscopy and chiroptical measurements.

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1 Overall Module Objectives

It is now possible using a computer to accurately model many aspects of organic structure and reactivity, and such modelling can often be used not only to rationalise the outcomes of reactions, but to predict useful modifications or even new types of reaction, and to predict various properties of molecules. The selection of (short) modelling experiments contained in this module of the course attempts to illustrate some of the diversity of such molecular modelling. The module comes in two parts, the first a series of set exercises to get you familiar with the basic operational techniques, and in the second part to apply these techniques to assigning the stereochemistry of a compound synthesized in the associated synthetic part of this experiment. The two parts carry 45% and 55% respectively of the marks.

1.1 Objectives for Set exercises: Part 1.

1. To use molecular mechanics to predict the geometry and regioselectivity of:
 1. the hydrogenation of cyclopentadiene dimer
 2. the conformation/atropisomerism of a large ring ketone intermediate in one synthesis of the anti-cancer drug Taxol
2. To predict the ¹³C and ¹H NMR spectra of a related Taxol intermediate and to compare the predictions with the measured values reported in the literature.
3. To gain familiarity with the use of a digital data repository ("assigning a doi to data")
4. To perform searches of the literature for each topic in order to cite in your final report any relevant references to each experiment as appropriate
5. To present the results in the form of a Wiki page

This first part of the module carries **45% of the marks** for the module.

1.1.1 Learning outcome

You will be able to use molecular modelling techniques to investigate the structure and spectroscopic of small and medium sized organic molecules.

1.2 Objectives for assigning the absolute configuration of a synthesized epoxide: Part 2.

In the second part of the module you will apply your experience of the programs gained earlier to:

1. **search** the Cambridge crystallographic database for the crystal structure of the precursor to the oxygen transfer catalyst
 - from which to identify any interesting structural features in this species
2. **compute** the **NMR spectra** of the epoxide you have made/will make.
3. **compute** the **optical rotation** of the epoxide you have made/will make.
4. combine the theory and experiment to assign the absolute configuration of the epoxide you made using the asymmetric catalyst.
5. analyse the transition states for the reactions for possible reasons for enantioselection
6. **search** Reaxys for potential epoxides with high values of optical rotation for future inclusion in the course.

This second part of the two-week course will carry **55% of the marks**.

1.2.1 Learning outcome

You will be able to assign the absolute configuration of a chiral compound new to science using a variety of computational techniques.

1.3 The software available to you

A computer lab is largely about familiarising yourself with appropriate tools for the task at hand. Some of the software you may wish to use is listed briefly below

1. The course **Wiki**. This is a read/write environment. You will use it to read the notes and instructions, and then to create your lab notebook/project report on-the-fly as you do the experiment.
2. **Avogadro+Chemdraw**. You will need to draw molecules and prepare the calculations using this combination of software.
3. **ChemBio3D+ChemDraw**. Another combination of programs, more or less equivalent to Avogadro+Chemdraw. You may wish to try both combinations, and then comment on the pros and cons of each in your report.
4. The **HPC computing portal**. This Web-based interface (using a normal Web browser) is where the files created using either of the software combinations above are actually run, producing **Gaussian** outputs.
5. **Avogadro** or **Gaussview**. These programs serve to analyse the outputs from **Gaussian**.
6. **G09W** (a Windows version of Gaussian) can be used directly on your issued laptops.
7. **Jmol** is embedded into the Wiki, and is used there to create rotatable 3D models of molecules and their computer properties (such as vibrations, surfaces, etc).

1.4 Preparation and planning

This lab module will be carried out using computers, either a desktop or laptop computer which you are the exclusive user of, or a remote (*high performance* or *HPC*) system which you share with other users, and to which you will submit jobs. Because the calculations can take anything from seconds to many hours to complete, it is especially important to carefully plan your experiments beforehand. You have the considerable advantage and flexibility of having access to the computers not just during a six-hour period during a working day for four days a week, but in fact 24/7! But you also have to be aware, like any laboratory instrument, that the HPC system is a shared resource and that queues may form for it. So most importantly you will have to identify the time consuming calculations and ensure that you allow enough time to complete them (mindful that queues are most likely to form on the day before the project has to be submitted).

Since this module is conducted during a two-week period, you will have one two-day weekend available to submit long-running calculations, which you are urged to take advantage of. Another aspect of planning is to check that the inputs for the calculations do not contain errors that will cause the job to fail after 1 second. Take care to always check your submissions for simple errors that may cause you to lose 1-2 days worth of time.

1.5 The literature available to you

In the 1S experiment that accompanies this module, you are given a variety of lead references, and all the techniques that you need to use are described in detail in these articles (and others you may find by yourself). This computational module has a number of relatively new techniques, and only a few are well described in literature articles. Some key references are given at the end of each section. It is our intention in fact to produce a descriptive article for publication associated with this experiment. Please bear this in mind, and if you have any points that you think could be usefully included in such an article, please include them in your report.

You will cite the literature (and the data you produce) using digital-object-identifiers (**doi**) as well as conventional "RSC-style" citations.

2 Conformational analysis using Molecular Mechanics (~2 days, Part 1).

A general introduction to the ^[1] MM2/MMFF94 method should be consulted before attempting any calculations. The present techniques illustrate several more complex applications of this method to typical chemical problems and the type of information that such modelling is capable of providing. This involves optimising molecular geometry to an energy minimum and analysing the final energy in terms of bond length and angle strain, steric effects and van der Waals contributions.

Before discussing specific applications of such a model, it is worth noting some of the limitations of the molecular mechanics approach. It is essentially a parametric method, using data from experimentally well characterised and known molecules. It is therefore used as an interpolative rather than an extrapolative technique, which cannot stray too far from "known chemistry". Thus it is not easily possible to model "kinetic control" of a reaction using the standard approach, since that requires knowledge of the transition state structure and energy. For the same reason, new molecules with unusual bonding are rarely amenable to modelling, and recourse has to be sought in the full quantum mechanical treatment of the system. Similarly, for molecular properties such as stereoelectronic effects, aromaticity, hyperconjugation and frontier orbital interactions which require a knowledge of the electron distribution within the molecule, recourse has to be made to quantum mechanical methods such as molecular orbital theory. Finally, molecular mechanics parameters are available only for certain types of bonds, and frequently are not available for many functional groups. Metal ions are also a category less easily handled at present by this type of model.

You will be using the as implemented in the ChemBio3D/Avogadro^[2] programs. These include:

1. MMFF94s (the recommended force field, but limited only to certain combinations of certain elements)

2. UFF^[3] This force field can be used across the entire periodic table, but it is a very simplistic model which assumes fixed hybridisations for each atom.

Information Produced by the Programs: Avogadro using MMFF94s produces an energy (in kcal mol⁻¹) together with optimised values for bond lengths, angles etc. This energy is a rather odd quantity. It is NOT related to any thermodynamic quantity such as ΔH , and energies obtained using two different force fields CANNOT be compared. You CAN however compare two energies calculated using the same force field for two different ISOMERS. You can also calculate energy differences for simple reactions such as the hydrogenation of alkenes, particularly if this is compared across a series of related reactions. The energy itself can be dissected into contributions. Proceed as follows to obtain this dissection:

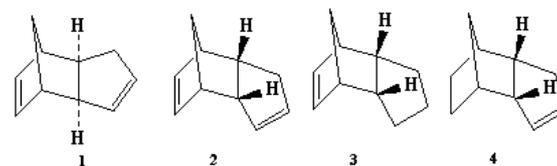
1. In Avogadro, **Extensions/Molecular Mechanics/Calculate energy**.
2. Click on the **Messages** box on the bottom of the display.
3. **Total bond stretching energy = 0.356 kcal/mol** gives the stretching energy
4. **Total angle bending energy = 0.027 kcal/mol** is the bending term
5. **Total torsional energy = 5.000 kcal/mol** gives the torsion term
6. **Total van der Waals energy** is the non-bonded energy
7. **Total electrostatic energy** is the term due to electrostatic interactions between atoms with non-zero charges.

Each term indicates the deviation from "normality" of the particular function. For example, a very positive stretch term would indicate the predicted bonds are far from the "natural" lengths, due to some geometrical feature of the molecule. Comparing these terms across say two isomers provides a natural explanation for why one isomer may be more stable than the other. Documentation for the programs being used is found here:

1. Molecular Mechanics: Avogadro
2. Ab initio/DFT MO: Gaussian/Gaussview

2.1 The Hydrogenation of Cyclopentadiene Dimer

Cyclopentadiene dimerises to produce specifically the endo dimer **2** rather than the exo dimer **1**. Hydrogenation of this dimer proceeds to give initially one of the dihydro derivatives **3** or **4**. Only after prolonged hydrogenation is the tetrahydro derivative formed. The modelling technique here involves calculation of the geometries and energies of all four species **1-4**.



The relative stabilities of the pairs of compounds **1/2** and **3/4** should indicate which of each pair is the less strained and/or hindered in a thermodynamic sense. The observed reactivity towards cycloaddition and hydrogenation can of course be due to either thermodynamic (*ie* product stability) or kinetic (*ie* transition state stability) factors. In pericyclic reactions in particular, regio and/or stereoselectivity is controlled by the electronic properties of the molecules (stereoelectronic control), and hence can only be understood in terms of *eg* the molecular wavefunction (*cf* 2nd year lectures on pericyclic reactions).

- The **objective** of this part of the module is to establish on the basis of the results obtained from the molecular mechanics technique whether the cyclodimerisation of cyclopentadiene and the hydrogenation of the dimer is kinetically or thermodynamically controlled.
- You should then search the literature to establish what the actual experimental outcomes are.

2.1.1 Procedure

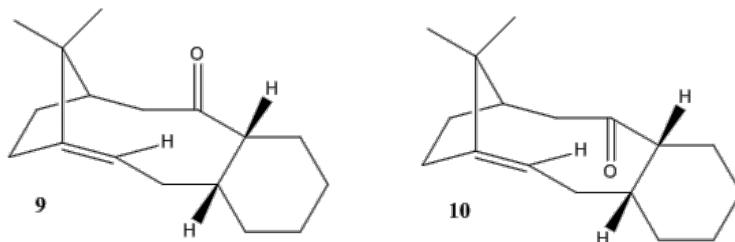
Using Avogadro or ChemBio3D, define the two products **1** and **2** and optimise their geometries using the MMFF94(s) force field option. In the light of the above discussion, relate your results to the observed mode of dimerisation. The two products of hydrogenation, **3** and **4**, can be similarly compared so that a thermodynamic prediction of the outcome of hydrogenation of each of the double bonds in **2** can be obtained. Analyse the relative contributions from the stretching (str), bending (bnd), torsion (tor), van der Waals (vdw) and electrostatic energy terms in terms of the relative stability of **3** and **4**.

Estimated time for completion: < 2 hours

2.2 Atropisomerism in an Intermediate related to the Synthesis of Taxol.

A key intermediate **9** or **10** in the total synthesis of Taxol (an important drug in the treatment of ovarian cancers) proposed by Paquette^[4] is initially synthesised with the carbonyl group pointing either up or down. On standing, the compound apparently isomerises to a single carbonyl isomer. This is an example of atropisomerism^[5]. Clearly the stereochemistry of carbonyl addition depends on which isomer is the most stable. It is also noted that during subsequent functionalisation of the alkene, this reacted abnormally slowly!

- The **objective** is to explore which of the two atropisomers is the more stable.



2.2.1 Procedure

Use the MMFF94s force-field to determine the most stable isomer (**9** or **10**), and to rationalise why the alkene reacts slowly (hint: read the literature on hyperstable alkenes!^[6]). Pay particular attention to the conformations of the resulting optimised structure, to see if any aspect of these structures could be improved by further minimisations (preceded if necessary by a manual edit of the structure to move atoms into more correct orientations).

Estimated time for completion: < 3 hour in total.

2.2.2 Files for your Wiki write-up

Collect the following files for your Wiki writeup.

1. Saving geometries from Avogadro as CML (.cml) or MDL Molfile (.mol) allows the model to be displayed in the Wiki. See here for instructions.
2. You can export a fixed static Graphics using **File/Export** and save as .jpg or .png
3. You can of course also take *screen dumps* at any stage, and include them as a static picture.

2.3 General References for this part of the module

1. ↑ Overview to Molecular Mechanics

- ↑ Force Fields in Avogadro (http://avogadro.openmolecules.net/wiki/Tutorials:Force_fields)
- ↑ A. K. Rappe , C. J. Casewit , K. S. Colwell , W. A. Goddard III, W. M. Skiff *J. Am. Chem. Soc.*, **1992**, *114*, 10024–10035. DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/ja00051a040) (<http://dx.doi.org/10.1021/ja00051a040>) .C. J. Casewit , K. S. Colwell , A. K. Rappe *J. Am. Chem. Soc.*, **1992**, *114*, 10046–10053 DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/ja00051a042) (<http://dx.doi.org/10.1021/ja00051a042>) .C. J. Casewit , K. S. Colwell , A. K. Rappe *J. Am. Chem. Soc.*, **1992**, *114*, 10035–10046 DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/ja00051a041) (<http://dx.doi.org/10.1021/ja00051a041>)
- ↑ S. W. Elmore and L. Paquette, *Tetrahedron Letters*, **1991**, 319; DOI ([http://en.wikipedia.org/wiki/Digital_object_identifier:10.1016/S0040-4039\(00\)92617-0](http://en.wikipedia.org/wiki/Digital_object_identifier:10.1016/S0040-4039(00)92617-0)) ([http://dx.doi.org/10.1016/S0040-4039\(00\)92617-0](http://dx.doi.org/10.1016/S0040-4039(00)92617-0))
- ↑ See J. G. Vinter and H. M. R. Hoffman, *J. Am. Chem. Soc.*, **1974**, *96*, 5466–5478 (DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/ja00824a025) (<http://dx.doi.org/10.1021/ja00824a025>)) and **95**, 3051 for another nice example of atropisomerism. Another well known example is within Vancomycin: *J. Am. Chem. Soc.*, **1999**, *121*, 3226. DOI: DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/ja990189i) (<http://dx.doi.org/10.1021/ja990189i>) . An interesting variation is of "atropenantioselective cycloetherification", G. Islas-Gonzalez, M. Bois-Choussy and J. Zhu, *Org. Biomol. Chem.*, **2003**, 30-32. DOI: DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1039/b208905j) (<http://dx.doi.org/10.1039/b208905j>)
- ↑ W. F. Maier, P. Von Rague Schleyer, *J. Am. Chem. Soc.*, **1981**, *103*, 1891. DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/ja00398a003) (<http://dx.doi.org/10.1021/ja00398a003>)

3 Spectroscopic Simulation using Quantum Mechanics (~2-3 days, part 1)

This part introduces spectroscopic simulations^{[1],[2],[3],[4][5]} concluding with the prediction for the molecule to be synthesised in the synthetic part of this experiment. This part should take about three working days.

3.1 A practice molecule: Spectroscopy of an intermediate related to the synthesis of Taxol

The molecules **17** and **18** are derivatives of **9** and **10** shown above, for which spectroscopic information has been reported^[6] Your objective here is to simulate the ¹H and ¹³C spectra and compare them with the literature values to see if the latter have been correctly interpreted and assigned.

3.1.1 Procedure using the HPC

- Using the Avogadro or ChemBio3D program, sketch **ONE** of the starting molecules **17** OR **18**, and using the **MMFF94s** mechanics force field, minimise the geometry as the first stage of optimising the geometry. Ensure that whatever you learnt about the geometry from the first part of this experiment is used to good effect here.
- To calculate the geometry at the density functional level (DFT), from Avogadro, **Extensions/Gaussian** and set the following parameters
 - Calculation: **Geometry optimisation** (or **Opt+Freq** in Gaussview)
 - Theory: **B3LYP**
 - Basis: **6-31G(d,p)** (d= carbon polarisation, p=hydrogen polarisation)
 - Append a solvation model keyword **SCRF(CPCM,Solvent)** (where solvent = the solvent the spectra were recorded in) to the keyword line.
 - Append two keywords **FREQ** and **NMR**.
 - Append a keyword **EmpiricalDispersion=GD3**. This is a newly introduced keyword which corrects the energy for dispersion attractions.
 - Press **Generate** and save the input file in the form **nameforjob.com** on the Desktop or other easily locatable folder.
 - Open this file with Windows text editor (**NotePad++** highly recommended) and check that the keyword line contains something like:

```
# B3LYP/6-31G(d,p) Opt SCRF=(CPCM,Solvent=chloroform) Freq NMR EmpiricalDispersion=GD3
```

- Submit this file to the HPC system here (<https://scanweb.cc.imperial.ac.uk/uportal2/>).
 - When the HPC job is indicated as Finished (this should take about five hours of running time, more if the job has to first pend), select the **Formatted checkpoint file** as the output option, and download it to your computer. Double click this file to unzip it and again to load into Gaussview.
 - From **Results/NMR** option in Gaussview, inspect the predicted NMR spectrum. If NMR is greyed out, the calculation failed for some reason.
 - After **setting the appropriate nucleus and TMS reference value** (remember that observed methyl group shift is the average of the three protons), compare the calculated chemical shifts against those reported in the literature. Devise a way of illustrating succinctly how good the match is.
- The .log file from the calculation also reports a vibrational analysis (invoked by the **freq** keyword) which is used to compute an entropy and Zero-point-energy correction to give a **free energy ΔG** (this energy is labelled **Sum of electronic and thermal Free Energies** in this file). You can use this energy to e.g. compare the relative energies of two isomeric configurations of the molecule.

3.1.1.1 Procedure using the Laptop

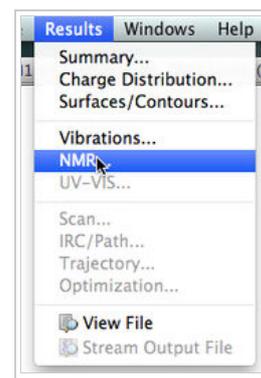
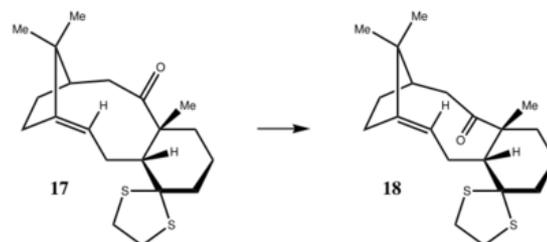
It is also possible to run the calculation directly on your laptop or computer room desktops:

- To prepare the file **nameforjob.gjf** file you created earlier for local calculation, edit in **NotePad++** as follows
 - Add two lines at the stop, each starting with a % as below (set the number of processors to **4** if you are using a desktop and to **2** if you are using a laptop):

```
!nprocshared=2
!mem=2GB
# B3LYP/6-31G(d,p) Opt SCRF=(CPCM,Solvent=chloroform) Freq NMR EmpiricalDispersion=GD3
```

- Open **G09W** from the Windows start menu.
 - Drag-n-drop the file **nameforjob.com** into the main G09W window. The Run Progress box should read **Ready for processing start**.
 - Press **Process/Begin processing** to start the job on the desktop/laptop. This will invoke a dialog asking for the destination of the output file. Ensure you select an easily found folder for this. Molecules the size of **17** or **18** take about 8 hours on your laptop (you really are better off submitting to the HPC system), but this time will reduce as the molecules get smaller.
 - Open the resulting output file using Gaussview.

3.1.2 Files for your wiki write-up



Thermochemistry analysis follows the frequency and normal mode data:			
Zero-point correction=	.02261	(Hartree/Particle)	
Thermal correction to Energy=	.02694		
Thermal correction to Enthalpy=	.02738		
Thermal correction to Gibbs Free Energy=	.02698		
Sum of electronic and zero-point Energies=	-527.492585	$E_0=E_{el}+ZPE$	
Sum of electronic and thermal Energies=	-527.489751	E_0+E_{th}	
Sum of electronic and thermal Enthalpies=	-527.488805	$E_0+E_{th}+P_{Vib}$	
Sum of electronic and thermal Free Energies=	-527.463167	$G=H-TS$	

Thermodynamic quantities

Collect the following files for your Wiki writeup. In addition to the other files as described below, you can export a spectrum as a .svg file. This is a scaleable version of the spectrum that can be included directly in the Wiki. In Gaussview, right-click in the spectrum view to pop-up a menu, and from there, select **Export** to save a .svg file. Upload this to the Wiki.

3.2 General References for this part of the module

1. ↑ K. Mori, "Synthetic examination of incorrectly proposed structures of biomolecules", *The Chemical Record*, **2005**, ii5, 1-16. DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1002/ocr.20030) (<http://dx.doi.org/10.1002/ocr.20030>)
2. ↑ K L. McPhail et al, "Survey of marine natural product structure revisions: A synergy of spectroscopy and chemical synthesis", *Bioorganic & Medicinal Chemistry*, **2011**, 19, 6675–6701. DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1016/j.bmc.2011.06.011) (<http://dx.doi.org/10.1016/j.bmc.2011.06.011>) (there are some serious errors in the *corrected* structures here for **obtusallene**, viz DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/np0705918) (<http://dx.doi.org/10.1021/np0705918>), *Structural Reassignment of Obtusallenes V, VI, and VII by GIAO-Based Density Functional Prediction*)
3. ↑ M. G. Banwell et al, "Structure of the Lycorinine Alkaloid Nobilisinine A", *J. Org. Chem.*, **2011**, 76, 8560–8563. DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/jo2016899) (<http://dx.doi.org/10.1021/jo2016899>)
4. ↑ M. W. Lodewyk, C. Soldi, P. B. Jones, M. M. Olmstead, J. Rita, J. T. Shaw, and D. J. Tantillo, "The Correct Structure of Aquatolide—Experimental Validation of a Theoretically-Predicted Structural Revision", *J. Am. Chem. Soc.*, **2012**, 134, 18550–18553. DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/ja3089394) (<http://dx.doi.org/10.1021/ja3089394>)
5. ↑ See <http://cheshift.com>
6. ↑ Spectroscopic data: L. Paquette, N. A. Pegg, D. Toops, G. D. Maynard, R. D. Rogers, *J. Am. Chem. Soc.*, **1990**, 112, 277-283. DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/ja00157a043) (<http://dx.doi.org/10.1021/ja00157a043>)

4 Analysis of the properties of the synthesised alkene epoxides (~ 3-4 days, part 2)

4.1 Objectives for Spectroscopic simulations

In the 1S two week module you will use/have used both the Shi and the Jacobsen asymmetric epoxidation catalysts to produce four samples of different chiral alkene epoxides of unknown absolute configurations in an enantiomeric excess, using two different alkenes. The **objectives** of this part require you to investigate the following aspects of the asymmetric epoxidation, using the modelling experience you have gained in the first week (see above) to predict that configuration and if possible to rationalise its formation by studying the catalyst structure, the product NMR, the absolute configuration and interactions in the active site.

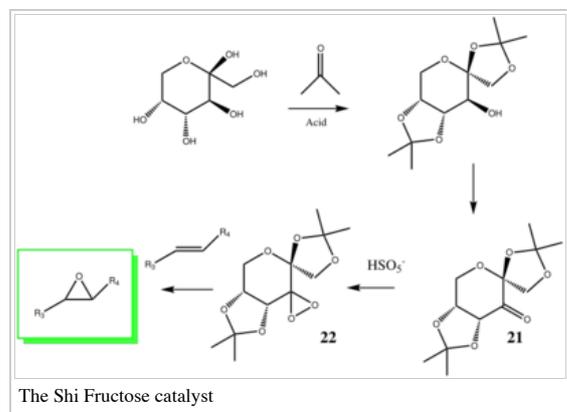
You will need therefore to model two epoxides from the following selection of four:

1. Styrene, 2. β -methyl styrene 3. trans-Stilbene, 4. 1,2-dihydronaphthalene

4.2 The two catalytic systems

You have/will use **both** of these catalysts to epoxidize two alkenes.

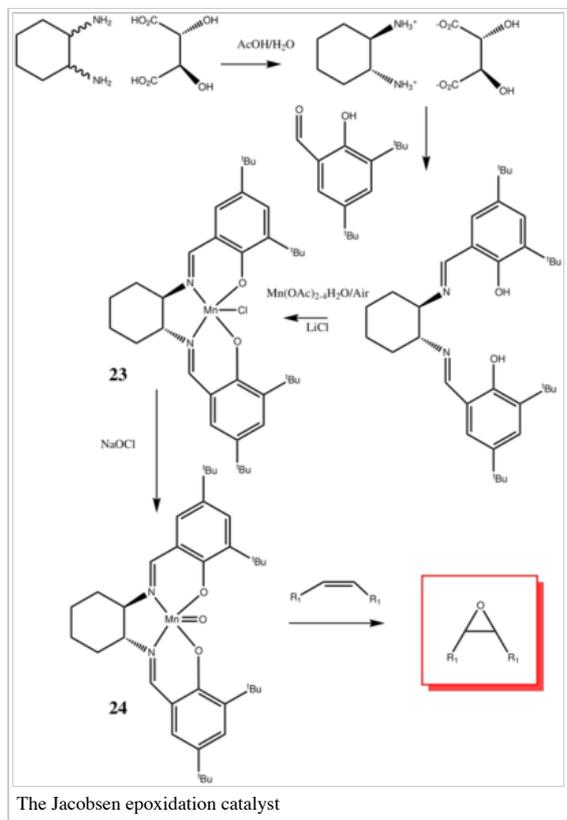
4.2.1 The Shi Fructose-derived chiral catalyst



The synthetic sequence shown above is described by Hanks *et al*^[1] following an original procedure by Shi *et al*^[2] and you will follow this synthetic procedure on two specified alkenes to obtain the corresponding epoxide. Species **21** is the stable precursor to the catalyst, and **22** the active catalyst generated from persulfuric acid.

4.2.2 The Jacobsen salen-derived chiral catalyst

Hanson^[3] has adapted the procedure reported by Jacobsen *et al*^{[4],[5]} to asymmetrically epoxidise a series of cis-alkenes. System **23** is the stable pre-catalyst and **24** the active species generated from hypochlorite.



4.3 The crystal structures of the two catalysts above

You should search the Cambridge crystal database (CCDC) using the **Conquest** program for the pre-catalysts **21** and **23** (you will only synthesize **ONE** of these catalysts in the lab, your partner will make the other).

1. For **21** analyse and discuss the C-O bond lengths for any anomeric centres (*i.e.* those with O-C-O substructures) using the Mercury program and any other interesting features you might discover.
2. For **23** analyse and discuss the close approach of the two adjacent t-butyl groups on the rings and any other interesting features you might discover.

4.4 The calculated NMR properties of your products

You can compute the expected ^{13}C and ^1H spectra (chemical shifts and coupling constants) of your epoxides to check the integrity of what you have made. The technique for doing this was illustrated for taxol above. This on its own however will not identify the absolute configuration of your product.

4.5 Assigning the absolute configuration of the product

Your task is to assign the absolute configuration of the epoxides you obtain using either catalyst above. This can be done in **three** quite different ways.

4.5.1 The reported literature for optical rotations

If (as is very likely) you are using a known alkene for the epoxidation, you can check the literature for the rotation of the (R,R) or the (S,S) enantiomers. This is best searched for using Reaxys (<https://www.reaxys.com/>). However, it is not unknown for literature assignments to be wrong, and moreover one needs a procedure which can be used if the rotation of the epoxide has never previously appeared in the literature!

4.5.2 The calculated chiroptical properties of the product

Your task in the computational part of the experiment is to calculate what the expected chiroptical properties of this epoxide should be for a specified enantiomer and by comparing this with the value you will have measured in the experimental part to predict what the enantioselectivity of this catalyst is. Three chiroptical properties can be useful in this regard:

1. The optical rotation at a specified wavelength of light (the optical rotatory power, or ORP) or the values for a range of wavelengths (the Optical rotatory dispersion, or ORD).
2. The electronic circular dichroism (ECD)
3. The vibrational circular dichroism (VCD).

All these can be computed nowadays. However, only the first (the optical rotation) can be readily measured in the 3rd year laboratory. The ECD, which in effect is the UV/Vis spectrum recorded with polarised light, is actually useless for the epoxides because no appropriate chromophore exists for the epoxides. VCD is an excellent technique^[6] but the appropriate instrument is not available in the department.

4.5.3 Using the (calculated) properties of transition state for the reaction

The relative computed free energy of the transition state can be used as a check for the enantiomeric assignment obtained by comparing computed and calculated optical rotations of the epoxide. You should acquire the job output (as a .log file) from the data repository entries listed below, identify the total energy for each system as corrected for entropy and zero-point thermal energies and including a solvation correction for water as solvent and discuss whether this theoretical prediction matches what has been reported for this reaction in the literature (and whether it matches your observations if you used this alkene in your experiments. These geometric models could of course be used as the starting template for editing to correspond to other alkenes). Your discussion could include:

1. Indicating the free energy difference between two diastereomeric transition states
2. Convert this to **K**, the ratio of concentrations of the two species based on this energy difference
3. Use **K** to work out the predicted enantiomeric excess of one epoxide over the other.

4.5.3.1 Shi catalyst

For a fixed chirality for the fructose-based catalyst, eight transition states can be envisaged for oxygen transfer from the dioxirane to *e.g.* phenylprop-1-ene ($R_3=Ph$, $R_4=Me$).

1. One of two choices can be made regarding whether the (R,R)-epoxide or the (S,S) epoxide is formed (or (R)/(S) for styrene), in other words whether the **Re** or the **Si** face of the alkene is reacted.
2. One of two choices can be made regarding which of the two dioxirane oxygens is used for the transfer (they are not equivalent)
3. One of two choices can be made regarding how the phenyl group of the alkene is oriented with respect to the fructose, **endo** or **exo**.

The transition states themselves have >60 atoms, and although they can be computed at a reasonably high level, each calculation takes about 24 hours to complete. Because the total time required for all eight calculations is prohibitive for this experiment, the results for **trans-phenylprop-1-ene** (trans β -methyl styrene), styrene, stilbene or dihydronaphthalene as alkenes are presented here for you to analyse.

Transition states for Shi epoxidation of trans- β -methyl styrene

R,R series	S,S Series
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.738028) (http://dx.doi.org/10.6084/m9.figshare.738028)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.738038) (http://dx.doi.org/10.6084/m9.figshare.738038)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.749615) (http://dx.doi.org/10.6084/m9.figshare.749615)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.739115) (http://dx.doi.org/10.6084/m9.figshare.739115)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.738036) (http://dx.doi.org/10.6084/m9.figshare.738036)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.739116) (http://dx.doi.org/10.6084/m9.figshare.739116)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.738037) (http://dx.doi.org/10.6084/m9.figshare.738037)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.739117) (http://dx.doi.org/10.6084/m9.figshare.739117)

Transition states for Shi epoxidation of styrene

R series	S Series
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.822152) (http://dx.doi.org/10.6084/m9.figshare.822152)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.823545) (http://dx.doi.org/10.6084/m9.figshare.823545)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.828520) (http://dx.doi.org/10.6084/m9.figshare.828520)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.822136) (http://dx.doi.org/10.6084/m9.figshare.822136)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.822135) (http://dx.doi.org/10.6084/m9.figshare.822135)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.828519) (http://dx.doi.org/10.6084/m9.figshare.828519)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.822137) (http://dx.doi.org/10.6084/m9.figshare.822137)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.826003) (http://dx.doi.org/10.6084/m9.figshare.826003)

Transition states for Shi epoxidation of Stilbene

R,R series	S,S Series
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.828552) (http://dx.doi.org/10.6084/m9.figshare.828552)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.829524) (http://dx.doi.org/10.6084/m9.figshare.829524)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.830388) (http://dx.doi.org/10.6084/m9.figshare.830388)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.829525) (http://dx.doi.org/10.6084/m9.figshare.829525)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.829522) (http://dx.doi.org/10.6084/m9.figshare.829522)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.830389) (http://dx.doi.org/10.6084/m9.figshare.830389)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.829523) (http://dx.doi.org/10.6084/m9.figshare.829523)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.830390) (http://dx.doi.org/10.6084/m9.figshare.830390)

Transition states for Shi epoxidation of Dihydronaphthalene

R,S series	S,R Series
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.832492) (http://dx.doi.org/10.6084/m9.figshare.832492)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.832538) (http://dx.doi.org/10.6084/m9.figshare.832538)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.832510) (http://dx.doi.org/10.6084/m9.figshare.832510)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.832536) (http://dx.doi.org/10.6084/m9.figshare.832536)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.832511) (http://dx.doi.org/10.6084/m9.figshare.832511)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.832545) (http://dx.doi.org/10.6084/m9.figshare.832545)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.832512) (http://dx.doi.org/10.6084/m9.figshare.832512)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.832544) (http://dx.doi.org/10.6084/m9.figshare.832544)

4.5.3.2 Jacobsen catalyst

For a fixed chirality for the Mn-based catalyst, two transition states can be envisaged for oxygen transfer from the Mn=O oxygen to **phenylprop-1-ene**; whether the (R,S)-epoxide or the (S,R) epoxide is formed (there are other possibilities, such as a transition state via a metalla-oxacyclobutane, but we will ignore these here). The transition states each have >90 atoms, and although they can be computed at a reasonably high level, each calculation takes about 96 hours to complete, which is impractical for this course. So they have been pre-computed for you to analyse. There are four possibilities, depending on whether the S,R or the R,S enantiomer is formed, and the **endo/exo** arrangement of the substrate in relation to the catalyst.

Transition states for Jacobsen epoxidation of cis- β -methyl styrene	
S,R series	R,S Series
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.740436) (http://dx.doi.org/10.6084/m9.figshare.740436)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.740437) (http://dx.doi.org/10.6084/m9.figshare.740437)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.783851) (http://dx.doi.org/10.6084/m9.figshare.783851)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.783898) (http://dx.doi.org/10.6084/m9.figshare.783898)
Transition states for Jacobsen epoxidation of trans- β -methyl styrene	
S,S series	R,R Series
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10042/25945) (http://dx.doi.org/10042/25945)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.856649) (http://dx.doi.org/10.6084/m9.figshare.856649)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.856650) (http://dx.doi.org/10.6084/m9.figshare.856650)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.856651) (http://dx.doi.org/10.6084/m9.figshare.856651)
Transition states for Jacobsen epoxidation of styrene	
S series	R Series
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.860441) (http://dx.doi.org/10.6084/m9.figshare.860441)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.860446) (http://dx.doi.org/10.6084/m9.figshare.860446)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.860445) (http://dx.doi.org/10.6084/m9.figshare.860445)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.860449) (http://dx.doi.org/10.6084/m9.figshare.860449)
Transition states for Jacobsen epoxidation of Stilbene	
S,S series	R,R Series
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.903625) (http://dx.doi.org/10.6084/m9.figshare.903625)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.899176) (http://dx.doi.org/10.6084/m9.figshare.899176)
Transition states for Jacobsen epoxidation of Dihydronaphthalene	
S,R series	R,S Series
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.903752) (http://dx.doi.org/10.6084/m9.figshare.903752)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.909346) (http://dx.doi.org/10.6084/m9.figshare.909346)
DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.907473) (http://dx.doi.org/10.6084/m9.figshare.907473)	DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.6084/m9.figshare.907332) (http://dx.doi.org/10.6084/m9.figshare.907332)

4.5.3.3 Other Alkenes

Optional If you do want to be adventurous, you might want to see if you can use the structures computed for the **phenylprop-1-ene** transition state to convert this into a initial guess for the transition state of your own alkene. If you do succeed, we will use your structure next year!

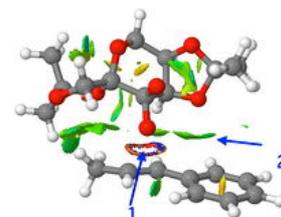
4.5.4 3D Printed models of the transition states

Four 3D printed colour models of the transition states for four different types of asymmetric epoxidation are available for you to inspect from Dr Rzepa upon request, including a Shi (<http://shpws.me/pR6O>) and a Jacobsen (<http://shpws.me/pR6W>) transition state (which are also available for purchase). You can also make your own by following the instructions.



4.6 Investigating the non-covalent interactions in the active-site of the reaction transition state

Non-covalent interactions (NCI) include hydrogen bonds, electrostatic attractions and dispersion-like close approaches of pairs of atoms. As for normal covalent bonds, such NCI interactions can be defined by the properties of the electron density (and its curvatures)^[7]. An example of an NCI analysis is shown on the right, where the colours indicate whether the interaction is attractive (colour means blue is very attractive, green mildly attractive, yellow mildly repulsive and red is strongly repulsive). Arrow 1 points to the bond forming in a transition state (which can be considered *half-covalent*) and this type of NCI interaction is normally ignored entirely. Arrow 2 points to a real NCI interaction between *e.g.* the reacting substrate and the catalyst. Being green in this case means it is mildly attractive. Such diagrams help to identify (in a semi-qualitative manner) those regions of a reacting system where substrate and catalyst may be interacting, and hence may provide some clues as to the origins of stereoselectivity between the two.

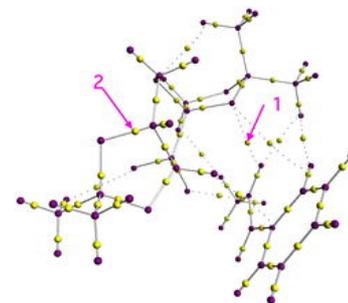


Your task is to download one of the transition states listed in the tables above, compute the electron density for the system and subject it to an NCI analysis.

4.7 Investigating the Electronic topology (QTAIM) in the active-site of the reaction transition state

This is complementary to the NCI (non-covalent) analysis, since it has the focus on the electron density (and its curvature) in the covalent regions of molecules (i.e. much stronger interactions we grace with the term **bond**) as well as the weaker interactions identified in a NCI analysis. Arrow 2 in the diagram to the right for example identifies a topological point known as a BCP (bond critical point, defined by a region where the first derivative of the electron

density with respect to each of the three coordinates of that point is **zero**) which has a curvature (defined mathematically by the Hessian of the density $\rho(r)$) appropriate for a bond (C-O in this instance). There are three other types of critical point, those associated with nuclei (na), those associated with rings (rcp) and those associated with cages (ccl), but we are not concerned with those here. Arrow 1 points to a weak non-covalent BCP (associated with weak interaction between oxygen and hydrogen).



Your task is to download one of the transition states listed in the tables above and subject it to a QTAIM analysis. Identify any interesting BCPs, and discuss whether they are associated with a covalent bond or not. Note the position of the BCP (approximately) relative to the two atoms it may connect.

4.8 Suggesting new candidates for investigations

You can search Reaxys (<https://www.reaxys.com/>) for small epoxides (as a substructure) that have the measured (advanced) property: **(ORP.ORG<-300' or ORP.ORG>300')** AND **IDE.MW<200.0'**. Adjust the molecular weight or optical rotation range so that the query produces a reasonable number of hits (~20-40?). Most will be synthetically inaccessible, but the corresponding alkene for some of them may be in the Sigma-Aldrich catalogue. Try to find one such candidate and discuss it in your report. And remember, its absolute configuration has probably never been checked by computation! There must be a realistic prospect that some of the literature assignments are actually wrong!

4.9 References for this part of the module

- ↑ A. Burke, P. Dillon, Kyle Martin and T. W. Hanks, "Catalytic Asymmetric Epoxidation Using a Fructose-Derived Catalyst", *J. Chem. Educ.*, **2000**, *77*, 271; DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/ed077p271) (<http://dx.doi.org/10.1021/ed077p271>)
- ↑ O. A. Wong, B. Wang, M-X Zhao and Y. Shi *J. Org. Chem.*, **2009**, *74*, 335–6338; DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/jo900739q) (<http://dx.doi.org/10.1021/jo900739q>)
- ↑ J. Hanson *J. Chem. Educ.*, **2001**, *78*, 1266; DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/ed078p1266) (<http://dx.doi.org/10.1021/ed078p1266>)
- ↑ E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, L. Deng *J. Am. Chem. Soc.*, **1991**, *113*, 7063–7064; DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/ja00018a068) (<http://dx.doi.org/10.1021/ja00018a068>)
- ↑ M. Palucki, N. S. Finney, P. J. Pospisil, M. L. Güler, T. Ishida, and E. N. Jacobsen, *J. Am. Chem. Soc.*, **1998**, *120*, 948–954; DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/ja973468j) (<http://dx.doi.org/10.1021/ja973468j>)
- ↑ M. J. Fuchter, Ya-Pei Lo and H. S. Rzepa, *J. Org. Chem.*, **2013**, DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1021/jo401316a) (<http://dx.doi.org/10.1021/jo401316a>)
- ↑ J. L. Arbour, H. S. Rzepa, J. Contreras-García, L. A. Adrio, E. M. Barreiro, K. K. Hii, *Chem. Euro. J.*, **2012**, *18*, 11317–11324, DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10.1002/chem.201200547) (<http://dx.doi.org/10.1002/chem.201200547>)

5 The use of Digital Repositories for sharing data (part 2)

Curating and sharing research data is a big topic at the moment^[1] Why is sharing data important?

1. Reproducibility is a cornerstone in science
2. To achieve this, it is important that scientific research be open and transparent.
3. Openly available research data is central to achieving this. It is estimated that less than 20% of the data collected in chemistry is made available in any open manner.
4. RCUK (the UK research councils) wish *increased transparency of publicly funded research and availability of its outputs*^[1]

To give you some experience of data curation and sharing, you will publish some of your key calculations on the HPC portal, following the principles of the **Amsterdam Manifesto**^[2], resulting in data citable by quoting its DOI. You will need to set up your publishing profile first however.

1. Log into the HPC portal (<https://scanweb.cc.imperial.ac.uk/uportal2/>)
2. Click on **Profile**
3. Make sure that only the box **Publish to DSpace** is selected. You are now set to publish any calculation performed on the HPC.
4. If the entry in the portal column labelled **Repository** reads **DSpace**, this means a **doi** is enabled for the calculation on that repository. You can obtain the doi by right-clicking with the browser on the link and performing **Copy link**. This should give you something like <http://hdl.handle.net/10042/25042> (hdl.handle.net is a synonym for doi.net)
5. You can invoke that on the Wiki as `{{DOI|10042/25042}}`, which gives the result DOI (http://en.wikipedia.org/wiki/Digital_object_identifier:10042/25042) (<http://dx.doi.org/10042/25042>)
6. Another digital repository available from the HPC is Figshare. To use this however, you first need to create yourself an account on Figshare (it is an external organisation). There is no need to do this for the purposes of this course.
7. This combination of a HPC portal, this Wiki and a doi assignment for your data functions very similarly to a modern **electronic laboratory notebook**, or **ELN**.

5.1 References for this section

1. ↑ 1.0 1.1 See the EPSRC policy (<http://www.epsrc.ac.uk/about/standards/researchdata/Pages/policyframework.aspx>)
2. ↑ The Amsterdam Manifesto on Data Citation Principles (<http://www.force11.org/AmsterdamManifesto>)

6 Assessment and Mark distribution

The marks for this module are split:

1. 45% for **2 + 3**
 - 20% for **2**
 - 25% for **3**
2. 55% for **4 + 5**:
 - 5% for **4.3**
 - 5% for **4.4**
 - 35% for **4.5**
 - 10% for **4.6-4.8** and **5**.

You will be assessed not simply on whether you got the *right* answer, but on your analysis/interpretation of the problem, how you might have designed control calculations, or *e.g.* worked out ways of making the modelling more efficient, for any interesting/unusual observations you made and **especially** for your final conclusions about each part.

The project is at least as much about how you go about organising your **workflows** in the time you have decided to spend on it, as it is about getting the right answer. Marks for each individual component will also be awarded for how you cite and quote the literature (in particular for citing any relevant references that we do **not** give you in the notes). Remember, being critical is more important than merely reproducing quotes from an article. After all, the original people who reported the chemistry may have not understood what happened themselves, and it is perfectly possible that you may actually be able to critically improve that understanding!

Your grade will be emailed to you and comments on your experiment will appear in the **discussion section** of your Wiki report. If you want to discuss your experiment and its grade, please contact Laura Patel (mailto:laura.patel@imperial.ac.uk?subject=Experiment_1C) directly.

7 Help

1. In addition to demonstrators (present for two hours only each day) and staff, you may wish to keep an eye out on the late breaking news page for general updates.
2. The Gaussian manual (http://www.gaussian.com/g_tech/g_ur/l_keywords09.htm) is the definitive source of information, although it can be quite terse in places and inscrutable in others.

See also: 1C comp-lab startup, 1C Timetable, Laptop use, Programs, **Module 1C Script**, Module 1C Toolbox, Writing up, Don't panic.

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