The Stability of (E) and (Z) Anethole

In this exercise we will perform semi-empirical quantum mechanical calculations on (E) and (Z) Anethole to determine which isomer is more stable. Our focus will be on the differences in the stability of the Alkene functionality.

Of course, what we mean by “stability” is somewhat of an open question. Experimentally, “stability” is generally expressed in terms of measurable Enthalpy changes (ΔH°) relative to some reference compound. As an example, the stability of cis-2-Pentene can be compared to that of trans-2-Pentene because Hydrogenation of each of these compounds produces the same product; Pentane. So, the Heats of Hydrogenation (ΔH_{Hyd}^o) for each alkene can be directly compared.

\[
\begin{align*}
\text{cis:} & \quad \text{H}_3\text{C} \quad \text{C} = \text{C} \quad \text{CH}_2\text{CH}_3 \\
& + \quad \text{H}_2 \\
& \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\
& \quad \Delta H^o = -28.6 \text{ kcal/mol}
\end{align*}
\]

\[
\begin{align*}
\text{trans:} & \quad \text{H}_3\text{C} \quad \text{C} = \text{C} \quad \text{CH}_2\text{CH}_3 \\
& + \quad \text{H}_2 \\
& \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\
& \quad \Delta H^o = -27.6 \text{ kcal/mol}
\end{align*}
\]

Based on this data, the cis isomer is seen to be less “stable” than the trans isomer. In other words, the cis compound sits at a higher enthalpic level, relative to Pentane, than the trans compound.
Data of this type leads us to the following generalizations:

I. A *trans* isomer is more stable than the corresponding *cis* isomer.

II. More substituted double bonds are usually more stable than less substituted double bonds. (Zaitsev’s Rule)

However, these rules are generalizations. For concreteness, compounds must be examined as individual cases before conclusions regarding their relative stability can be drawn.

As an alternative to the experimental approach, molecular properties can many times be determined using appropriate computational models. Depending on the accuracy required, these model results may resolve any questions under consideration, negating the need for experiments to be performed.

For the present problem, we will use molecular modeling software to determine the Heats of Formation ($\Delta H_f^\circ$) for the (E) and (Z) isomers of Anethole.
Because the reactants are the same for each Formation Reaction, the two Formation Enthalpies can be directly compared to determine the relative stability of the isomers.

Now, onto how we “calculate” $\Delta H_f^0$’s.

From a fundamental theoretical point of view, for an isolated molecule, all molecular properties can be determined using a solution to the Schrodinger Wave Equation:

$$\hat{H} \Psi = E \Psi$$  \hspace{1cm} (Eq. 1)

In the Wave Equation, $\hat{H}$ is the Hamiltonian Operator for the molecular system, $\Psi$ is its wavefunction and $E$ is the system energy. The Hamiltonian Operator contains information about the kinetic and potential energies of each electron and nucleus in the molecule under consideration. Once the Hamiltonian is constructed, the Wave Equation can be solved for the $\Psi_i$’s and associated $E_i$’s.

Historically, the Wave Equation was developed by Erwin Schrödinger to explain the observed energy levels ($E_i$) of the Hydrogen atom.

He found, for the Hydrogen atom:

$$E_n = \frac{hc}{R_H} \frac{1}{n^2} \quad n = 1, 2, 3, ...$$

where $h$ is Planck’s constant, $c$ is the speed of light, $R_H$ is the Rydberg constant and $n$ is the principle quantum number. His results for the $\Psi_i$’s can be found tabulated in most elementary physical chemistry textbooks.

It was Max Born who gave us an interpretation for $\Psi$; $\Psi^2$ determines the probability of finding the electron in a given region of space. It is $\Psi^2$ that provides us with the atomic orbitals for
Hydrogen; 1s, 2s, (2px, 2py, 2pz), 3s, (3px, 3y, 3pz), etc. In molecular systems, it is $\Psi^2$ that tells us something about the distribution of the electrons within the molecule; bonds, lone pairs, etc.

Unfortunately, the Wave Equation is a differential equation that is extremely difficult to solve analytically. The number of chemically important systems for which exact solutions are available is extremely limited; the Hydrogen atom, the diatomic molecule, and a few others. Solving this equation for something as simple as the Helium atom requires approximation techniques that are beyond the current discussion.

Fortunately, a number of different computational methodologies have been developed to solve the Wave Equation, at least in an approximate way, for the Ground State energy ($E_{GS}$) of simple molecules. Some of these methodologies are quick and dirty; taking only a few minutes. Others are quite sophisticated and can take many days worth of computer processing time. Of course, the more sophisticated the methodology, the better the results provided.

Generally, current computational methods for solving the Wave Equation for small molecules fall into two categories: *ab initio* algorithms and semi-empirical algorithms. *Ab initio* algorithms involve a direct assault on the Wave Equation and are typically very time consuming. Semi-empirical algorithms generally cut-corners and involve patching things-up with experimentally determined data.

In the semi-empirial method, for example, we may parameterize $\Psi$ with “fitting” parameters, making it easier to solve the Wave Equation. Then, we can determine the values for the fitting parameters by repeatedly solving the Wave Equation with adjusted parameters until the solution gives results we know to be experimentally correct. We can then use these parameters to solve the Wave Equation for chemically similar systems. This generally speeds things along and gives results which are not too bad.

Another issue that needs dealing with is that the solutions to the Wave Equation will depend upon the geometric positions of all the atomic nuclei within the molecule, which are generally treated as fixed. However, the geometry of the molecule may be one of the things we wish to determine. So, in a “geometry optimization,” we typically start with a good guess for the molecular structure. Then the Wave Equation is repeatedly solved as we tweak the geometry until the overall ground state energy is minimized. The structure for which a minimum energy is found is taken as the optimal geometry for the molecule.

For a simple example, consider the geometry of Ethane; CH$_3$CH$_3$. If we were to start our calculations with this molecule in an eclipsed conformation, we would find a relatively high ground state energy. Rotating the H-C-C-H dihedral angle towards a staggered conformation will result in lowered energies. At the point where the molecule is fully staggered the energy will be minimized and the geometry optimized.
Finally, the calculated ground state energy $E_{\text{GS}}$ must be converted to $\Delta H_f^\circ$ for the compound. This is a two step process; the elements needed to form the compound are first atomized and then the atoms are used to form the compound in question. This is illustrated for Anethole:

$$
10 \text{C}(\text{g}) + 6 \text{H}_2(\text{g}) + 1/2 \text{O}_2(\text{g}) \rightarrow 10 \text{C}(\text{g}) + 12 \text{H}(\text{g}) + \text{O}(\text{g}) \rightarrow \text{Anethole}
$$

The Formation Enthalpy can be calculated by subtracting the calculated atomic energies and atomization energy from $E_{\text{GS}}$ for the molecule. A small correction factor must be applied to convert the energy $E$ of the system to the enthalpy $H$. This result must be multiplied by Avogadro’s Number $N_A$ in order to convert from an enthalpy on a per molecule basis to an enthalpy on a per mole basis.

$$\Delta H_f^\circ = \left( E_{\text{GS}} - \sum E_{\text{GS},a} - \Delta e_{f,a} + \text{corr} \right)N_A$$

Typically, the last three terms in this expression are subsumed into a single empirical parameter $\alpha_a$. Thus:

$$\Delta H_f^\circ = (E_{\text{GS}} - \sum \alpha_a)N_A$$

If the software package being used includes a database of $\alpha_a$ values, it can automatically determine $\Delta H_f^\circ$ for the molecule once the geometry has been optimized and $E_{\text{GS}}$ has been determined.

We will use AM1, a semi-empirical methodology, for our calculations of $\Delta H_f^\circ$ for (E) and (Z) Anethole. AM1 was developed at the University of Texas at Austin by Dewar et al [Michael J.S. Dewar, Eve G. Zoebisch, Eamonn F. Healy, and James J.P. Stewart; AM1 A New General Purpose Quantum Mechanical Molecular Model JACS 107 3902 (1985).] This method deals only with the valence electrons in the molecule and is parameterized for the organic elements C, H, O, and N. Levine reports “A study of compounds of all the elements for which the methods are parameterized found the following average absolute error in bond lengths and bond angles; ...0.050 Å and 3.3° for AM1, ... . For 16 dihedral angles, average absolute errors are ..., 12.5° for AM1, ... . For a sample of 88 compounds, ... $\Delta H_f^\circ$ values ... had an average absolute error of 6.7 kcal/mole for AM1.” [Ira N. Levine, Quantum Chemistry, 4th Ed.; Prentice Hall; 1991.] The AM1 software comes packaged together with other semi-empirical routines in a package called MOPAC. MOPAC, in turn, is available via the Chem3D Ultra software suite. Other versions of MOPAC are available for download for free.

We will start by using ChemDraw to construct a crude “picture” of our Anethole molecule. This software package will allow us to specify the positions of all the molecule’s atoms relative to each other. It has a simple interface that includes a palette of chemical structures that can be placed on a working canvass. Once the molecule is constructed, the relative coordinates of the atoms can be saved in a *.cdx file. This file is readable by MOPAC and will provide us with our guess for the initial geometry of the molecule.
Once the ChemDraw file has been opened in Chem3D Ultra, we can select the MOPAC routines and “Minimize” the energy of the molecule.
Once AM1 is finished with the minimization, the molecular geometry will be displayed and $\Delta H_f^o$ reported.

Thus, using AM1, we can calculate $\Delta H_f^o$ for both the (E) and (Z) isomers of Anethole and determine which is more stable.

Two general cautions regarding these results are in order. First, this is a modeling experiment. The results are only as good as the model. For more realistic cases, different input configurations need to be considered and different methodologies need to be tried. Second, the results are only representative of a single molecule in the gas phase. Interpretation of condensed phase behavior based on these results should be considered carefully.
Exercises

1. Use *ChemDraw* to construct the (E)-Anethole molecule. Save these results as a *.cdx* file.

2. Launch *Chem3DUltra* and open the *ChemDraw* output file.
   
   i) Configure the molecule so that the ring substituents are *syn* to each other.
   
   ii) Select the *MOPAC* package and run an Energy Minimization procedure. *Click* on the “Theory” tab and select the *AM1* semi-empirical methodology. Run the minimization.
   
   iii) Check the “Message” bar for $\Delta H_f^\circ$ once the calculation is complete. Record this result.
   
   iv) Determine the H-C-C-C dihedral angle as indicated below:

   ![Note Angle](image)

   Note the position of the propene unit relative to the planar benzene ring.

   v) Save the results in a *.tif* file and print this file.

   vi) Repeat this for the case where the ring substituents are *anti* to each other. Does the position of the Methoxy group matter?

3. Do this same thing for (Z)-Anethole.

4. Which isomer is more stable? Is this consistent with your expectations? Explain.

5. Rationalize the orientation of the propene group relative to the aromatic ring’s plane for both isomers. You will need to consider both Resonance Delocalization of the Alkene unit with the ring and Steric effects due to overlapping atomic groups.