D1CH9116 - MMCO
Molecular Modelling applied to organic chemistry

Practical 4: Simulation of classical organic reactions

A/ OVERALL COMPUTATIONAL PROCEDURE

1/ Optimize the geometry of the reactant (R) and product (P) and confirm with vibrational frequencies, i.e. verify (by opening the visualization (.vis) file using AGUI) that vibrational frequencies are all positive, in consistence with a minimal-energy equilibrium structure. Note that the use of the CHAIN procedure in Step 2 imposes that *the same atom ordering is used in both the A and B structures*. The best way to fill this requirement is to build the initial structure of P by starting from the structure of R. *Note that for some cases (e.g. addition reactions), it is easier to build the reactant structure from the product structure.*

2/ Model the R⇋P reaction mechanism by using the CHAIN method. The CHAIN method is used to locate the transition-state structure, starting from the equilibrium geometries of the R and P forms. The input file can be constructed easily with the help of the graphical interface. This calculation provides the energy and gradient of a finite number of geometrical structures ('nodes') along the chain reaction coordinate. When the calculation is completed, use the visualization file to identify the node corresponding to the transition-state (TS) structure.

3/ Confirm the optimized transition-state structure by a frequency calculation. To proceed, copy/paste the geometry of the TS obtained in Step 2 in a new window, and compute the vibrational frequencies. Confirm that the computed structure corresponds to a first-order saddle point of the PES, by checking the presence of a single imaginary wavenumber arising from a negative force constant. The normal vibrational mode associated to the imaginary frequency is referred to as the 'unstable mode' in the AMPAC output file. Use the graphical interface to check that this vibrational mode actually corresponds to the reactive process under study.

4/ Once the transition state is fully characterized, perform an intrinsic reaction coordinate (IRC) calculation in both the reverse and forward directions to obtain the minimal energy reaction pathway that connects the transition state with the equilibrium structures R and P. Use the graphical interface to visualize the energy profile of the reaction.

B/ PROTON TRANSFER IN ANIL DERIVATIVES

In salicylideneanilines and related Schiff bases, generally called anils, an intramolecular proton transfer reaction between the enol-imine (E) and keto-amine (enaminone) (K) forms can occur both in solution and in the crystalline state (Fig. 1). This reaction can be triggered either by light or by heat and can even be encountered in biological media. Thermodynamic data (reaction enthalpies ΔH^o et entropies ΔS^o) deduced from

UV/visible spectroscopy measurements[1], are gathered Table 1 as a function of the nature of the substituent R grafted on the phenyl group. Model this reaction at the PM6 level in the gas phase and in a solvent (ethanol), by using the SM5.2 continuum solvation model.
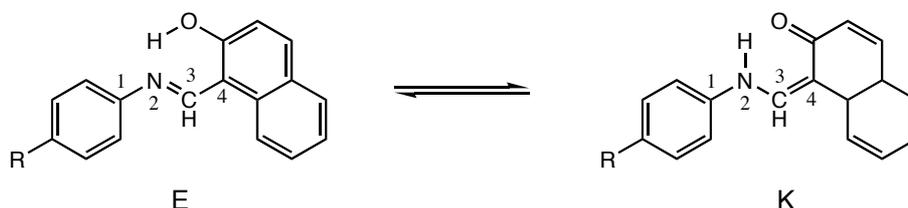

Figure 1: Tautomeric equilibrium of 2-hydroxynaphthaldehyde derivatives

Table 1: Thermodynamic parameters of the $E \rightarrow K$ equilibrium in ethanol.

Substituent	$\Delta H°$/kcal mol^{-1}	$\Delta S°$/cal mol^{-1} K^{-1}
N(CH$_3$)$_2$	-1.595 ± 0.126	-4.995 ± 0.413
CH$_3$	-2.061 ± 0.117	-5.951 ± 0.385
OCH$_3$	-2.089 ± 0.185	-6.153 ± 0.608
H	-1.848 ± 0.130	-6.308 ± 0.426
Cl	-1.225 ± 0.207	-4.800 ± 0.678
Br	-1.298 ± 0.291	-4.616 ± 0.917
I	-1.586 ± 0.198	-5.946 ± 0.652

C/ ADDITION REACTION

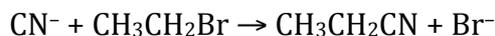We consider the addition reaction of the methanol on the benzaldehyde.
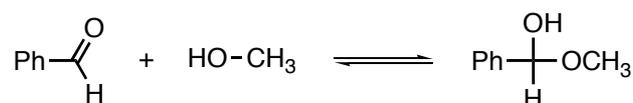
a. Model this reaction at the AM1 level in the gas phase.

b. Plot the evolution of the C_1-C_2-H_3 angle along the reaction coordinate, and comment.

c. Plot the evolution of the net charge of the two oxygen atoms along the reaction coordinate.

d. With the help of the results obtained above, write down the reaction mechanism in the Lewis formalism.

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[1] L. Antonov, W. M. F. Fabian, D. Nedeltcheva, F. S. Kamounah, *J. Chem . Soc. Perkin Trans.* **2000**, *2*, 1173.

D/ SN₂ NUCLEOPHILIC SUBSTITUTION

We consider the SN$_2$ reaction implying the cyanide ion and the ethyl bromide. Model this reaction at the PM6 level in the gas phase and in a solvent (acetone), by using the SM5.2 continuum solvation model.

$$CN^- + CH_3CH_2Br \rightarrow CH_3CH_2CN + Br^-$$

E/ ADDITION REACTION

We consider the addition of the oxirane on the diethylamine. Model this reaction at the PM6 level and determine whether the C–N bond formation and the proton transfer from the nitrogen to the oxygen atom occur synchronously or not.
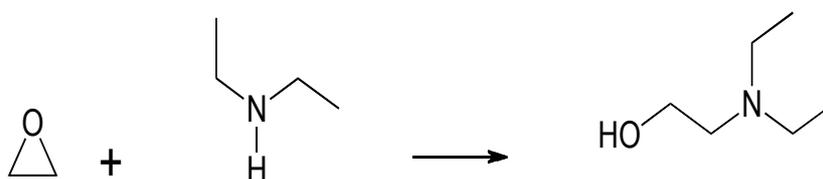
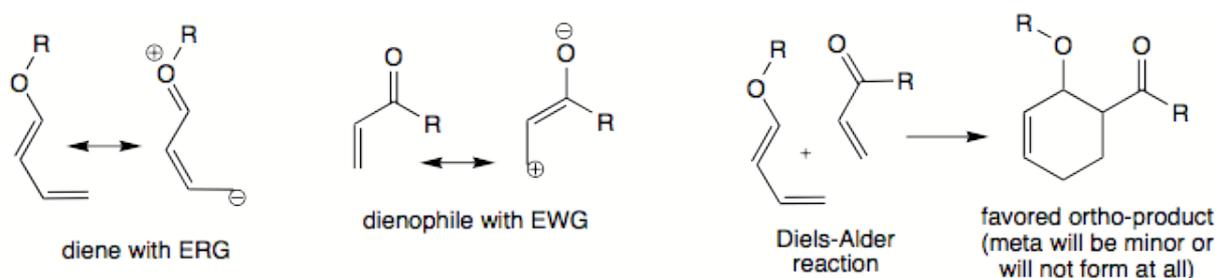## F/ DIELS ALDER [4+2] REACTION

1/ Basic reaction

Model the [4+2] Diels Alder addition of the ethylene onto the butadiene molecule.
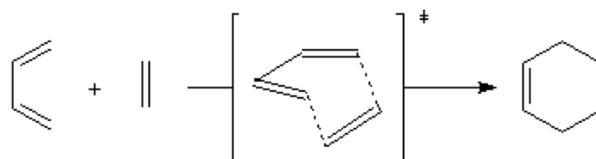
2/ Substitution effects and regioselectivity

a/ We consider the Diels Alder addition in which a methoxy and an aldehyde substituent are grafted respectively on the diene and the dienophile, as schematized below. Model the [4+2] Diels Alder additions leading to the *meta-* and *ortho*-product, and check whether the computational result is consistent with experiments regarding the stereoselectivity of the reaction.

diene with ERG

dienophile with EWG

Diels-Alder reaction

favored ortho-product (meta will be minor or will not form at all)

Note that the complete modeling of the chemical reaction implies considering both the *endo* and *exo* approaches schematized below.
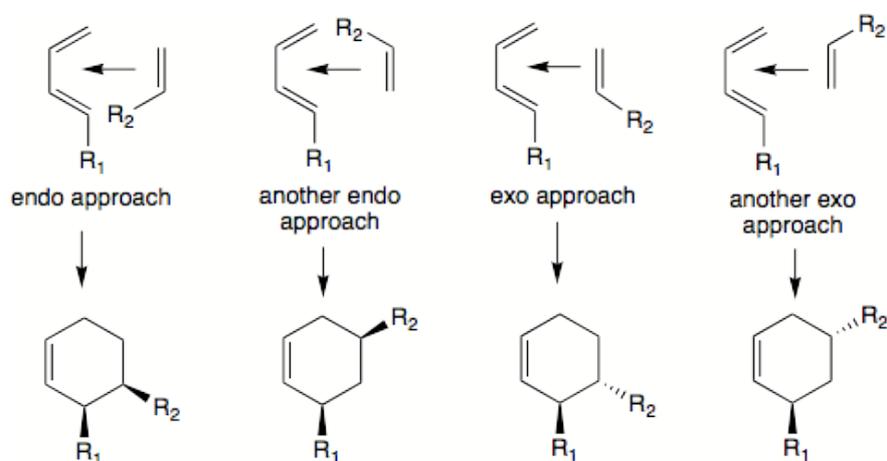
b/ By analyzing the frontier MOs of the diene and dienophile, predict the selectivity of the reactive process by using the Fukui model. Check its consistency with the computational results.

G/ ELECTROPHILIC SUBSTITUTION REACTION

Model the electrophilic substitution reaction below at the AM1 level. Solvent effects will be accounted for by using the SM5.2 solvation model.
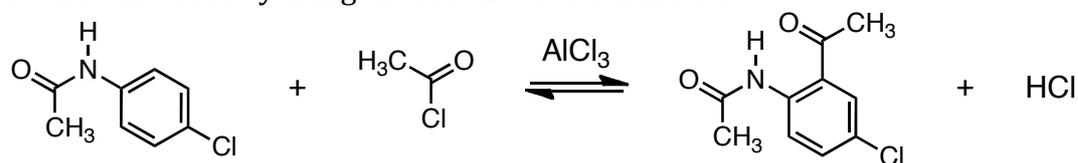
a/ How many steps does involve this reaction?

b/ Plot the evolution of the net charge of the chlorine atom of the acetyl chlorine along the reaction coordinate, and comment.