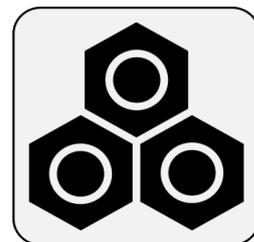




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Theoretical Chemistry and Molecular Modeling

Structure and Reactivity – Applications of Frontier Molecular Orbital Theory

Tutorials and Computational Exercises Using the Hückel Method



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1 Preamble

We place ourselves in the context of the LCAO approximation, meaning that we will use both the energy and the shape of molecular orbitals (MOs). Depending on the case, the relevant MOs are:

- given in the appendix A
- available on the vChem3D website, at the page https://vchem3d.univ-tlse3.fr/vM_MO-misc.html.

Some of the MOs given in the appendix are **only π orbitals**, which are generally the most relevant for studying the reactivity of organic compounds with multiple bonds. These MOs were obtained using the Hückel method, a very simplified way to solve the Schrödinger equation. Their energy is expressed as a function of two parameters, noted α and β :

- α_C , usually simply named α , is the **energy of the 2p subshell of carbon**. $\alpha \approx -11.4$ eV
- β_{CC} , usually simply named β , is related to the **bond formation energy** of the ethylene π bond. $\beta \approx -3.5$ eV

These two parameters serve as references for all organic compounds with π bonds, including those containing heteroatoms (N, O, S, F, Cl) or atoms with an electron vacancy (B). That is, the Hückel energies of the π MOs of any organic compound are positioned relative to α , and their relative stability is expressed using β :

$$\alpha_X = \alpha + h_X\beta$$
$$\beta_{XY} = \alpha + k_{XY}\beta$$

Warning! $\alpha, \beta < 0$

The π MOs of some compounds in these exercises are not available in the appendix A. They can easily be calculated using dedicated software. We will use HMO, which runs on Windows and Linux. It is very easy to use. You simply need to **draw the topological representation**, also called the σ skeleton, **of the part of the molecule that contains a π system**. The HMO tool then solves the Schrödinger equation in the Hückel approximation and provides a graphical solution in the form of a π MO diagram (see figure 1.1).

Computational Exercise 1.1: π MOs of simple conjugated molecules

Use HMO to reproduce the energies and shapes of the frontier π MOs of some of the compounds listed in the appendix A:

- ethylene

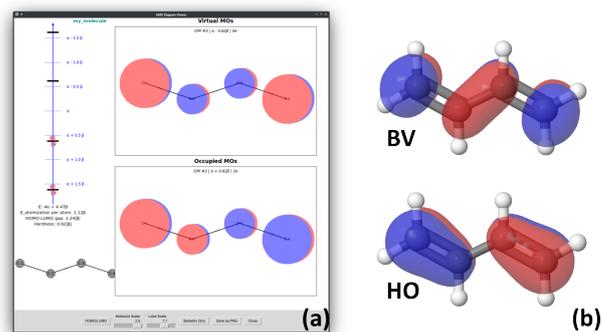


Figure 1.1: (a) π molecular orbital diagram of the butadiene molecule, computed using the HMO application; (b) frontier π orbitals (HOMO and LUMO) of butadiene, available on vChem3D. These were obtained using a significantly more advanced method for solving the Schrödinger equation than the Hückel approximation.

- allyl cation
- butadiene
- formaldehyde H_2CO
- cyclohexene

In each case, analyze whether the HOMO and LUMO orbitals are bonding, antibonding, or non-bonding.

2 Electronic Structure Calculation Using the Hückel Method

Computational Exercise 2.1: π Electronic Structure of the Allyl Radical $C_3H_5^\bullet$

We aim to determine the π molecular orbitals and their energies using the Hückel method. Compute the eigenvalues of the corresponding determinant using the HMO software tool.

1. Draw the energy level diagram ε_i for the ground state of this π system.
2. Calculate the corresponding total π energy (E_π).
3. Sketch the molecular orbitals. Indicate whether each one is bonding, non-bonding, or antibonding.

Computational Exercise 2.2: The Butadiene Molecule

Determine the π molecular orbitals and their corresponding energies for the *s-trans* conformation of butadiene using the Hückel method.

1. Using the HMO software, calculate the π electronic structure of butadiene.
2. For each π molecular orbital, indicate whether it is bonding, antibonding, or non-bonding.
3. Based on the calculated π bond indices, how would you revise the conventional structural formula $H_2C=CH-CH=CH_2$?
4. Compare the calculated π bond indices with the experimental C–C bond lengths in butadiene:

- $d(C-C)_{\text{terminal}} = 1.34 \text{ \AA}$
- $d(C-C)_{\text{central}} = 1.47 \text{ \AA}$

Discuss your results in comparison with typical C–C bond lengths in ethane and ethylene (refer to appendix XXXXX Handbook Annex XXXX).

5. Estimate the conjugation energy and the bond dissociation energy.
6. Repeat the entire analysis for the *s-cis* conformation of butadiene.

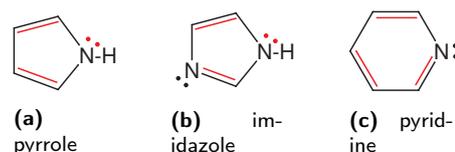


Figure 2.1: Planar conjugated molecules.

Exercise 2.1: Secular Determinants

Consider the molecules shown in Figure 2.1.

We aim to determine their π electronic structure using the Hückel method. For this purpose, the secular determinant has been constructed following the change of variable $x = \frac{\alpha - \varepsilon}{\beta}$.

1. Determine the total number of π electrons in each compound. Justify your answer.
2. Consider the five secular determinants below, three of which correspond to the molecules above. Identify which determinant matches each compound.

$$A : \begin{vmatrix} x + 0.5 & 1 & 0 & 0 & 1 \\ 1 & x & 1 & 0 & 0 \\ 0 & 1 & x & 1 & 0 \\ 0 & 0 & 1 & x & 1 \\ 1 & 0 & 0 & 1 & x \end{vmatrix} = 0$$

$$B : \begin{vmatrix} x + 1.5 & 0.8 & 0 & 0 & 0.8 \\ 0.8 & x & 1 & 0 & 0 \\ 0 & 1 & x & 1 & 0 \\ 0 & 0 & 1 & x + 0.5 & 1 \\ 0.8 & 0 & 0 & 1 & x \end{vmatrix} = 0$$

$$C : \begin{vmatrix} x & 1 & 0 & 0 & 0 & 1 \\ 1 & x & 1 & 0 & 0 & 0 \\ 0 & 1 & x & 1 & 0 & 0 \\ 0 & 0 & 1 & x & 1 & 0 \\ 0 & 0 & 0 & 1 & x & 1 \\ 1 & 0 & 0 & 0 & 1 & x \end{vmatrix} = 0$$

$$D : \begin{vmatrix} x + 1.5 & 0.8 & 0 & 0 & 0.8 \\ 0.8 & x & 1 & 0 & 0 \\ 0 & 1 & x & 1 & 0 \\ 0 & 0 & 1 & x & 1 \\ 0.8 & 0 & 0 & 1 & x \end{vmatrix} = 0$$

$$E : \begin{vmatrix} x + 0.5 & 1 & 0 & 0 & 0 & 1 \\ 1 & x & 1 & 0 & 0 & 0 \\ 0 & 1 & x & 1 & 0 & 0 \\ 0 & 0 & 1 & x & 1 & 0 \\ 0 & 0 & 0 & 1 & x & 1 \\ 1 & 0 & 0 & 0 & 1 & x \end{vmatrix} = 0$$

Exercise 2.2: π Electronic Structure of Formaldehyde H_2CO

Determine the π molecular orbitals and their energies using the Hückel method. Relevant data from appendix XXXXXXXX "Wavefunctions" XXXXXXXXXXXX and A may be useful.

1. Apply the variable substitution $x = \frac{\alpha - \varepsilon}{\beta}$.
2. Calculate the roots x_i of the secular determinant, and construct the energy level diagram ε_i for the π system in its ground state. Compute the corresponding total π energy (E_π).
3. Compute the molecular orbital coefficients, and deduce the LCAO expressions for each orbital. Comment on the relative magnitudes of the atomic orbital coefficients within the LCAO expansions.
4. Provide schematic representations of the molecular orbitals on an energy diagram expressed in terms of α and β . Also indicate the approximate position of the atomic orbitals. Specify whether each MO is bonding, non-bonding, or antibonding.
5. Check your results with HMO.

Exercise 2.3: Stabilization of radicals by substitution: captodative radicals

Captodative radicals^[1] (Figure 2.2a) are carbon-centered radicals featuring an electron-donating group (D) and an electron-withdrawing group (A). These species are particularly relevant in the context of radical polymerization.^[2]

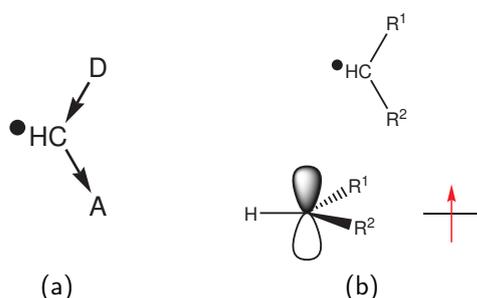


Figure 2.2: (a) Schematic of a captodative radical; (b) Schematic representation of a radical as a singly occupied molecular orbital.

In general, a radical is represented by a singly occupied atomic orbital (Figure 2.2b), provided that R^1 and R^2 are not conjugated with $\bullet\text{HC}$.

We aim to understand, using the Hückel method, the benefit of such substitution compared to unsubstituted radicals, such as **1** (Figure 2.3). To do this, we will compare the π -electronic structure of radicals **2, 3**, and **4**, assuming a planar geometry for all.

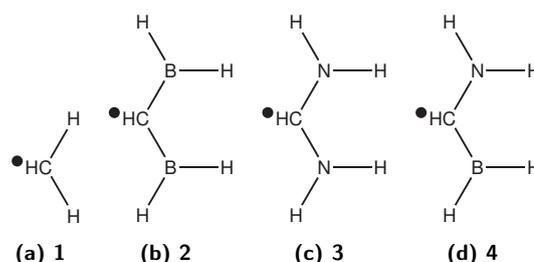


Figure 2.3: $\bullet\text{CH}(\text{R}_1)(\text{R}_2)$ radicals.

1. Atomic orbital basis and π electrons.
 - (a) In radical **1**, the CH_2 group participates in the π system through a singly occupied $2p$ orbital perpendicular to the molecular plane. True or false?
 - (b) In radicals **3** and **4**, the NH_2 group contributes to the π system through a doubly occupied $2p$ orbital perpendicular to the molecular plane. True or false?
 - (c) In radicals **2** and **4**, the BH_2 group contributes to the π system via a $2p$ orbital perpendicular to the molecular plane. True or false? Complete the assertion if needed.
 - (d) In radicals **1** to **4**, the $\bullet\text{CH}$ group contributes to the π system through a singly occupied $2p$ orbital. True or false? Complete the assertion if needed.
 - (e) Based on the previous answers, determine the total number of π electrons for each species.
2. Write the secular determinant for each species in terms of the parameters α and β .
3. Check with the HMO tool that diagonalization of the Hückel Hamiltonian provides the π -molecular orbital energies reported in Table 2.1.

	2	3	4
ε_1	$\alpha + 0.83\beta$	$\alpha + 2.12\beta$	$\alpha + 1.86\beta$
ε_2	$\alpha - 0.45\beta$	$\alpha + 1.37\beta$	$\alpha + 0.18\beta$
ε_3	$\alpha - 1.28\beta$	$\alpha - 0.75\beta$	$\alpha - 1.12\beta$

Table 2.1: Hückel molecular orbital energies for captodative radicals **2, 3**, and **4**, as calculated with HMO, *i.e.* with the Van-Catledge parametrization^[3].

Draw the π -molecular orbital diagram of each species, clearly indicating orbital occupancy.

4. Recall the expression used to calculate the total π -electron energy of a molecule.
5. Calculate the total π -electron energy of each species from **1** to **4**.
6. The atomization energy is a measure of molecular stability. It is calculated as the difference between the energy of the molecule E and the sum of the energies of its constituent atoms E_I :

$$E_a = E - \sum_I E_I$$

where E_I for an atom I is calculated using the same expression as the one recalled in Question 4. For instance, for ethylene with an energy of $2\alpha + 2\beta$, its dissociation energy is calculated as: $E_a = E - 2E_C$, that is: $E_a = (2\alpha + 2\beta) - 2(\alpha)$.

- Calculate the π -atomization energy of each species. Check that you find the same energies as HMO.
- Discuss the relative interest of $\bullet\text{CH}(\text{NH}_2)(\text{BH}_2)$ compared to the other species.

Computational Exercise 2.3: Hückel's Rule: Electronic Structure of Monocyclic Polyenes C_nH_n

These polyenes are assumed to be planar. Hückel's rule is stated as follows:

For even values of n , two cases are possible (k is a positive integer):

- If $n = 4k$, the molecule is an unstable open-shell biradical and the HOMO's are non-bonding.
- If $n = 4k + 2$, the molecule is a closed-shell stable species and all occupied molecular orbitals are bonding.

- Compute the π -molecular orbital energies of polyenes C_nH_n for $n = 4, 6, 8, 10, 12$ using an HMO software.
- Draw the MO diagrams side by side and using the same energy scale.
- Do the conclusions regarding the filling of the π -molecular orbitals agree with Hückel's rule?
- Calculate the conjugation energy for each system and plot it as a function of n . Discuss your results in light of Hückel's rule.

Comment:

- A hydrocarbon is aromatic if it is monocyclic, planar, and has $4k + 2$ π electrons.
 - A hydrocarbon is antiaromatic if it is monocyclic, planar, and has $4k$ π electrons.
- Cyclooctatetraene (COT) C_8H_8 is not planar. It adopts the conformation shown in Figure 2.4a^[4]. Is this result surprising in view of the above conclusions?
 - COT can coordinate with a cerium atom (a lanthanide), upon which it adopts a nearly planar geometry^{[5]a}. The resulting sandwich complex $(\text{COT})_2\text{Ce}$ adopts the structure shown in Figure 2.4b. Given that lanthanides tend to donate electrons upon coordination, deduce the oxidation state of cerium in this complex.

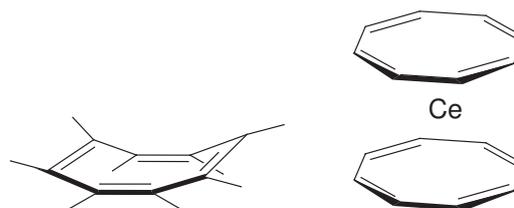


Figure 2.4: (a) Boat-like conformation of the COT molecule C_8H_8 ; (b) sandwich complex $(\text{C}_8\text{H}_8)_2\text{Ce}$.

^aNote: This statement is somewhat debatable. A more cautious formulation would be that the COT ligand tends toward planarity upon complexation.

3 Application de la théorie des OF : Structure et Réactivité

A. Background

Background Knowledge Check 3.1: Reactions under control

1. In a frontier-controlled chemical reaction, is the energy change governed by the equation::

$$\Delta E = \frac{S^2}{\Delta \varepsilon} \quad (3.1)$$

or by the equation :

$$\Delta E = \frac{1}{4\pi\varepsilon} \frac{Q_{R_1} Q_{R_2}}{d_{R_1 R_2}} \quad (3.2)$$

Justify your answer by commenting on the meaning of each term in both equations.

2. What is the domain of applicability of the other equation?
3. Consider two competing frontier-controlled reactions:



Given a better overlap between frontier orbitals in reaction (a), $\Delta E_{(a)} > \Delta E_{(b)}$. Which product is expected to be preferentially formed? Would this be the kinetic product or the thermodynamic product of the reaction?

Background Knowledge Check 3.2: Nucleophiles and Electrophiles

1. In a reaction between a nucleophile Nu^- and an electrophile E^+ , a lone pair of electrons is transferred. Does this transfer occur from $Nu^- \rightarrow E^+$ or from $E^+ \rightarrow Nu^-$?
2. In this type of reaction, typically only one dominant interaction between frontier orbitals remains relevant.

Draw a schematic molecular orbital diagram and indicate, using a double arrow, the predominant interaction—also referred to as the “normal” electron demand.

B. Molecular geometries

Exercise 3.1: Geometry of H_3^- : Linear or Bent?

We will use frontier molecular orbital (FMO) theory to determine whether the H_3^- ion adopts a linear or bent geometry. To this end, we consider two hypothetical reaction pathways: in one, the H^- ion approaches the H_2 fragment laterally (Figure 3.1a); in the other, the H^- ion approaches along the bisector of the H–H bond (Figure 3.1b).

1. Recall the molecular orbitals of the H_2 molecule.
2. According to frontier orbital theory, what governs the selectivity of this reaction?
3. Which reaction pathway is preferentially followed?

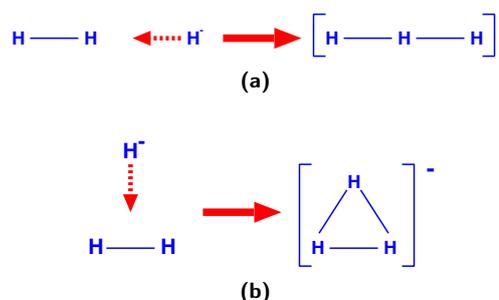


Figure 3.1: Idealized reaction pathways for the hypothetical reaction: $H^- + H_2 \rightarrow H_3^-$.

Exercise 3.2: Geometry of the Ethanal Molecule

We aim to account for the relative stability of the staggered (1) and eclipsed (2) conformations of ethanal in its electronic ground state, using frontier molecular orbital (FMO) theory (Figure 3.2).

The approach consists in formally splitting the molecule into a methyl fragment and a CHO fragment, considering a hypothetical reaction between the two, and analyzing the interactions that arise between their frontier molecular orbitals during this ‘reaction’ (Figure 3.3).

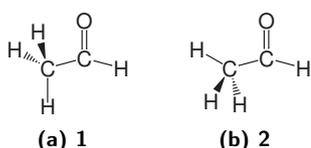


Figure 3.2: Ethanal (a) staggered ; (b) eclipsed.

Note: A singly occupied HOMO generally has limited impact on the course of a reaction. It is therefore advisable to consider the HOMO-1 when analyzing frontier orbital interactions.

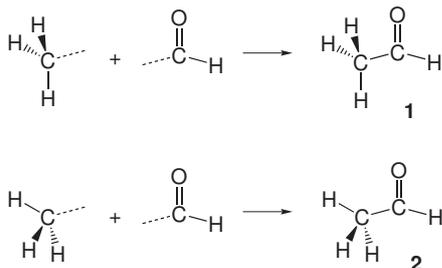


Figure 3.3: Hypothetical reaction $\text{H}_3\text{C} + \text{CHO} \rightarrow \text{H}_3\text{CCHO}$ (ethanal).

- When several structural isomers are in competition, frontier molecular orbital (FMO) theory can help rationalize the greater stability of one over the others.
- State the rule that allows prediction of which structural isomer is the most stable.
- Identify the unique symmetry element of the transition state (TS) of this hypothetical reaction.
- The relevant frontier orbitals of the CHO group are the π_{CO} and π_{CO}^* molecular orbitals.
 - Illustrate these two orbitals schematically and briefly explain the relative magnitude of their atomic orbital coefficients.
 - Indicate their symmetry with respect to the TS symmetry element.
- The molecular orbitals of the methyl (CH_3) fragment are given in Appendix A.
 - Identify the occupied and virtual orbitals.
 - What is special about orbital φ_4 ? Relate this to the Lewis structure of the methyl group.
 - Analyze the symmetry of the CH_3 molecular orbitals with respect to the symmetry element of the transition state in the hypothetical $\text{CH}_3 + \text{CHO} \rightarrow \text{CH}_3\text{COH}$ reaction.
- Apply FMO theory to this structural problem in order to draw a conclusion about the relative stability of the two conformations.

- Microwave spectroscopy shows that the eclipsed conformation is more stable than the staggered one by approximately $4 \text{ kJ}\cdot\text{mol}^{-1}$.

Can frontier molecular orbital theory account for such a small energy difference between the two forms?

C. Chemical reactivity

Exercise 3.3: Selected cases of cycloaddition reactions

- Draw the Lewis structures of the following compounds, indicating any lone pairs or electron vacancies:
 - butadiene
 - benzene
 - allyl cation (C_3H_5^+)
 - allyl anion (C_3H_5^-)
- For each of these species:
 - draw the resonance hybrid if relevant.
 - Discuss whether the compound belongs to a conjugated system, both:
 - in terms of alternating single and double bonds,
 - and by explicitly showing the atomic orbitals involved in the π -system.
- Determine how many **active** π electrons participate in each of the cycloaddition reactions shown in Figure 3.4.
- Using the generalized Woodward–Hoffmann rules^[6] to predict whether each of the previous reaction is symmetry-allowed under thermal or photochemical conditions.

Exercise 3.4: Reactions of 1,3-Dienes with Sulfur Dioxide

The concerted cycloaddition of sulfur dioxide (SO_2) with 1,3-dienes such as butadiene, **1**, leads to the formation of compounds known as sultines, **2**. It has been shown experimentally that the product of this reaction readily undergoes retrocycloaddition, regenerating the starting materials.^[7] A more favorable addition subsequently occurs, resulting in sulfolene-type compounds, **3**. The overall reaction pathway is summarized in Figure 3.5.

More generally, many dienes exhibit this same behavior when reacted with sulfur dioxide, as illustrated in figure 3.6. It is typically observed that sultines form at low temperature, while increasing the temperature leads to sulfolenes due to the thermal decomposition of sultines, according to the mechanism shown in the figure.

- Draw the Lewis structure of SO_2 . What is the VSEPR geometry of the sulfur atom?

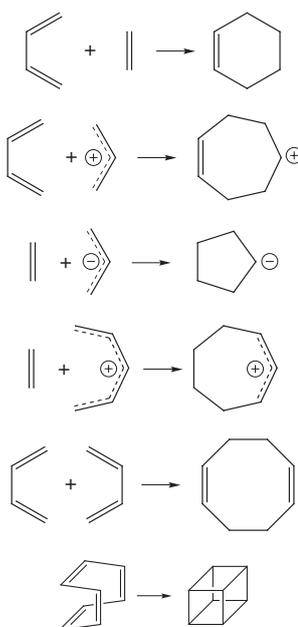


Figure 3.4: $[n + m]$ cycloadditions.

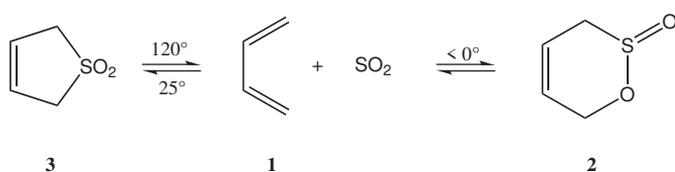


Figure 3.5: Two possible reactions between sulfur dioxide (SO_2) and butadiene, **1**. Compound **2**: sultine; compound **3**: sulfolene (adapted from reference^[7]).

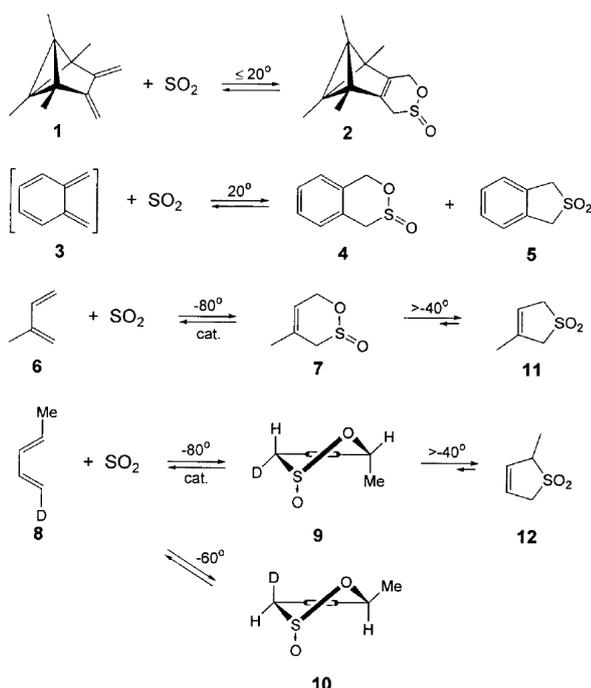


Figure 3.6: Various reactions between 1,3-dienes and sulfur dioxide (adapted from reference^[8]).

- Identify the type of reaction mechanism that leads to compounds **2** and **3**. Justify whether these reactions are thermally allowed based on the number of π -electrons involved.

Exercice 3.5: Réaction de Diels-Alder : addition supra-supra du butadiène sur l'éthylène

L'addition supra-supra du butadiène sur l'éthylène (figure 3.7) est une réaction stéréospécifique ; l'addition d'un éthylénique *Z* conduit à la formation d'un produit *syn*, alors que l'addition d'un éthylénique *E* conduit à la formation d'un produit *anti*. Que vous suggèrent ces résultats ? Justifier votre réponse.

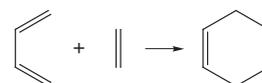


Figure 3.7: Addition supra-supra du butadiène et de l'éthylène.

- Rappeler et justifier l'approximation qui régit la stéréochimie des cycloadditions.
- Rappeler les règles prédisant la réactivité entre deux systèmes π possédant respectivement n et m électrons π .
- Rappeler la forme des orbitales frontières π de l'éthylène. D'après l'annexe A, indiquer quelles sont les orbitales frontières du butadiène. Vérifiez que vous trouvez les mêmes OM en utilisant le programme Huckel.exe.
- On considère l'approche des deux réactifs dans des plans parallèles.
 - quel est l'élément de symétrie qui se conserve tout au long de la réaction ?
 - appliquer la méthode des orbitales frontières pour montrer que cette approche est favorable.

Exercice 3.6: Dimérisation de la thymine dans l'ADN

La composante UV de la lumière du soleil peut endommager l'ADN. L'effet majeur est de relier des dimères de thymine adjacents le long d'un brin ADN, entraînant l'impossibilité de répliquer si la lésion n'est pas réparée.^[9-11] La réaction de dimérisation est schématisée figure 3.8. On peut aussi consulter sur vChem3D (page macromolécules, PDB ID 1TTD) la structure RMN NOE d'un décimère d'ADN qui a subi ce dommage.^[12]

- De quel type de réaction s'agit-il ?
- Pourquoi cette lésion est-elle si facile à réaliser sous irradiation UV ? Justifier simplement.

Exercice 3.7: Regio- and stereoselectivity in a hetero-Diels-Alder reaction

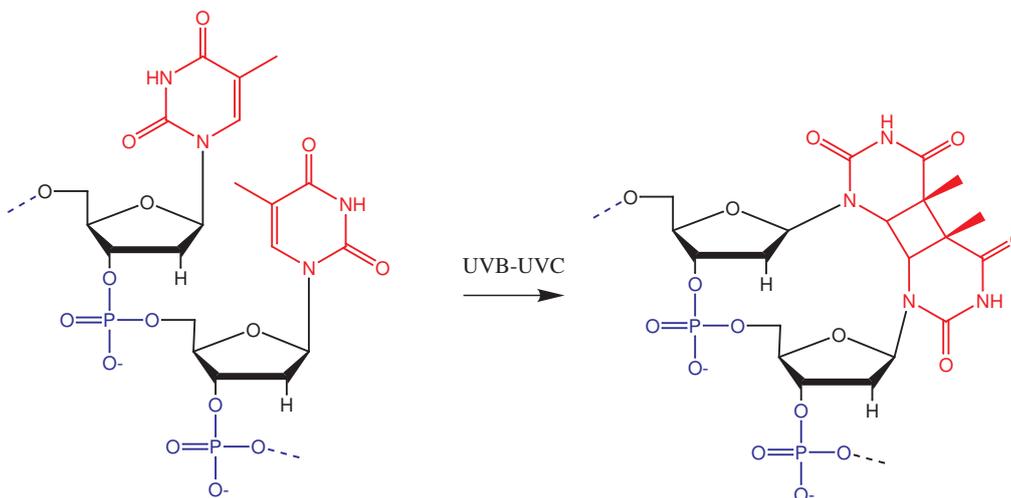


Figure 3.8: Dimérisation de la thymine dans l'ADN.

This problem aims to analyze the Diels–Alder reaction between the conjugated imine **1** and methoxyethylene **2** (see Figure 3.9). Using a relatively simple molecular orbital analysis, the objective is to rationalize the regioselectivity and stereoselectivity of this hetero-Diels–Alder reaction. This transformation involves reactants that feature heteroatoms and therefore extends beyond classical carbon–carbon Diels–Alder chemistry.

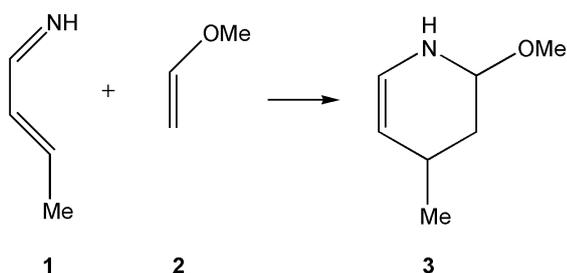


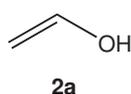
Figure 3.9: Réaction de Diels-Alder entre une imine conjuguée et le méthoxyéthylène.

Although this reaction could, in principle, lead to two different products depending on the orientation of the approach between **1** and **2**, only compound **3** is experimentally observed. The regioselectivity of a reaction can be rationalized by analyzing the frontier molecular orbitals (FMOs). Recall that the preferred reaction pathway is typically the one that maximizes FMO overlap.

Note: given four numbers such that $1 > A > a > 0$ & $1 > B > b > 0$, it comes: $AB + ab > Aa + Bb$

Molecular orbitals of methoxyethylene (**2**)

We will now examine the π molecular orbitals of compound **2**. To simplify the analysis, we model compound **2** as the corresponding enol **2a**, and perform a simple Hückel calculation on this model system.



1. Complete the Lewis structure of molecule **2**.

- (a) What is the geometry around the oxygen atom?
- (b) What is the total number of π electrons?
- (c) Which Hückel description should be adopted for the oxygen atom: one unpaired electron ($O\bullet$) or two lone pairs ($O\bullet\bullet$)?
- (d) Recall the sign convention for the parameter β .

2. Solving the Hückel secular equation for the enol **2a** gives the following π molecular orbital energies:

$$\varepsilon_1 = \alpha + 2.32\beta$$

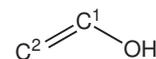
$$\varepsilon_2 = \alpha + 0.84\beta$$

$$\varepsilon_3 = \alpha - 1.07\beta$$

- (a) Sketch the π orbital energy diagram for **2a**, indicating the orbital occupancy in the ground state.
- (b) Identify the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO).
- (c) The normalized expression for the HOMO of **2a** is given below, and may prove useful in subsequent questions:

$$\pi_{\text{HO}} = -0.32(2p_{\text{O}}) + 0.61(2p_{\text{C}^1}) + 0.73(2p_{\text{C}^2})$$

with the following atom numbering:



Sketch the qualitative shape of this orbital. Be sure to reflect the relative magnitudes of the coefficients accurately in your drawing. Specify the nature of the interaction between atoms in this orbital, *i.e.* bonding, antibonding, or nonbonding.

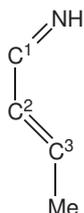
Frontier orbitals of the conjugated imine, **1**

A Hückel molecular orbital calculation provides the following expressions for the HOMO and the LUMO of the conjugated imine **1**:

$$\Pi_{\text{HO}} = -0.61(2p_{\text{N}}) - 0.12(2p_{\text{C}^1}) + 0.54(2p_{\text{C}^2}) + 0.5(2p_{\text{C}^3}) - 0.27\pi_{\text{Me}}$$

$$\Pi_{\text{BV}} = 0.52(2p_{\text{N}}) - 0.52(2p_{\text{C}^1}) - 0.23(2p_{\text{C}^2}) + 0.64(2p_{\text{C}^3}) - 0.18\pi_{\text{Me}}$$

where the atom numbering is:



The corresponding Hückel energies are: $\varepsilon_{\text{HO}} = \alpha + 0.71\beta$ et $\varepsilon_{\text{BV}} = \alpha - 0.55\beta$

1. What is the origin of the methyl group contribution in these expressions?

Why has compound 2 been simplified into the model compound 2a for this study?

Hint: refer to appendix XXXparamHMxxxx.

2. Sketch the shape of both the HOMO and LUMO of compound 1 based on the coefficients given by the Hückel calculation. Try to respect the relative sizes of the orbital lobes. Discuss the bonding, antibonding or nonbonding character of the interactions between atomic centers within each MO.

Diels-Alder reaction

In this final section, we examine the Diels-Alder reaction described at the beginning of the problem. This is a [4s+2s] supra-supra cycloaddition. The frontier molecular orbitals of compound 2 are assumed to be well represented by those of the simplified model 2a.

1. Within the framework of frontier molecular orbital theory, identify the **primary orbital interaction** that occurs during this Diels-Alder reaction. Is it a normal or inverse electron demand?

Hint: Analyzing the orbital energies may help clarify this.

2. Given the two possible approaches of the reactants, predict the two possible regioisomers that could form from this reaction.
3. Use the shapes of the interacting orbitals and the regioselectivity rule provided in the appendix to rationalize why only regioisomer 3 — in which the methoxy group (OMe) ends up adjacent to the nitrogen — is experimentally observed.

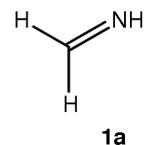
When the two reactants approach each other, one of the two new σ -bonds is expected to form more readily than the other. Identify which one and explain why. Relate this to the exclusive formation of regioisomer 3.

4. This cycloaddition proceeds via a concerted mechanism.

- (a) What does the term concerted reaction imply in this context?
- (b) What is the stereochemical relationship of the Me and OMe substituents with respect to the newly formed ring plane? Justify your answer based on the orbital symmetry and mechanism of the reaction.

Reactivity of an imine towards nucleophiles

Consider now the imine 1a:



The Hückel energies of its π molecular orbitals are:

$$\varepsilon_1 = \alpha + 1.31\beta$$

$$\varepsilon_2 = \alpha - 0.80\beta$$

1. Which molecular orbital of the imine is likely to interact with a nucleophile?
2. Would you classify this imine as more or less electrophilic than formaldehyde (H_2CO)? Justify your answer, using the Hückel model or the HMO software if needed.

Computational Exercise 3.1: Influence of Electron-Donating and Electron-Withdrawing Groups. Alder's Rule

The objective of this exercise is to justify Alder's Rule, which states that a Diels-Alder reaction (Figure 3.10a) is accelerated when the diene is electron-rich and the dienophile is electron-poor (Figure 3.10b). To this end, we will examine prototypical molecules representing such substituent effects.

You will use a numerical Hückel method to solve the secular determinant, for example with the HMO program.

Before beginning the computational part, consider the following experimental data^[13]:

- The simplest Diels-Alder reaction, between ethylene and butadiene, has a relatively high activation enthalpy of 27 kcal·mol⁻¹. It requires elevated temperature and pressure. Even at 200 °C and under very high pressure, the reaction yields only 18% of cyclohexene after 17 hours.
- In contrast, the reaction between butadiene and propenal leads to 100% yield of the corresponding cyclic compound (3-cyclohexene-1-carboxaldehyde) after 1 hour at 100 °C.

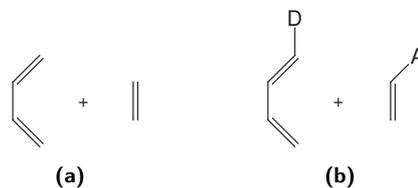


Figure 3.10: (a) Frontier molecular orbital diagram for the [4s+2s] cycloaddition between butadiene and ethylene; (b) Same reaction, with donor (D) and acceptor (A) substituents introduced to enhance the reaction rate.

1. Consider the supra-supra cycloaddition between butadiene and ethylene (Figure [FIG:regle_alder]a).
 - (a) Recall the Hückel energies of the HOMO and LUMO π molecular orbitals of each of these two molecules. Use the HMO tool if needed.

- (b) Based on symmetry considerations, draw the frontier molecular orbital interaction diagram that describes the reaction between these two reactants. Is it a thermally accepted or forbidden reaction?
- (c) Consider now the substituent groups $-\text{OH}$, $-\text{CHO}$, and $-\text{NH}_2$. Indicate whether each group acts as a π electron-donating or π electron-withdrawing substituent.

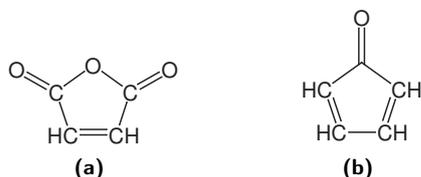


Figure 3.11: Molecular structure of (a) maleic anhydride; (b) cyclopentadienone.

2. Consider the following dienophiles:

- $\text{H}_2\text{C}=\text{CHR}$ with $\text{R} = \text{H}, \text{OH}, \text{CHO}, \text{NH}_2$.
- the maleic anhydride molecule (Figure 3.11a).

- (a) Calculate their π molecular orbital energies.
- (b) Compare the HOMO and LUMO energies of each molecule. Based on your results, discuss whether each compound can be classified as an electron-rich or electron-poor dienophile.
- (c) Deduce qualitatively how the HOMO and LUMO energies evolve upon introducing a donor substituent. Discuss similarly for an acceptor substituent.

3. Consider the following dienes:

- $\text{H}_2\text{C}=\text{CH}-\text{CH}=\text{CHR}$, with $\text{R} = \text{H}, \text{OH}, \text{CHO}, \text{NH}_2$.
- the cyclopentadienone molecule (Figure 3.11b).

- (a) Calculate their π molecular orbital energies.
- (b) Compare the HOMO and LUMO energies of each molecule. Based on your results, assess whether each compound is an electron-rich or electron-poor diene.
- (c) Deduce qualitatively how the HOMO and LUMO energies change upon introduction of a donor substituent. Discuss similarly for an acceptor substituent.

4. Consider a diene substituted with electron-donating groups and a dienophile substituted with electron-withdrawing groups.

- (a) Draw the frontier molecular orbital interaction diagram, indicating the relative positions of the HOMO and LUMO of unsubstituted ethylene and butadiene.
- (b) Based on your previous results, is the improvement in orbital overlap (HOMO–LUMO interaction) more significant than the increase in the energy gap?
- (c) Link your orbital interaction diagram to Alder's rule.

Computational Exercise 3.2: Nucleophilic Addition to a Carbonyl Group

During a nucleophilic addition reaction, the carbonyl group acts as an electrophile and reacts via its LUMO (lowest unoccupied molecular orbital).

1. Use the vChem3D (page "MOs and Electrostatic Potential") platform to compare the electrophilic character of the following compounds. Rank them in order of increasing electrophilicity:

- an acid anhydride
- an aldehyde
- a ketone
- an ester
- an amide
- an acyl chloride

2. Consider now the reaction between a nucleophile and acetone.

(a) Suppose the nucleophile can approach from either face of the carbonyl group and that its HOMO (highest occupied molecular orbital) interacts with the carbonyl LUMO. Is this reaction stereoselective?

(b) There exists a preferred angle of approach, known as the Bürgi–Dunitz angle.^[14]

Use frontier molecular orbital theory to determine which of the three approach angles illustrated in Figure 3.12 is the most favorable.

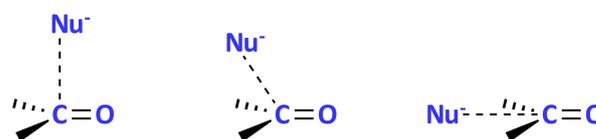


Figure 3.12: Possible approach angles of a nucleophile reacting with acetone.

Exercise 3.8: Endo/Exo stereochemistry in a Diels–Alder reaction

This [4+2] cycloaddition reaction is governed by frontier orbital interactions, which typically favor the formation of the endo stereoisomer when the diene is cyclic (see Figure 3.13). If the reaction is allowed to proceed for a long time, equilibrium will eventually favor the exo product.

1. What are the kinetic and thermodynamic products of this reaction? Justify your answer based solely on the introductory text of this exercise.
2. Does the application of frontier molecular orbital (FMO) theory allow us to identify the kinetic product, the thermodynamic product, or both?
3. Apply frontier molecular orbital theory to discuss the stereochemical outcome of this reaction. Use the schematic representations of the transition states shown in Figure 3.14, beginning by indicating the forming bonds.

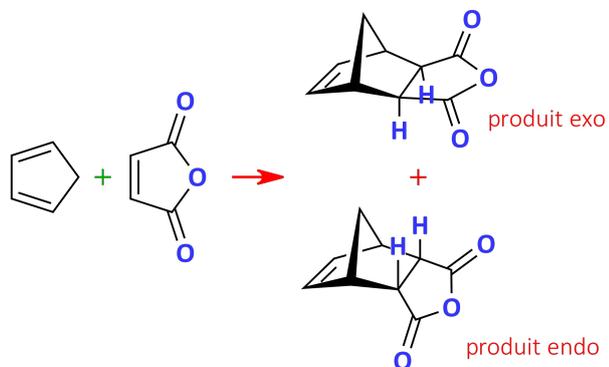


Figure 3.13: Reaction of cyclopentadiene with maleic anhydride.

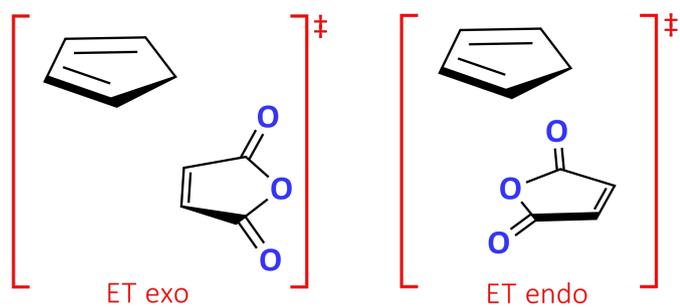
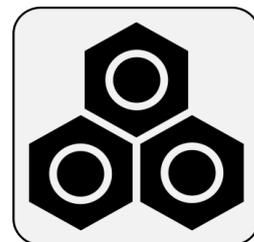


Figure 3.14: Schematic transition states for the endo and exo pathways of the Diels-Alder reaction.



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H M O



[p y P R O J E C T S @ M P C]

Theoretical Chemistry and Molecular Modeling

Structure and Reactivity – Applications of Frontier Molecular Orbital Theory

Appendices

4ème édition (juillet 2007)

A Molecular Orbitals

A. Hückel parameters

A.1 Streitwieser and Julg parameters

Atoms	n	α_i	β_{ij}
Boron	0	$\alpha_B = \alpha - \beta$	$\beta_{CB} = 0.7\beta$
Carbon	1	$\alpha_C = \alpha$	$\beta_{CC} = \beta$
Oxygen	1	$\alpha_O = \alpha + \beta$	$\beta_{CO} = \beta$
	2	$\alpha_O = \alpha + 2\beta$	$\beta_{CO} = 0.8\beta$
Nitrogen	1	$\alpha_N = \alpha + 0.5\beta$	$\beta_{CN} = \beta$
	2	$\alpha_N = \alpha + 1.5\beta$	$\beta_{CN} = 0.8\beta$
Fluorine	2	$\alpha_F = \alpha + 3\beta$	$\beta_{CF} = 0.7\beta$
Chlorine	2	$\alpha_{Cl} = \alpha + 2\beta$	$\beta_{CCl} = 0.4\beta$
Bromine	2	$\alpha_{Br} = \alpha + 1.5\beta$	$\beta_{CBr} = 0.3\beta$
Methyl	2	$\alpha_{Me} = \alpha + 2\beta$	$\beta_{CMe} = 0.7\beta$

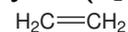
Table A.1 : Atomic α_i et β_{ij} Hückel parameters expressed in terms of the atomic parameter α of carbon and the bond integral β of ethylene; n = number of electrons contributed by the atom or chemical group (after^[15]).

A.2 Van-Catledge parameters, used in HMO

B. OM π Hückel

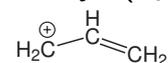
Les paramètres utilisés sont ceux de Streitwieser^[15] (tableau A.1). Pour l'atome de carbone, on peut prendre $\alpha = -11.4$ eV et $\beta = -3.51$ eV (ce dernier paramètre est ajusté de façon à reproduire l'énergie de la transition $\pi \rightarrow \pi^*$ observable pour l'éthylène.

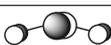
éthylène (C_2H_4)



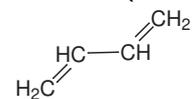
π_2	$\alpha - \beta$	
π_1	$\alpha + \beta$	

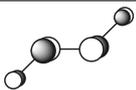
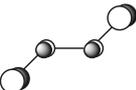
cation allyle ($C_3H_5^+$)



π_3	$\alpha - \sqrt{2}\beta$	
π_2	α	
π_1	$\alpha + \sqrt{2}\beta$	

butadiène (C_4H_6)



π_4	$\alpha - \sqrt{\frac{3+\sqrt{5}}{2}}\beta$	
π_3	$\alpha - \sqrt{\frac{3-\sqrt{5}}{2}}\beta$	
π_2	$\alpha + \sqrt{\frac{3-\sqrt{5}}{2}}\beta$	
π_1	$\alpha + \sqrt{\frac{3+\sqrt{5}}{2}}\beta$	

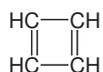
Atoms	Bond	α_p	β_{pq}
Carbon-Carbon	C=C	$\alpha_C = \alpha$	$\beta_{CC} = \beta$
Carbon-Oxygen	carbonyle, C=O	$\alpha_C = \alpha + 0.2\beta$ $\alpha_O = \alpha + 0.7\beta$	$\beta_{CO} = 1.1\beta$
	ether, C-Ö	$\alpha_C = \alpha$ $\alpha_O = \alpha + 2\beta$	$\beta_{CO} = 0.6\beta$
	carboxylate	$\alpha_C = \alpha - 0.7\beta$ $\alpha_O = \alpha - 0.6\beta$	$\beta_{CO} = 0.9\beta$
Carbon-Nitrogen	pyridine, C-N	$\alpha_C = \alpha$ $\alpha_N = \alpha + 0.2\beta$	$\beta_{CN} = \beta$
	vynilamines, pyrrole C-N aniline	$\alpha_C = \alpha$ $\alpha_N = \alpha + 1.4\beta$	$\beta_{CN} = 0.6\beta$
		$\alpha_{N_{sp^3}} = \alpha + 1.8\beta$	
nitrogen derivatives	$\alpha_C = \alpha$ $\alpha_N = \alpha + 1.7\beta$	$\beta_{CN} = 0.6\beta$	
Carbon-Halogen	C-F	$\alpha_C = \alpha$ $\alpha_F = \alpha + 2.7\beta$	$\beta_{CF} = \beta$
	C-Cl	$\alpha_C = \alpha$ $\alpha_{Cl} = \alpha + 1.7\beta$	$\beta_{CCl} = 0.6\beta$
	C-Br	$\alpha_C = \alpha$ $\alpha_{Br} = \alpha + 1.4\beta$	$\beta_{CBr} = 0.4\beta$
Nitrogen-Oxygen	NO group	$\alpha_N = \alpha + 1.7\beta$ $\alpha_O = \alpha + 0.4\beta$	$\beta_{NO} = 0.9\beta$
Methyl [†] C _α -CH ₃	hyperconjugation	$\alpha_{C_\alpha} = \alpha - 0.1\beta$ $\alpha_C = \alpha$ $\alpha_{H_3} = -0.5\beta$	$\beta_{C_\alpha C} = 0.8\beta$ $\beta_{C(H_3)} = 3\beta$

Table A.2 : α_X and β_{XY} integrals expressed in terms of the atomic parameter α of carbon and the bond integral β of ethylene (after^[16]; † the parameters for the methyl group are taken from^[15]).

Symbol	Expression for α_i	F_x	n_π
B	$\alpha - 0.45\beta$	1.705	0
C•	$\alpha + 0.00\beta$	1.732	1
N•	$\alpha + 0.51\beta$	1.393	1
N :	$\alpha + 1.37\beta$	1.583	2
N ⁺ •	$\alpha + 2.00\beta$	-	1
O•	$\alpha + 0.97\beta$	0.909	1
O :	$\alpha + 2.09\beta$	0.942	2
O ⁺ •	$\alpha + 2.50\beta$	-	1
F :	$\alpha + 2.71\beta$	0.179	2
Si•	$\alpha + 0.00\beta$	1.732	1
P•	$\alpha + 0.19\beta$	1.409	1
P :	$\alpha + 0.75\beta$	1.666	2
S•	$\alpha + 0.46\beta$	0.962	1
S :	$\alpha + 1.11\beta$	1.229	2
Cl :	$\alpha + 1.48\beta$	0.321	2
Br :	$\alpha + 1.50\beta$	-	2
Me :	$\alpha + 2.00\beta$	-	2

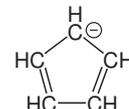
Table A.3 : ddd

cyclobutadiène (C₄H₄)

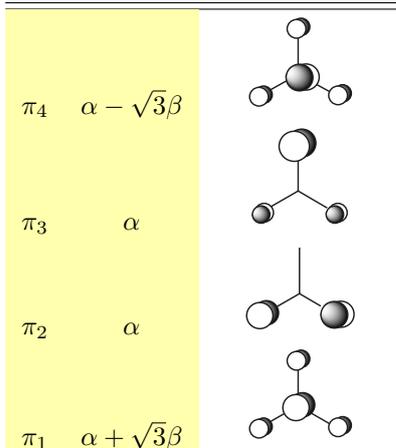
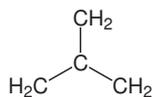
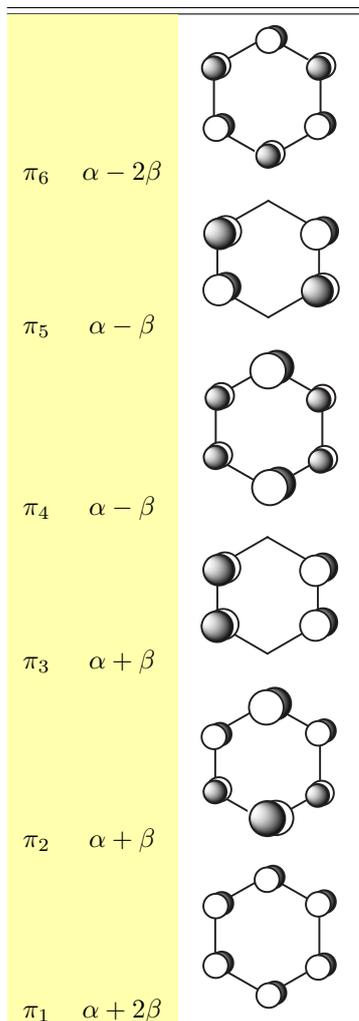
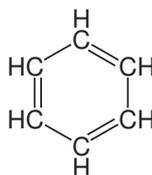
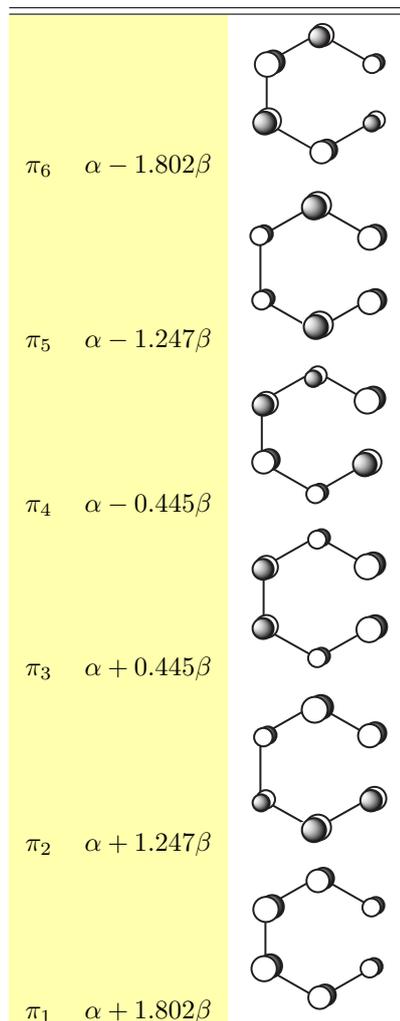
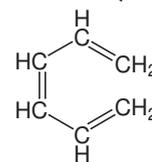


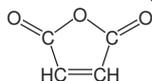
π_4	$\alpha - 2\beta$	
π_3	α	
π_2	α	

cyclopentadiényle (C₅H₅⁻)



π_6	$\alpha - \frac{\sqrt{5}+1}{2}\beta$	
π_4	$\alpha - \frac{\sqrt{5}+1}{2}\beta$	
π_3	$\alpha + \frac{\sqrt{5}-1}{2}\beta$	
π_2	$\alpha + \frac{\sqrt{5}-1}{2}\beta$	
π_1	$\alpha + 2\beta$	

triméthylène méthane (C₄H₆)**benzène (C₆H₆)****hexatriène (C₆H₈)**

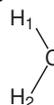
anhydride maléïque (C₄H₂O₃)

π_7	$\alpha - 1.732\beta$	
π_6	$\alpha - 1.272\beta$	
π_5	α	
π_4	$\alpha + 1.000\beta$	
π_3	$\alpha + 1.496\beta$	
π_2	$\alpha + 1.732\beta$	
π_1	$\alpha + 2.776\beta$	

C. OM Hückel étendu de fragments moléculaires

Les OM de valence des fragments sont obtenues par un calcul de type Hückel étendu. Les énergies sont données en électron-volts (eV) :

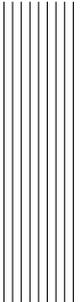
H : $\varepsilon_{1s} = -13.6$ eV
 C : $\varepsilon_{2s} = -21.4$ eV ; $\varepsilon_{2p} = -11.4$ eV
 N : $\varepsilon_{2s} = -26.0$ eV ; $\varepsilon_{2p} = -13.4$ eV

méthylène (CH₂)

φ_6	26.0	
φ_5	11.2	
φ_4	-11.4	
φ_3	-12.3	
φ_2	-16.9	
φ_1	-25.3	

méthyl (CH₃)

φ_7	35.8	
φ_6	8.8	
φ_5	8.8	
φ_4	-11.9	
φ_3	-16.7	
φ_2	-16.7	
φ_1	-26.0	



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