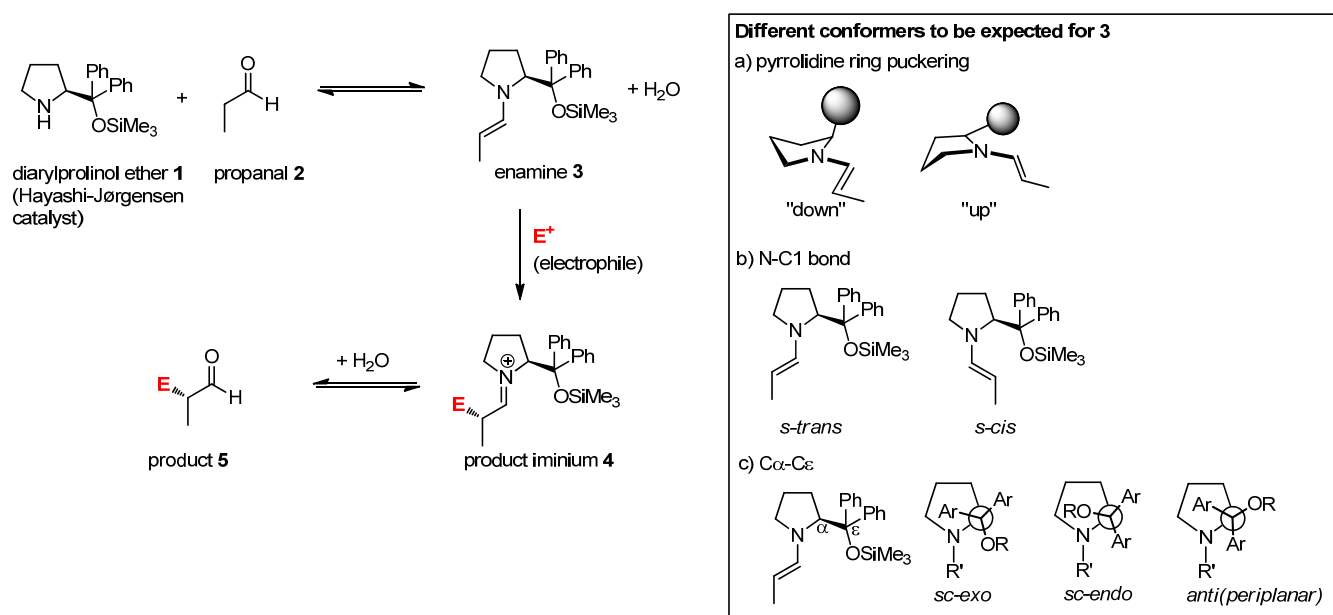


Computational Exercise

The success of small-molecule organic catalysts in enantioselective catalysis can be partially attributed to the simplicity of the catalyst structures, allowing researchers all over the world to test their reactions with a minimum synthetic effort.¹

In this computational exercise, we will study the conformational behavior of one of the most successful families of small-molecule organocatalysts, the Hayashi-Jørgensen diarylprolinol ethers.² These compounds can readily engage aldehydes and ketones covalently, giving rise to iminiums and enamines, which are in (relatively) rapid equilibrium with the starting materials. For example, propanal and diphenylprolinol silyl ether form an enamine which is well known to react with various electrophiles with good to outstanding enantioselectivities. Is it possible to trace this selectivity to the conformational aspects of the covalent enamine?



The solution structure of enamine **3** has been explored by NMR methods in a very careful study by Gschwind and co-workers. The NMR data suggests that **3** prefers a *down* conformation for the pyrrolidine ring and a *sc-exo* conformation for the C α -C ϵ -bond. Both *s-trans* and *s-cis* conformers can be detected. However, the energies of the different conformations have not been examined computationally.

The purpose of this exercise is to examine the conformation of **3** using computational methods. For conformational searches, the usual starting point is to generate several different structures using a combination of random movements (Monte Carlo) and controlled or guided (Low-Mode) search – this can be easily automated by the computer program. The structures will be (partially) optimized and arranged in order of increasing energy using a *force field* – an

¹ For reviews of enamine catalysis, including a discussion of different activation modes, see: (a) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416. (b) S. Mukherjee, J. W. Yang, S. Hoffman, B. List, *Chem. Rev.* **2007**, *107*, 5471. (c) For a detailed NMR study of enamine intermediates such as **3**, see: M. B. Schmid, K. Zeitler, R. M. Gschwind, *Chem. Sci.* **2011**, *2*, 1793.

² For recent reviews, see: (a) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 6138. (b) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178. (c) C. Palomo, A. Mielgo, *Angew. Chem. Int. Ed.* **2006**, *45*, 7876. (d) S. Sulzer-Mosse, A. Alexakis, *Chem. Commun.* **2007**, 3123.

empirical collection of basic “strain” functions that gives a rough idea of the overall energy of the conformation.

In order to obtain a more accurate view of the structures and the energies, selected structures generated by the conformational search(es) will usually be subjected to DFT (density functional theory) optimization. This can also be readily performed by the program but these calculations take up much more time – sometimes hours, sometimes even days! As such, it is not realistic – even for a small molecule – to optimize hundreds of structures with DFT. Furthermore, for more accurate calculations of the relative energies, more intensive DFT functionals (e.g. M06-2X) are often used, especially if the systems involve hydrogen bonding. Therefore we recommend caution when interpreting the computational results.

Procedure:

1. The structure of **3** will be provided to you in a mol2 format (diarylprolinol_silyl_ether_enamine_start.mol2).
2. Log in with the student account. If you are using computer #1, use the Student1 account, if you use computer #2, use the student2 account, etc. The passwords will be provided to you separately.
3. After logging in, click the star at the lower left corner and open the **Dolphin** (file browser).
4. Copy the starting structure of **3** (diarylprolinol_silyl_ether_enamine_start.mol2) to your home directory.
5. Click the star at the lower left corner and open **Konsole**.
6. Type in **Maestro** in the Konsole window.
7. After starting Maestro, select **Project -> New**. Create a new project with the following name: JSS2012_CH2_yourfamilynames
8. Import the structure to the project. Select **Project -> Import Structures** and select the diarylprolinol_silyl_ether_enamine_start.mol2 file. Note that the file type needs to be changed to mol2.
NOTE: If the structures are not displayed properly, select *Draw bonds in tube* at the left panel (double-click the orange sausage-like cyclohexane structure). This usually helps.
9. Select **Applications -> MacroModel -> Conformational Search** and select the following options:
 - From the **Potential** panel, select the force field **MMFFs**. You can also try out other force fields later but MMFFs is a generally good force field for conformational searches of a variety of organic molecules.
 - In the **CSearch** panel, select **RMSD cutoff** and change this to **2.0 Å**. This will reduce the number of conformers generated.
10. Start the conformational search. The search will request a filename for the search file – you can use the default but the next time you start the search Maestro you should give a different name. A better option is to give a name that informs about the molecule as well as the force field (i.e. JSS2012_yourname_enamine_MMFFs_search_1, please modify the number and the force field part of the name if you perform different searches).
NOTE: the conformational search will take anytime between 10 minutes and a full hour. You may want to leave the computer at this point (please lock the screen – select the star at the lower left corner and then select **Leave -> Lock screen**. Important – DO NOT LOG OUT as this will shut down all the calculations!

11. After the conformational search has finished, you should find an array (group) of structures in the Project Table window. If the Project Table is not visible, select Project and Show Table.
12. Select up to four structures for optimization by DFT. If you select more structures, the computations may not be finished by the time the course finishes.
 - The structures are selected in the Project Table. You can select multiple structures by pressing Ctrl and selecting the structures with the mouse. Note that 1) the selected structures are shown in yellow in the Table, and 2) there is an info field at the bottom of the Project Table that displays how many structures you have selected and also how many are displayed “included”.
13. Select **Applications -> Jaguar -> Optimization**. This opens up the Jaguar window – the module used for DFT calculations.
14. **Important!** In the Jaguar window – on the top – select “Use structures from: Project Table (Selected Entries)”. This is to make sure that the calculations will be performed on *all* of the selected structures.
15. In the Solvation tab, make the following changes:
 - Change the solvent model to PBF
 - Change the solvent to Chloroform
16. Now you should have at the bottom of the Jaguar window the following text:
 - Job: B3LYP/6-31G**, Optimization, Solvation
17. Click **Start**. You can now close the Jaguar window.
18. Select **Applications -> Monitor Jobs**. You should see a message showing how many jobs will be run.
19. Lock the computer: Select the star at the lower left corner and then select **Leave -> Lock screen**. Important – DO NOT LOG OUT as this will shut down all the calculations!

Analysis of results:

1. First, check that the calculations have indeed finished. This can be done by clicking **Applications -> Monitor Jobs**. There should be a message that explains that the calculations have finished.
2. You can also see the entries corresponding to the DFT calculations in the Project Table.
3. **Rename** the DFT results in the Project Table (click on the text in the Title column and give a new name), e.g. **Hayashi_cat_enamine_sc_exo_up_strans_1** (i.e. the name should reflect the conformational descriptors of the result; if there are multiple entries with all the same descriptors, use numbers to differentiate them).
4. You can now examine the results by energy. If you scroll to the right in the Project Table, you should be able to find a column titled **Gas Phase Energy** and also **Solution Phase Energy**. The lower the number, the more stable the structure. You will now have several structures which can be ranked (qualitatively) by their predicted order of stability.

To obtain a more detailed view of the energies, it is easiest to export the structures in a csv format and open the results in Excel. This will also allow a quick calculation of the energies in kJ/mol or in kcal/mol. The energies in Jaguar are reported in *hartrees* – one hartree is 2625.499 62 kJ/mol or 627.509 469 kcal/mol.

5. Select the entries you want to export.
6. In the Project Table window (NOT the main window), click **Sort** and select Gas Phase Energy as the Primary Key. Then click **Sort Selected Rows**. This will reorder the entries in the order of increasing energy.

7. In the Project Table window, select **Table -> Export -> Spreadsheet**. Type in a file name (e.g. JSS2012_CH2_computational_exercise_yourname_DFT or something similar). This will create a .csv file that can be opened in Excel. You can copy this file to your USB stick using the Dolphin file browser.
8. You can also export the structures as well. In the Project Table window, select Table -> Export -> Structures. This will open an Export window. In this window, make the following changes:
 - Files: change this setting to **Export each entry as an individual file**.
 - File names are: **Just entry titles**. (This is OK *if* you have renamed the entry titles as detailed above at step #3).
 - Finally, select Files of type: MOL2 (*.mol2). These files can be opened by almost any structure viewer. You can also choose a variety of other file types (e.g. xyz coordinate files, sdf files, pdb format etc.)
 - Remember to copy these files also to your memory stick.
9. In Excel, open the file DFT_results_cheatsheet.xlsx. Open a new worksheet (click on "Sheet2" at the bottom of the window).
10. Select File -> Import. Select CSV file and then choose the file (from your USB stick). Then click "Get Data". Then click "Next" as many times as necessary to complete the import wizard.
11. You will now have an Excel file that contains a lot of data. The easiest way to use the cheatsheet is to copy only the data that you will need (i.e. the entry titles that describe the conformations and the *corresponding* gas phase and solution phase energies) to the Cheat sheet DFT worksheet. One way to do this is to select those rows that are not relevant (i.e. everything between Entry ID and Gas Phase Energy) and then click on the right mouse button and select "Hide". Then it is easy to copy the relevant data.
12. Copy first the entry titles, then the Gas Phase Energies, and finally the Solution Phase Energies to their relevant locations in the Cheat Sheet DFT worksheet. The cheatsheet should then calculate the relative energies in kJ/mol.

You will now have an Excel sheet containing the results, and an array of molecular structures. The rest of the analysis requires further data, e.g. NMR data, or (if your peers are not convinced about your results) heavier DFT functionals and other justifications for the results.

Please note that energy differences of the order of 1-2 kcal/mol (4-8 kJ/mol) will easily fall within the error margin of the methods.