

Supplemental Materials

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Iona College
Department of Chemistry

The Use of Isodesmic Isomerization Reactions to Predict Aromaticity

A Computational Exercise for CHM 218 Laboratory

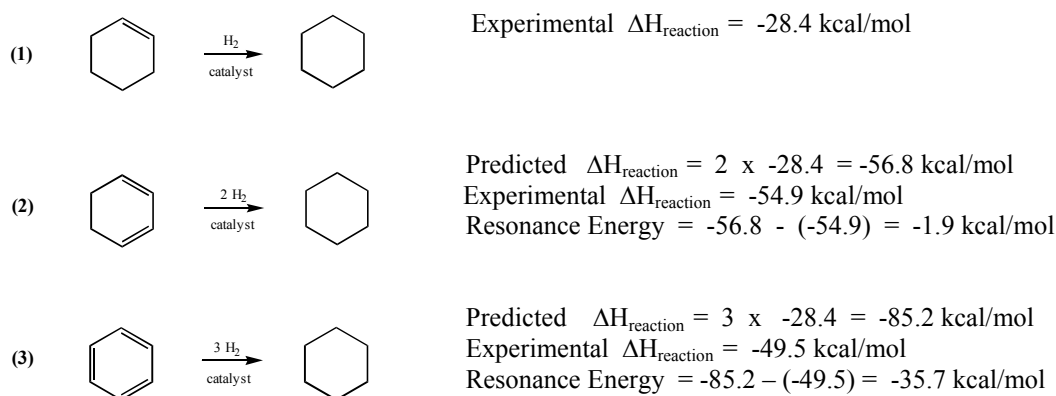
Terrence Gavin, Ph.D.

Aromaticity

Chemists in the 19th Century discovered that a large number of naturally occurring organic compounds contained the benzene ring as a unit. Because some of the earliest studies focused on highly fragrant compounds such as vanillin, molecules containing benzene rings were classified as aromatic. Ultimately, modern chemists articulated the theory of *aromaticity* in order to describe benzene and other molecules and ions, including heterocycles, deemed similar to benzene. Such species have high stability, specialized reactivity¹ and possess a closed ring of electrons. Specifically, it can be said that conjugated, cyclic molecules or ions with a planar geometry containing $4n + 2$ *pi* or non-bonding electrons ($n = 0, 1, 2, 3 \dots$) are aromatic. Quite naturally, the question arises as to how a specific structure can be characterized as aromatic and whether such designations can be made in a quantitative fashion. Textbooks for introductory organic chemistry courses use both thermodynamic² and spectroscopic³ methods to define and explain aromaticity in qualitative terms and researchers in this area have used these and other methods to produce several reasonable models to quantify such phenomena.

Thermodynamic Evaluation of Aromaticity

The purpose of this exercise is to investigate some of the thermodynamic criteria that have been used to assess aromaticity. This method defines aromatics as those molecules or ions that seem to possess special stability, i.e., they are lower in energy than they ought to be when compared to some reasonable reference point. The energy difference between the aromatic compound and the reference (usually the isolated double bond) is called the resonance energy. Hydrogenation reactions have typically been used to illustrate this. Consider the following example:



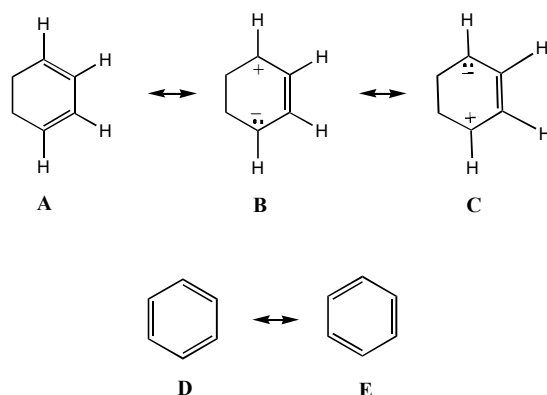
Equation (1) serves as an initial point of reference from which a prediction can be made regarding the reaction represented by equation (2). The discrepancy between the predicted value and the experimental value in this case would be explained by the resonance stabilization of the conjugated diene as seen in figures A, B and C. The rather large discrepancy between the predicted value and the experimental value for the

¹ For example, aromatic compounds undergo substitution reactions with electrophilic reagents, whereas alkenes and polyenes, whether conjugated or unconjugated, react by the addition of such reagents.

² See below

³ For example, the ring protons in aromatic compounds exhibit characteristic downfield (away from TMS) chemical shifts in the NMR spectrum.

hydrogenation of benzene shown in equation (3) is, in fact, the reason why benzene is classified as aromatic rather than simply resonance stabilized via resonance forms **D** and **E**. In reality cyclohexene and cyclohexadiene readily undergo catalytic hydrogenation, while benzene does not. Benzene can be converted to cyclohexane, but extremely high pressures of hydrogen and elevated temperatures are required.

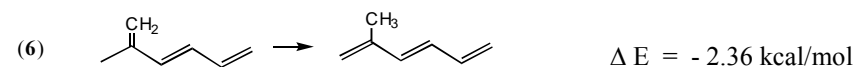


Using Isodesmic Isomerization Reactions to Evaluate Aromaticity

In addition to hydrogenations, energy differences obtained from certain isomerization reactions⁴ can be used as a thermodynamic criterion to assess aromaticity. Equation (4) is a typical example.



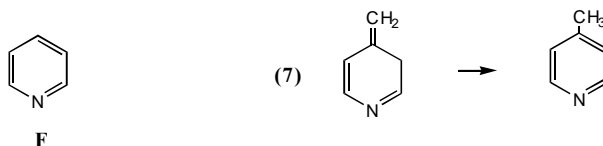
The two compounds involved are structural isomers that differ only in the position of one of the double bonds. Note that the difference in energy between the two isomers is virtually the same as the resonance energy of benzene. This value for ΔE is reasonable because the specific net result of this isomerization is the formation of a benzene ring. Alternatively, the reverse reaction can be interpreted as the amount of energy required to disrupt the aromaticity of the system and would in this case be endothermic (positive sign) by 35.2 kcal/mol- i.e., it would require the addition of 35.2 kcal/mol of energy. To appreciate the magnitude of this difference, equations (5) and (6) should be considered.



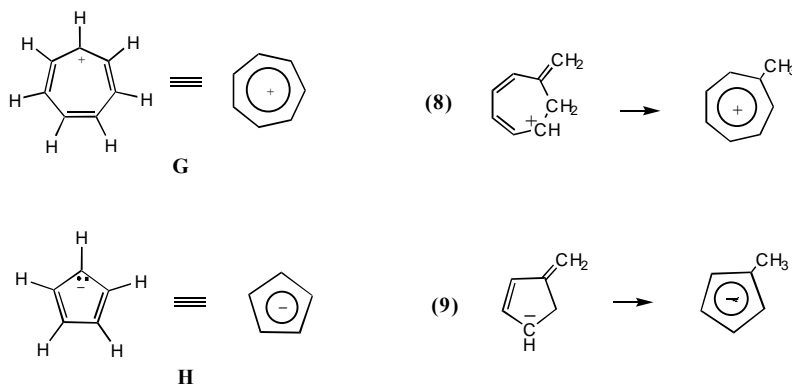
⁴ A generic term for this is isodesmic (equal bond). Thus, equations (4) through (9) represent isodesmic reactions.

As might be expected, rather small differences in energy are associated with the change from an exocyclic to an endocyclic double bond shown by equation (5) or for the rotation that converts the *s-cis* to the *s-trans* conformation in equation (6). The enormous difference in energy between the two isomers shown in equation (4) is indicative of the remarkable thermodynamic stability associated with the aromaticity of benzene.

Consequently, it should be possible then to use reactions analogous to (4) to assess whether compounds or ions other than benzene are aromatic. For example, one might ask if pyridine (**F**) is aromatic.



From its structure pyridine is shown to be cyclic and bonding considerations would provide a reasonable justification to assume the minimum energy geometry would be planar. The six *pi* electrons from the double bonds would constitute a $4n + 2$ number, in which $n = 1$, but there is also a pair of nonbonding electrons on the nitrogen atom. It is usual to argue that pyridine is aromatic because the nonbonding pair is in an sp^2 orbital perpendicular to the ring electrons and therefore, should not be counted. Confirmation of this conclusion might be attained in a number of different ways- e.g., determining whether pyridine reacts with electrophiles via substitution or addition, analysis of the chemical shifts of the ring protons in the NMR spectrum etc. However, obtaining the value of ΔE for equation (7) would also be significant in this regard, since the specific change in this reaction is the formation of the pyridine ring. If ΔE is large and negative, one could reasonably conclude that pyridine is aromatic because it possesses an enhanced thermodynamic stability similar to benzene. On the other hand, if the energy change is small (+ or -) the compound would be considered non-aromatic. Finally, if the energy change is large but positive the compound would be anti-aromatic. This method is widely applicable and can also be used to assess ions such as **G** and **H** as the corresponding equations indicate.




In the following exercises, a variety of compounds and ions will be assessed to determine whether they are aromatic or not. The cyclic nature and the number of relevant electrons can be determined from the structures. The geometry and the resonance energy of each will be acquired by computations. The value of ΔE for equations (4, 5, 6) given above were not obtained experimentally, but rather result from a quantum chemical calculations⁵. In essence, a computer is programmed to generate approximate solutions to the wave equations derived from the molecular structure submitted. From such calculations the thermochemical properties of the compounds can be derived. Computations are also used to determine the minimum energy geometry of the molecule. One obvious advantage to using such computational models is that a wide range of structures can be explored in a relatively short amount of time. The geometries and the energies of the relevant structures will be determined using *SPARTAN ES-02* software.

Exercises

General

Computations are carried out by the following sequence:

Build > Minimize > Setup > Submit > Save > Display

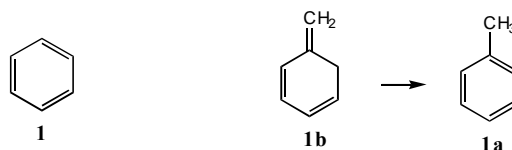
- (1) Building a molecule using the **new** icon from the **File** toolbar or by clicking on **File** and selecting **new molecule**. A model kit ("entry" is the default kit) will then be displayed on the right side of the screen that enables construction of the desired molecule.⁶
- (2) Minimizing⁷ the energy using  icon from the **File** toolbar or by clicking on **Build** and selecting **minimize**.
- (3) Selecting a "job" (i.e., a computation or a surface graphic) from **Setup** using **calculations** and/or **surfaces** (calculations and graphics are chosen independently but run simultaneously as part of the same job).
- (4) Performing the calculation by using **submit** from **Setup** or by clicking on **submit** in the **calculations** dialogue.
- (5) Naming the file from the dialogue box that appears after a job has been submitted.
- (6) Viewing the results. When a job is finished the user will be informed. After responding OK to the message, results may be viewed from **Display**.

⁵ Dhevi, D. M.; Priyakumar, U. D.; Sastry, G. N. *J. Org. Chem.* **2003**, 68, 1168-1171

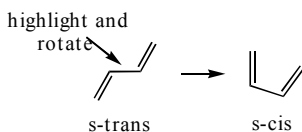
⁶ The kit is utilized by selecting (left click) the desired atom, ring or group and then clicking anywhere on the screen. Structures are built by selecting additional atoms, rings or groups and clicking on any open valence of the structure (or single atom) previously displayed. Operations (e.g., **delete**, **make bond**, **measure angle**, etc.) can be selected from the tool bar at the top, or from the pull-down menus **Geometry** or **Build**. Molecules can be rotated out of plane by holding down the left mouse button or rotated in plane by holding down the left mouse button and the **Shift** key. The right mouse button is used to move the molecule about the screen or with the **Shift** key to change the size of the displayed structure. Individual bond rotations can be accomplished by clicking on the bond (a highlight icon will appear) and then holding down the **Alt** key while using the left mouse button.

⁷ This function calculates the minimum energy geometry based on bond lengths, bond angles and dihedral angles by using the methods of classical mechanics.

Exercise 1: Calculating the Resonance Energy of Benzene

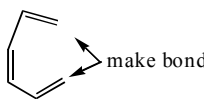


Open *SPARTAN ES-02* and click on **New** from the tool bar at the top (or choose **New** from the **File** menu). The build screen will appear with the **Entry** (default) model kit on the right side. Begin building molecule **1** (benzene) by selecting the trivalent carbon atom ($>\text{C}=\text{}$) from the kit and clicking anywhere on the build screen. Note that this fragment (or any other structure) can be rotated by using the left mouse button or moved about the build screen with the right mouse button. Then click on the open double bond and a second trivalent carbon atom will appear. Add the third trivalent carbon atom by clicking on one of the open single bond valences and a fourth by clicking on the open double bond valence of the third. Make sure that the diene is in the *s-cis* conformation.



If it is not, click on the single bond to highlight (the rotate icon will appear on the bond) and rotate about the selected bond by using the left mouse button while holding down the **Alt** key.

Next add two more trivalent carbon atoms to one end of the structure (make sure that the new double bond is also in the *s-cis* conformation) and then use the **Make Bond** function from the tool bar at the top (or select **Make Bond** from the **Build** menu) and click on two appropriate open carbon atom valences needed to close the ring as indicated in the figure below.



When the new bond is formed use the **Minimize** function from the tool bar (or select **Minimize** from **Build**) to obtain a reasonable geometry to begin the calculations. To calculate the minimum energy geometry of benzene, select **Calculations** from the **Setup** menu. In the ensuing dialogue make sure that after “Calculate:” (top line) the following selections appear: **Equilibrium Geometry** “with” **Semi-Empirical** and **AM1**. After “Start from”, **Initial** “geometry” should be selected. If any of these selections do not appear, choose them from the pull down menus in the dialogue box. Also check the boxes on the right and make sure that “Total Charge:” reads **Neutral** and “Multiplicity:” reads **Singlet**.⁸

The job (i.e., the calculation of the minimum energy geometry using a semi-empirical method called AM1) can now be submitted by clicking on **Submit** on the lower right of the **Calculations** dialogue (or click **OK** on the bottom right in the **Calculations** dialogue and then return to the **Setup** menu and select **Submit**).

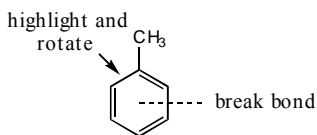
⁸ By default some other boxes may be checked, but these can be ignored at this point

Upon submission of the job a dialogue will appear that requires a name for the file. Either accept the default name (eg., Spartan 11) by clicking on **Save** immediately, or choose a name for the file by typing it in the highlighted box and then click **Save**. Respond **OK** when prompted to do so ("Spartan 11 has begun" - OK).

When the job has been completed, a prompt will appear ("Spartan 11 has finished"). Respond **OK**. Go to the **Display** menu and select **Properties**. Note that several properties of the molecule, including the energy, are displayed. Close the **Properties** inset by clicking **x** on the top right of the box. Finally, examine the structure of benzene by rotating with the left mouse button (and/or the left mouse button in conjunction with the **Shift** key for rotation in the plane of the screen) to determine whether the structure is planar or non planar and record your observation in *Table I*. Also record the number of *pi* electrons in the space provided in *Table I*.

The resonance energy of benzene will now be estimated by calculating the energy difference between **1b** (5-methylidene-1,3-cyclohexadiene) and **1a** (toluene). First, return to the **Build** screen by selecting **Add Fragment** from the **Build** menu or (+) from the toolbar⁹ at the top. To build toluene (**1a**), select the tetravalent carbon atom (>C<) from the model kit and click on one of the opening valences on the ring. Then click on the **Minimize** function to refine the geometry for subsequent calculations. The energy of isomer **1a** will now be determined by an *ab initio* calculation using the Hartree-Fock approximation at the 3-21G(*) level. To begin this job, select **Calculations** from the **Setup** menu. In the first line of the dialogue ("Calculate:") select **Single Point Energy**, "with" **Hartree-Fock** and **3-21G(*)**. In the second line ("Start from:") select **AM1** and then from the lower right side of the dialogue click **Submit**. When prompted, click **Save** for the default name (or name the file as desired and **Save**) and at the next prompt click **OK**. When the calculation has finished, click **OK** at the prompt and select **Properties** from the **Display** menu. Record exactly (including the sign) the energy that is displayed (in au) in the appropriate space in *Table II* on the data page.

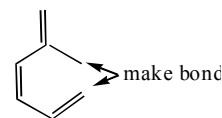
Return to the build screen by using the **Add Fragment** function to build **1b**. Select the **Break Bond** function by clicking its icon on the toolbar and select the bond indicated in figure below left.



Next click on any atom in the model kit to kill the **Break Bond** function and then select the bond indicated in the figure (left) and rotate about the bond (left mouse and **Alt** key) to obtain the structure below (right). **1b** (5-methylidene-1,3-cyclohexadiene)

is then completed by clicking the **Make Bond** function on the toolbar and selecting two open valences on the carbon atoms indicated in the figure (at right).

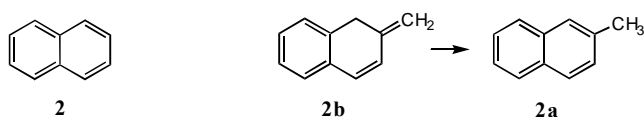
Use the **Minimize** function from the toolbar to obtain the starting geometry and then select **Submit** from the **Setup** menu to perform the same set of calculations that were run on toluene. That is, a **Single Point Energy** starting from the **AM1** geometry by using the **Hartree-Fock** method at the **3-21G(*)** level. When finished, record exactly the energy (au) in the appropriate space in *Table II* on the data page.



⁹ Use **View (V)** and **Add Fragment (+)** to toggle between the viewing screen and the building screen.

To obtain ΔE^{10} in au, subtract the energy of molecule **1b** from that of molecule **1a** and record the value (including sign) in the appropriate space. To convert this value in au to one in kcal/mole, multiply by 627.5 kcal/mole/au and record the result (including the sign) in the appropriate space in *Table II*. Next, record the value (rounded to two significant figures) and the sign of ΔE (kcal/mol) in the column in *Table I* labeled “Resonance Energy”. Finally, complete *Table I* by deciding whether benzene is aromatic, non-aromatic, or anti-aromatic.

Exercise 2: Calculating the Resonance Energy of Naphthalene and Predicting Aromaticity



Open *SPARTAN ES-02* and select **New**. Build the structure of naphthalene (**2**) and calculate the **Equilibrium Geometry** using **AM1**. Examine the structure and record whether the compound is planar or non-planar in *Table I*.

Next, switch to the build screen (+) and complete 2-methylnaphthalene (**2a**) by adding a tetravalent carbon atom (**>C<**) to naphthalene at the proper position on the ring. Calculate a **Single Point Energy** using **Hartree-Fock 3-21G(*)** starting from the **AM1** geometry and record (*Table II*) the value of the energy that is obtained. Finally, in a procedure analogous to that used in **Exercise 1**, build structure **2b** by breaking the single bond that joins the two rings at the top, selecting what was formerly the 2,3 C-C bond, rotating to the proper position and then making a bond between the ring and the sp^3 carbon atom. If the **Calculations** dialogue has not been changed, simply click on **Submit** in the **Setup** menu to obtain a **Single Point Energy** and record the value.



Determine the resonance energy for naphthalene using the same method as in **Exercise 1** and enter the values in the proper tables. Complete *Table I* and indicate whether naphthalene is aromatic, non-aromatic, or anti-aromatic.

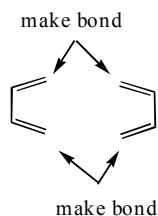
¹⁰ If desired a spreadsheet can be set up to do the calculations that follow.

Exercise 3: Predicting Aromaticity: Cyclobutadiene and Cyclooctatetraene



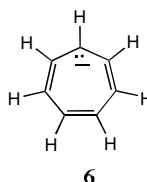
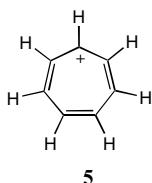
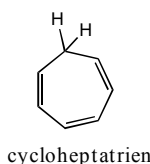
Using the methodology employed in **Exercise 1** and **Exercise II**, build the relevant structures, examine the geometry and calculate the energies necessary to determine whether cyclobutadiene (**3**) is aromatic, non-aromatic or anti-aromatic. Use a similar process to make such a determination for cyclooctatetraene (**4**). Record the data and observations in *Table I* and *Table II*.

The process of building cyclooctatetraene can be made somewhat easier using the **Make Bond** function to join two *s-cis* butadienes as shown in the figure below. First use the model kit to build butadiene in the *s-cis* conformation. Then select the trivalent carbon atom ($>\text{C}=\text{}$), click on the **Insert** box at the lower right just below the model kit and click anywhere on the screen to begin building a second *s-cis* butadiene. With two fragments on the screen the left mouse button will rotate both of them at the same time and the right mouse button will move them both at the same time. To manipulate either fragment individually, select the desired fragment by clicking on it with the left mouse button and hold down the **Ctrl** key. For example, using the right mouse button while holding down **Ctrl** will move only the selected fragment about the screen, or using the left mouse button while holding down **Ctrl** will rotate only the selected fragment.

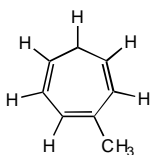


Align the two butadienes as shown and then use the **Make Bond** function twice to obtain an eight-membered ring. After the two bonds have been formed use the **Minimize** function to get the geometry required to begin calculations.

Exercise 4: Predicting the Aromaticity of Cycloheptatrienyl Ions



Begin this exercise by building cycloheptatriene and then using the **Delete** function to remove one of the hydrogen atoms from the tetravalent carbon atom in the ring. Select the **Delete** function (*) from the toolbar and then click on one of the open valences on the tetravalent carbon atom in the ring- it will disappear. Then click on **Minimize**. Enter the **Calculations** dialogue from **Setup** and select **Equilibrium Geometry**, **Semi-Empirical** and **AM1**. Next select “**cation**” from the pull down menu next to “Total Charge”. Then submit the job. When completed examine the geometry of the structure and record the observation for structure **5**. Repeat this process but select “**anion**” from “Total Charge” to obtain the geometry of the cycloheptatrienyl anion (**6**).



After the above observations have been completed, re-enter the build screen (+) and add a tetravalent carbon atom (>C<) to the ring as in the figure on the left. Then complete the process of determining the resonance energy first for the cycloheptatrienyl cation (**5**) and then for the anion (**6**).

Record all data and observations in the proper tables and predict whether either ion is aromatic, non aromatic or anti-aromatic

Table I


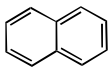




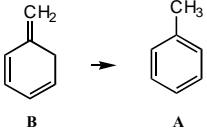
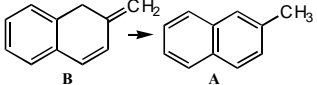
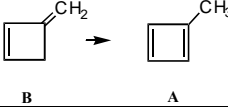
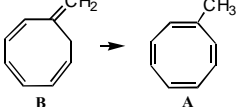
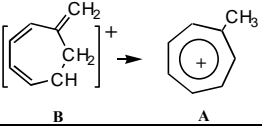
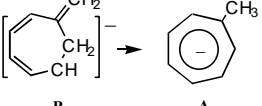
Structure	Number of <i>pi</i> Electrons	Geometry (planar or nonplanar)	Resonance Energy (kcal/mol)	Aromaticity ¹¹
				
				
				
				
				
				

Table II

	Energy of A (au)	Energy of B (au)	ΔE (au)	ΔE (kcal/mol)
 B A				
 B A				
 B A				
 B A				
 B A				
 B A				

¹¹ Compounds are considered aromatic, non-aromatic or anti-aromatic.

Exercise 5: Predicting Aromaticity in Heterocyclic Rings

7



8

Follow the methods used in the above exercises to predict whether thiophene (**7**) is aromatic, non-aromatic or anti-aromatic. Use the same methods to make a similar determination for pyridine (**8**). Finally, design a five or six membered, conjugated unsaturated heterocyclic compound. Use either one or two hetero atoms. Then predict whether the compound will be aromatic, non-aromatic or anti-aromatic. Record all results and observations in *Table III* and *Table IV*.

Table III: Heterocyclic Compounds

Compound	Geometry (planar/non-planar)	Resonance Energy (kcal/mol)	Aromaticity ^{††}

Table IV: Heterocyclic Compounds

	Energy of A (au)	Energy of B (au)	ΔE (au)	ΔE (kcal/mol)
 <div style="display: flex; justify-content: space-around; width: 100px;"> B A </div>				
 <div style="display: flex; justify-content: space-around; width: 100px;"> B A </div>				

Table IV: Aromaticity in Heterocyclic Compounds




Compound	Geometry (planar/non-planar)	Resonance Energy (kcal/mol)	Aromaticity
	Planar	36.3	Aromatic
	Planar	15.5	Aromatic
	Planar	11.2	Aromatic

Table V: Resonance Energy for Heterocyclic Compounds

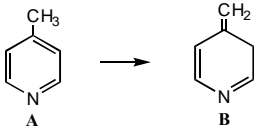
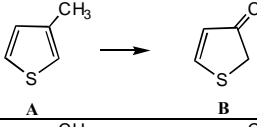





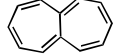

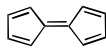



	Energy of B (au)	Energy of A (au)	ΔE (au)	ΔE (kcal/mol)
	-284.068642	-284.126551	0.057909	36.3
	-587.380992	-587.405768	0.024776	15.5
	-266.146157	-266.164071	0.017914	11.2

Table VI: Comparative Data for Determining Aromaticity

	Molecule	RE ^{a,b} (kcal/mol)	REPE (units of <i>beta</i>) ^c	Status ^c
benzene		37	0.065	Prototype of aromaticity
naphthalene		25	0.055	Aromatic
azulene		17	0.023	Aromatic
calicene		5.3	0.043	Derivatives isolated
heptalene		1.8	-0.004	Isolated, very reactive
fulvene		-3.7 ^d	-0.002	Isolated, very reactive
fulvalene		-5.4 ^d	-0.033	Prepared in dilute solution
pentalene		-13	-0.018	Observed in solution
benzocyclobutadiene		-27	-0.027	Quinone deriv. prepared, rapid dimerization ^e
cyclobutadiene		-45	-0.268	Spectrum Observed (8 K)

- Computed from isodesmic reaction analogous to Equation 1 using HF 3-21G(*) from AM1 geometries.
- In applying Equation 1 to structures with more than one ring the methyl group is placed on the larger ring at the point furthest from the ring juncture.
- From Schaad, L.J.; Hess Jr., B.A. *J. Chem. Educ.* **1974**, 51, 640.
- In applying Equation 1 the methyl group is at the point furthest from the exocyclic double bond.
- See Smith, M.B.; March, J. *March's Advanced Organic Chemistry* 5th Edition, John Wiley & Sons, Inc.: New York 2001; p 62.

