Chemistry 430 — Simulation in Chemistry & Biochemistry

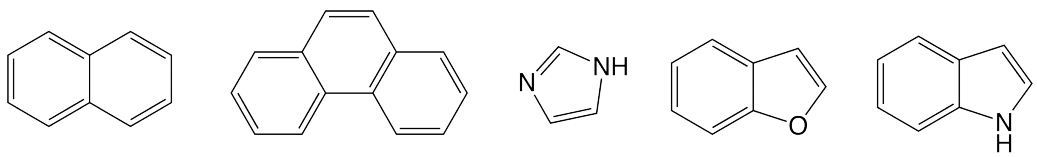
Laboratory #9 — Frontier Molecular Orbital Analysis of Regioselectivity

In this lab exercise you will perform extended Hückel and minimal basis set STO-3G calculations to generate frontier molecular orbitals (HOMO and LUMO), and then use FMO analysis to predict regioselectivity of three reactions: electrophilic aromatic substitution, Diels-Alder dimerization of acrolein, and nucleophilic addition to benzoquinones. The Extended Hückel method is available in Gaussian, but not in Spartan. Hartree-Fock calculations with the STO-3G basis set can be performed using either Gaussian or Spartan. The Avogadro program, which is already installed on all the lab computers, can display the orbitals generated by Gaussian.

Protocol

(1) As an initial exercise, generate the frontier orbitals for water using both an Extended Huckel theory (EHT) calculation and HF/STO-3G minimal basis set *ab initio* theory. The Gaussian input file for EHT is provided on the web page for this lab as **`ehuckel.com`**. To run the STO-3G computation, replace the **`ExtendedHuckel`** keyword (following **`#`**) with **`HF/STO-3G`** and copy the input file to some other name. Make sure that your Gaussian input file specifies production of a "checkpoint" **`.chk`** file (via the **`%Chk`** directive near the top of the file). The Gaussian job can be run in a tcsh terminal window via the command: **`g09 ehuckel >& ehuckel.log &`**. After running Gaussian 09, the **`.chk`** file can be converted to a formatted version (**`.fchk`**) using the formchk utility (for example, via: **`formchk ehuckel.chk`**). This **`.fchk`** file can in turn be used as input to Avogadro for display of the molecule orbitals. Copy pictures of the frontier orbitals into your lab report. *(Note: If Avogadro displays the orbitals incorrectly, as a dim black wire mesh, try clicking on the* **`Reset Display Types`** *option in the* **`View`** *menu to reset the display. If that fails, then try a different lab computer.)*

(2) Use frontier orbital analysis based on Extended Hückel theory (EHT) results to predict the preferred site of electrophilic aromatic substitution (nitration, for example) for the following molecules: naphthalene, phenanthrene, imidazole, benzofuran and indole. You can get starting coordinates by any of several methods, including: (a) draw the structure in Spartan, then use **`Minimize`** from the **`Build`** menu, and **`Save`** from the **`File`** menu, or (b) use the **`Download from PubChem...`** option from the **`File`** menu in Force Field Explorer (FFE). Pick any two of these molecules to calculate for your lab report, and then try the others if you have the time and interest. Is the HOMO or the LUMO of the aromatic molecule the one controlling the substitution site?

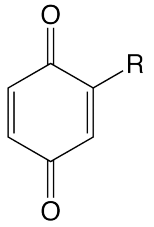


Naphthalene Phenanthrene Imidazole Benzofuran Indole

(3) Look up the experimental site of nitration for each of these molecules in the primary literature and compare with your calculations. For at least one of the aromatic molecules, perform additional STO-3G and PM3 calculations, and compare the frontier orbitals between EHT and these additional levels of theory.

(4) Acrolein is the simplest conjugated aldehyde, with formula $H_2C{=}CH{-}CHO$. There are two reasonable products from the Diels-Alder dimerization of acrolein, both of which use the C=C bond as the "dieneophile". Use MO calculations and frontier orbital arguments to predict the preferred regioselectivity of this dimerization reaction.

(5) Early in his career Ken Houk, a well-known applied quantum chemist and at UCLA, studied a number of organic reactions in terms of FMO theory. Following up on work by Houk, predict the site of nucleophilic addition to substituted benzoquinones. Consider three classes of substituents: electron-donating, conjugating and electron-withdrawing. Using R = $-CH_2^-$, $-CH{=}CH_2$ and $-CH_2^+$ as models for these three substituent types, run calculations (you may use either EHT or HF/STO-3G) to rationalize the site of attack by nucleophilic reagents in terms of FMO theory.



Substituted Benzoquinone

Questions

(1) How do the orbital energies and coefficients for water differ between Extended Hückel (EHT) and minimal basis set Hartree-Fock (for example, HF/STO-3G) calculations? Explain the differences. There is a good tutorial description of Extended Hückel theory taken from *Quantum Chemistry* by John Lowe under *Readings* on the course website.

(2) What do your calculations on water say about the concept of "rabbit ear" lone pairs in the water molecule? See if you can find direct experimental evidence that supports your MO results regarding the lone pairs. (Hint: look into the photoelectron spectrum of water)

(3) Organic chemists often debate the electron donating *vs.* withdrawing effect of methyl substituents. In fact, FMO theory suggests there is no single correct answer – that methyl substituents are often σ-withdrawing and π-donating. For example, the gas phase acidity order of amines increases with increasing methyl substitution, as does the basicity order, *e.g.*, $Me_2HN > MeH_2N > NH_3$ for acidity and $Me_3N > Me_2HN > MeH_2N > NH_3$ for basicity! Provide a frontier orbital explanation for seemingly odd result. Try running some simple calculations to support your answer.

(4) Consider the total electron density of each of the electrophilic aromatic substitution substrates above. Do the sites of greatest atomic charge density agree with the FMO-predicted sites of substitution? Explain why the FMO analysis gives superior predictions compared to simple analysis of the total electron density.

(5) For "typical" Diels-Alder reactions, which orbital generally plays the most important role for the diene, the HOMO or the LUMO? What about the dienophile? In terms of FMO theory, what is an "inverse electron demand" Diels-Alder reaction?

(6) Draw and use a "resonance structure" argument from basic organic chemistry to predict the preferred acrolein dimer product. Is the dimer predicted by FMO analysis consistent with the one predicted by your traditional resonance structure (or "valence bond") analysis?

(7) Consider the Klopman-Salem formula, which is described in a post on the course web site taken from the Wikipedia page. The Klopman-Salem formula is a quantitative FMO-based method to predict the "strength" of the bonds forming during the initial stages of an FMO-controlled reaction. Use the ideas contained in this formula to predict which of the two alternative acrolein dimerization products will be the major product.

(8) A recent research paper, *RSC Advances*, ***11***, 7459-7465 (2021), is provided on the lab web site. This article analyzes the acrolein dimerization using more sophisticated quantum calculations, after largely dismissing the FMO explanation. See if you can follow the discussion in this paper. What do you think of the author's arguments?