

# Asymmetric Epoxidation: A Twinned Laboratory and Molecular Modeling Experiment for Upper-Level Organic Chemistry Students

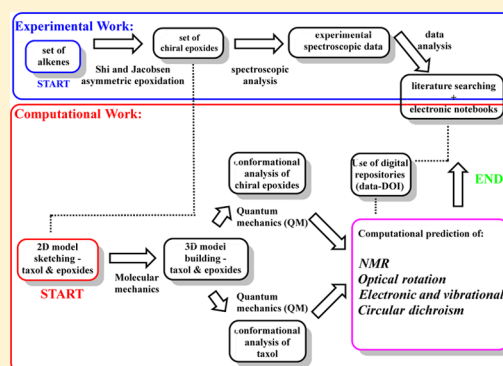
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## Supporting Information

**ABSTRACT:** The coupling of a student experiment involving the preparation and use of a catalyst for the asymmetric epoxidation of an alkene with computational simulations of various properties of the resulting epoxide is set out in the form of a software toolbox from which students select appropriate components. At the core of these are the computational spectroscopic tools, whereby a measured spectrum can be interpreted in some detail using theoretical simulations. These include a range of modern chiroptical methods to accompany the increased use of such techniques in modern teaching laboratories. Computational experiments are captured in a Wiki-based electronic laboratory notebook, which features data-stamping, authenticated entries, and inclusion of semantically intact data via interactive models rendered within the Wiki using JSmol and its referencing via a digital object identifier (DOI) to a digital data repository.

**KEYWORDS:** Upper-Division Undergraduate, NMR Spectroscopy, Molecular Modeling, Epoxides, Crystals, Conformational Analysis, Chirality, Asymmetric Synthesis, Problem Solving, Organic Chemistry



Organic syntheses are increasingly dependent on computational simulations to provide insight into the reactions being conducted in the laboratory. Quantum chemistry can nowadays provide quantitative estimates of a range of molecular properties, including molecular geometries and associated features such as hydrogen bonding and force constants that provide computed vibrational spectra, NMR shifts and couplings, and a range of measurable chiroptical properties. Mechanistic detail can also be obtained by locating the transition states for reactions to provide insights into the origins of stereoselectivity. Ideally, all of these concepts can be juxtaposed upon a well-defined existing experimental procedure to provide a student experiment where both the practical and the computational modeling can be carried out, and for which the whole would be greater than the sum of the parts. An asymmetric epoxidation of an alkene was identified as an ideal illustration of such computational spectroscopy. The experimental procedures for these reactions have already been reported in this *Journal*,<sup>1,2</sup> and here, a new computational laboratory counterpart is described. It is appropriate for advanced-level students, normally in their final undergraduate year and already having some experience of introductory-level modeling and the use of molecular sketching programs such as ChemDraw.

## OVERVIEW OF THE EXPERIMENT

An overview is shown in Scheme 1. Students are first introduced to modeling techniques, such as structure building, editing, and energy minimization, to refine the crude sketch

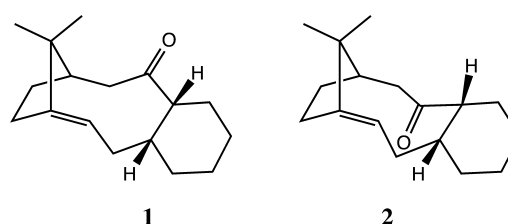


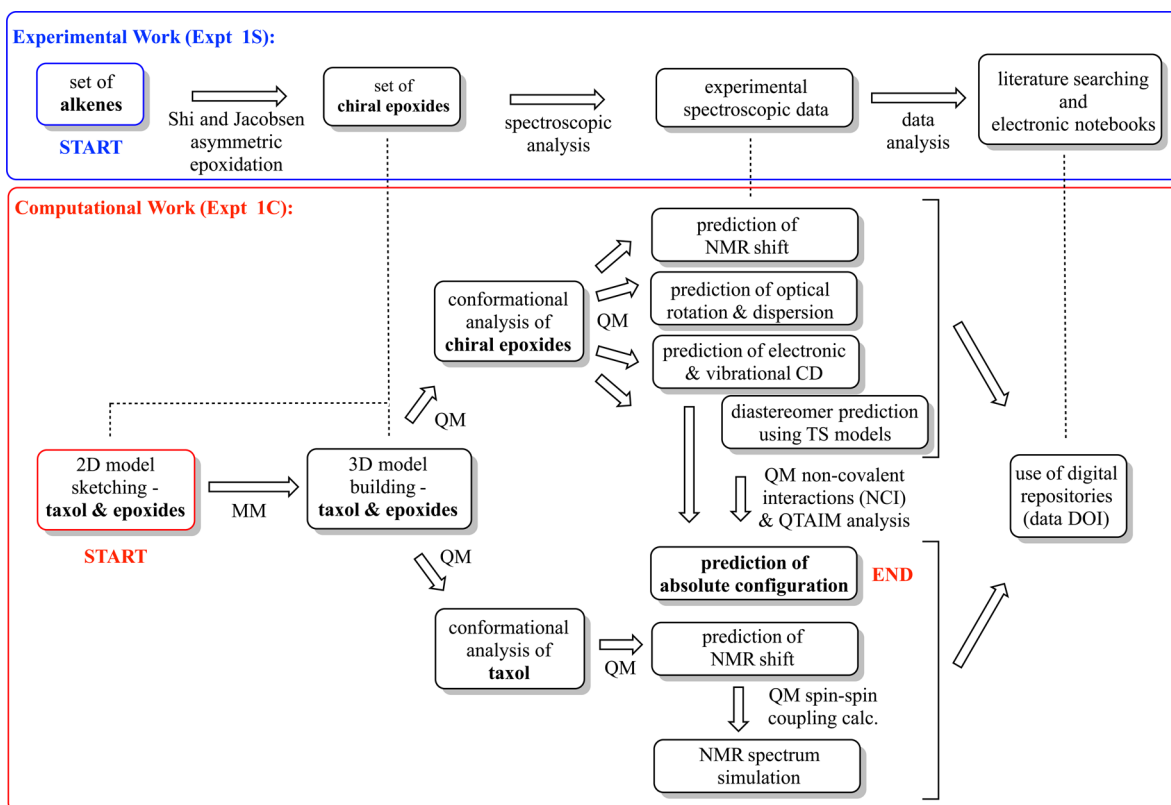
Figure 1. Two atropisomers of a taxol precursor.

into one with a sensible three-dimensional geometry. The metaphor of a computational toolbox is provided for this task. Students are then introduced to the procedures for quantum mechanical prediction of IR, NMR, and chiroptical properties for a real molecule, a task that also requires comparing these values with experimentally measured counterparts. The second half of the experiment is twinned with an experimental laboratory in which alkenes are asymmetrically epoxidized using two different catalysts, the Shi fructose oxidant<sup>1</sup> (Scheme 2) and the Jacobsen manganese oxidant (Scheme 3).<sup>2</sup> Students must then establish the **absolute** stereochemical configuration of their epoxide using an appropriate chiroptical measurement via the computational toolbox provided.

## COMPUTATIONAL EXPERIMENT

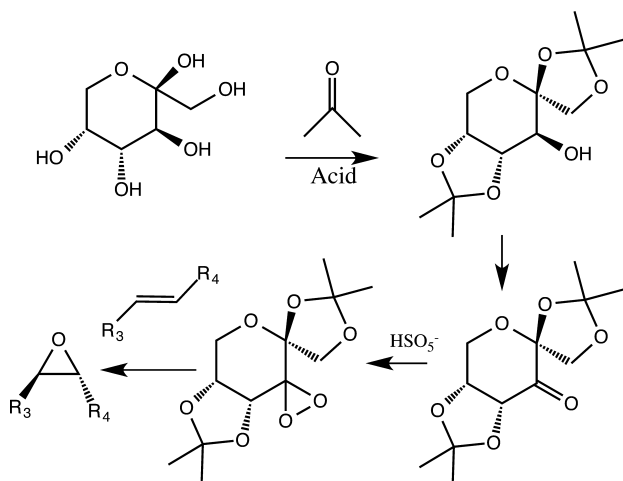
The familiarity exercise occupies the first week of the two-week exercise, with students working individually using a provided

Scheme 1. Experiment Workflow, Including the Relationships between the Computational Component<sup>a</sup> and the Synthetic Component<sup>b</sup>



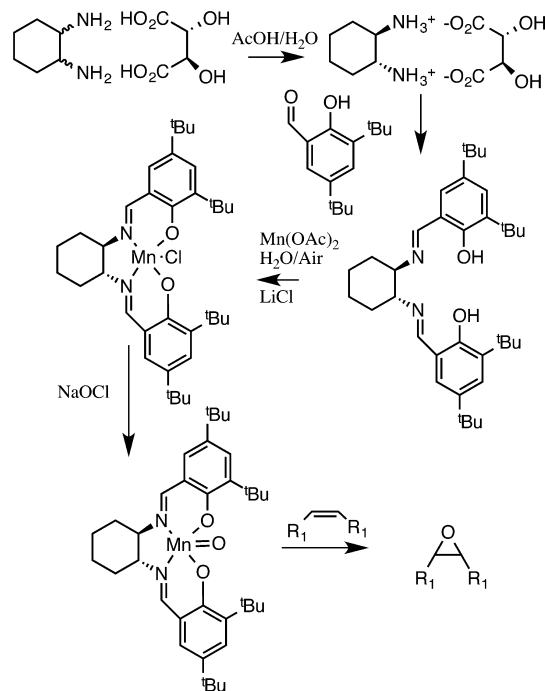
<sup>a</sup>Red box. <sup>b</sup>Blue box.

Scheme 2. Shi Procedure for Asymmetric Epoxidation of an Alkene<sup>1</sup>



laptop. There are no declared laboratory times and students are expected to manage their own time over this period, including working on weekends if they wish. Their task in the first week is to explore conformational analysis and atropisomerism in the pretaxol derivatives 1 and 2 (Figure 1) using a simple molecular mechanics force field. These molecules are part of a reported synthesis of taxol precursors,<sup>3</sup> and the objective is for a student to establish which of these two atropisomers is the thermodynamically more stable. The molecule tests a student's perception of stereochemistry at both the alkene and the ring

Scheme 3. Jacobsen Procedure for Asymmetric Epoxidation of an Alkene<sup>2</sup>

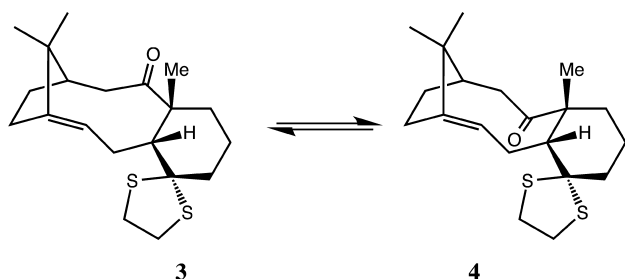


junction, his/her ability to map a 2D representation correctly into three dimensions, and to investigate the (nontrivial) conformational preferences of such molecules.

Students have access to two packages suitable for this task. Avogadro<sup>4</sup> is open source software with a unique molecular mechanics driven *rubber-band* feature, where each added atom or group quickly arrives at its optimal lowest-energy position as the molecule is being built. ChemDraw/ChemBio3D is commercial software where a familiar 2D sketching component is paired with a 2D  $\rightarrow$  3D tool that maps the structure on-the-fly to an approximate three-dimensional representation, followed by energy minimization using molecular mechanics to obtain an optimum structure.

Students are informed that spectroscopic information for two related molecules 3/4<sup>4</sup> (Scheme 4) is available and they have to

**Scheme 4. Two Atropisomers of a Taxol Precursor for Which NMR Data Are Available**



use their newfound expertise to build a conformationally sensible model and to predict the spectroscopic properties using the Gaussian 09 program.<sup>5</sup> The following keywords to accomplish this task summarize a great deal of the capability of such programs in this context:<sup>5</sup>

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

B3LYP is shorthand for the Hamiltonian for obtaining the total (nuclear + electronic) energy of a molecule. This density functional procedure replaces the previously used mechanics force field in the geometry optimization procedure. The keyword 6-31G(d,p) introduces an atomic orbital basis set for each atom. Students learn how to balance improving the quality of this basis set against the time-limited computational resources available to a class. Invoking Opt initiates an energy minimization with respect to the (3N - 6) geometric degrees of freedom for the molecule. Solvent is simulated using the keyword SCRF=(CPCM,Solvent=chloroform); a student has to identify from the literature the appropriate solvent used to record the experimental spectrum. The keyword Freq(vcd) computes the vibrational spectrum and its chiroptical response. NMR obtains the nuclear magnetic shieldings. In analyzing the results, a student must appropriately reference these against TMS and relate the static minimized computational structure (in which the three hydrogen atoms of a methyl group may be inequivalent) with the kinetically averaged results from a measured <sup>1</sup>H NMR spectrum (where a methyl group shows up as only one peak).<sup>6</sup> EmpiricalDispersion=GD3 (re)introduces a student to dispersion attractions, one of the terms used in a molecular mechanics force field and nowadays also commonly added as an empirical correction to quantum mechanical procedures.

A student must then select appropriate computational resources. A course laptop computer is provided that gives licensed access to software with convenient interactive processing power for the mechanics calculation. Students will also access their online electronic laboratory notebooks (ELNs)

from this device. A high-performance batch computing resource allows submitted jobs to run for up to 48 h, accessed via a Web portal<sup>7</sup> and authenticated via their institutional account and their ORCID identifier.<sup>8</sup> A digital repository<sup>9</sup> issues a digital object identifier (DOI) for each calculation, which must be quoted in a report.<sup>10</sup> The overall process has recently been described.<sup>7</sup> When the computation is complete, programs such as Avogadro<sup>4</sup> or Gaussview<sup>5</sup> are used to produce a visual representation of the spectroscopic prediction from the final Gaussian output files.

In comparing their predicted spectrum with experiment, a student must make several judgements. The calculated NMR spectrum does not provide nuclear spin–spin couplings. Not all peaks expected for a molecule may have been observed/resolved/reported in the experimental NMR spectra, whereas their prediction contains all the nuclei (not just hydrogen). Students need to devise some statistical method for estimating how well the calculated and measured spectra match, identifying any significant outliers and possible origins for errors. Where multiple conformations are possible, students have to judge the population of each and whether they interconvert on the spectroscopic time scale. This introduces subtle concepts such as whether atropisomerism is a configurational or a conformational phenomenon.

#### Asymmetric Epoxidation

In a separate, synthetic experiment of 2 weeks duration involving six laboratory sessions of up to 6 h each day, pairs of students will each prepare one of two catalysts: the Shi fructose oxidant<sup>1</sup> and the Jacobsen manganese oxidant.<sup>2</sup> Each student will then use both catalysts to epoxidise one or more alkenes chosen from the list: styrene, stilbene, trans- $\beta$ -methylstyrene or dihydronaphthalene using procedures previously described in this *Journal*<sup>1,2</sup> and ending with measuring the optical rotation of their products. Their task, recommended for the second week of the computational experiment described in the present article, is to identify which enantiomer of each resulting epoxide predominates. Because of space and timetabling limitations in our department, the two separate experiments currently have to be carried out consecutively, in either order. Freed of such constraints, it might be more instructive for the students to run the two experiments concurrently over, for example, a four-week period or longer as necessary.

#### Student Electronic Laboratory Notebook (ELN)

Students each keep an ELN of their investigations<sup>7</sup> in the form of a JSmol-enhanced Wiki,<sup>11</sup> a feature of which allows upload of the coordinates of their molecular models constructed during the laboratory, greatly facilitates subsequent assessment, and allows instructors to give detailed feedback to each student in the form of a Wiki-discussion.

Detailed information and other aspects of the experiment can be found in the Supporting Information.

#### HAZARDS

None for the computational part described here.

#### RESULTS AND DISCUSSION

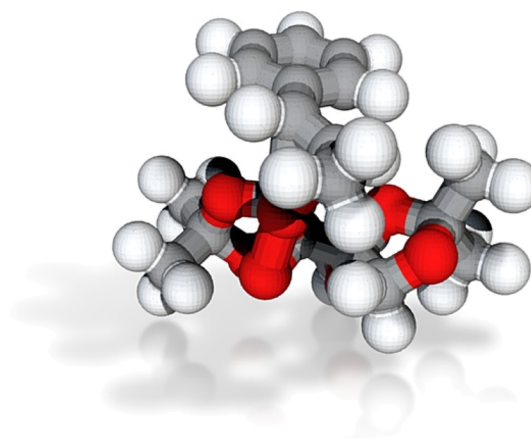
The initial task was to compare measured NMR properties of the synthesized epoxide with values calculated using the procedures introduced earlier. Students soon realized that they could not assess the absolute configuration of their samples from the NMR spectra alone. There are several chiroptical properties of these chiral epoxides that can be

computed to provide such information. Optical rotatory power (ORP) at one or more wavelengths (normally 589 and 365 nm) was first seminally applied by Kirkwood in 1952<sup>12</sup> to verify the correctness of Fischer's original guess for the absolute configuration of glyceraldehyde. Students discovered that their computed rotation (typical specific rotations or  $[\alpha]_{589}$  range from 130–300 depending on the alkene selected) may be quite variable because even such simple alkene epoxides can have several different conformations involving the phenyl group, and optical rotations can be highly sensitive to conformation.<sup>13</sup> Electronic circular dichroism (ECD) measures the differing optical absorption of the sample between left and right polarized radiation for the spectral range ~300–600 nm. If the compound is chiral, the difference in absorption  $\pm \Delta\epsilon$  (known as the Cotton effect) can be used to identify the excess enantiomer. This requires a good optical chromophore to be present between 300 and 600 nm; students recognized that this is something the simple epoxides above lacked. Vibrational circular dichroism (VCD) measures the chiral response of vibrations in the IR spectrum; VCD differs from ECD in always having multiple suitable chromophores.<sup>14</sup> The increasing availability of such instruments means this technique will become far more important in the future.

The relative calculated free energies  $\Delta\Delta G^\ddagger$  for all of the likely diastereomeric transition states for the reaction using the Shi and the Jacobsen catalysts can also be used for this purpose.<sup>15</sup> The difference in  $\Delta\Delta G^\ddagger$  between the lowest energy transition state leading to one enantiomer of the epoxide compared to that for the other enantiomer allows the absolute stereochemical outcome to be predicted.<sup>16,17</sup> Because both the Shi and the Jacobsen catalysts are relatively large systems, locating<sup>15</sup> each reaction transition state can take too long. The solution was to precompute all the systems and archive each calculation with an assigned DOI. Using these identifiers,<sup>8,9</sup> students downloaded the output files and analyzed the relative computed free energies ( $\Delta G_{298}$ ) to predict the anticipated enantiomeric ratio for each catalyzed reaction. The equation  $\Delta\Delta G^\ddagger = -RT\ln K$ , where  $K$  is the ratio of the populations of the two epoxide enantiomers was used. A library of quantitative 3D-printed models of the transition states was also available for students to explore in a more tactile manner (Figure 2). Further insights were obtained using toolbox components such as noncovalent-interaction (NCI) analysis and quantum topology.<sup>18</sup>

## STUDENT FEEDBACK AND LEARNING OUTCOMES

The following comments came from a cohort of ~140 students in eight sets of ~20 who consecutively undertook the two-week computational experiment and also derive from a graded assessment of their electronic laboratory notebook record of the experiment. Unlike a safety-conscious experimental laboratory, an *in silico* version can have a liberating effect on students. One student commented, “the computational sandbox gives you a freedom to play with ideas, related not just to the exercise in hand, but to lectures, and other labs in general.” Just like misbehaving apparatus in an experimental laboratory, computer programs can give mystifyingly obscure error messages and students came to “appreciate the skills one has to learn to track down such errors.” Rubbish in, rubbish out is an axiom often used for computer experiments because, as with any instrument, computational modelling can give incorrect answers or just obscure errors. The former is illustrated with the unreasonably high energies that can be associated with



**Figure 2.** 3D-printed model for one (DOI: tb2) of eight isomeric transition states for oxygen transfer from the Shi catalyst to  $\beta$ -methylstyrene.<sup>11</sup>

errors in mapping the 2D stereochemical representations (Figure 1) into three-dimensional models with, for example, unfeasible stereochemistry. Obscure errors occur when programs such as Gaussian are presented with keywords they cannot recognize or which conflict with each other; coping with this aspect is very much part of the training. To avoid analyzing what turns out to be rubbish, students noted, “It reminds you that reality checks in the form of effective searches of the literature are a useful skill.” Students can also fall into a mindset where they are expected to get the right answer; indeed that there is one “correct” answer for each problem they are set. In exploring the conformational possibilities of taxol, for example, students learned to appreciate that the correct answer might not actually be known. It can also be quite a revelation for students to discover the disparity in the reported literature values of properties such as optical rotation and the temptation to accept the first value tracked down or indeed to quote selectively the value that agrees best with their calculation. The realization dawns that literature values for optical rotations can be quite variable, not just in the magnitude but sometimes even the sign, and is a reflection of the real world.

## SUMMARY

In devising a twinned computational-synthesis experiment, computational modeling and, in particular, computational spectroscopy are nowadays considered as essential an instrument in an experimental laboratory as, for example, an IR, NMR, or chiroptical spectrometer. Computers do not just belong to a computer room but also, in fact, represent an instrument that can increasingly be accessed by a researcher and used when needed. Especially perhaps in spectroscopy, however, the computational and experimental aspects are increasingly twinned and are becoming inseparable. Students were also introduced to the increasingly prevalent concepts of digital electronic laboratory notebooks and digital data repositories as an integral part of the modern chemical laboratory.

## ASSOCIATED CONTENT

### Supporting Information

The computational experiment script, details of the computational toolbox, operation of electronic laboratory notebook, details of the quantum topological analysis, DOIs for transition



state calculations and additional student feedback for the overall experiment are available as SI1 (zip file). Example input and output files, graphical representations of spectra and interactive 3D models associated with the experiment are available as SI2 (zip file). This material is available via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

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### Notes

The authors declare no competing financial interest.

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