



# ORDEM DE ESTABILIDADE CONFORMACIONAL DE MOLÉCULAS ORGÂNICAS ACÍCLICAS REVISITADO: UM PROJETO DE APRENDIZAGEM DE ESTEROQUÍMICA BASEADO EM COMPUTADOR



## CONFORMATIONAL STABILITY ORDER OF ACYCLIC ORGANIC MOLECULES REVISITED: A COMPUTER-BASED PROJECT IN LEARNING STEREOCHEMISTRY

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### RESUMO

Aprendizagem estereoquímica hoje, especialmente no tópico da estabilidade conformacional, parece generalizar *anti*, *gauched*, conformações eclipsadas como uma ordem de estabilidade geral de todas as moléculas orgânicas acíclicas. Isto pode ser devido a que muitos manuais de química orgânicos só ênfase moléculas não polares simples, como propano ou butano, como exemplos para explicar este tópico que omite detalhes de polares. Este estudo propõe uma técnica baseada em computador simples como um projeto de estudantes na aprendizagem estereoquímica. Aplicando isto rápido, fonte aberta, e o software fácil de usar é altamente recomendado para promover o conceito e exatamente prever da estabilidade conformacional pelo experimento assistido por computador na sala de aula.

**Palavras-chave:** *Projeto Baseado em Computador, Química Orgânica, Estereoquímica, Estabilidade Conformacional*

### ABSTRACT

Learning stereochemistry today, especially on the topic of conformational stability, seems to generalize *anti*, *gauche*, *eclipsed* conformations as a general stability order for all acyclic organic molecules. This may be due to the fact that many organic chemistry textbooks only emphasis simple non-polar molecules, like propane or butane, as examples to explain this topic omitting details for polar ones. This study proposes a simple computer-based technique as a project for students in learning stereochemistry. Applying this fast, open-source, and user-friendly software is highly recommended for promoting the concept and accurately predicting of conformational stability through computer-assisted experiment in the classroom.

**Keywords:** *Computer-Based Project, Organic Chemistry, Stereochemistry, Conformational Stability*

## INTRODUCTION

Science of organic chemistry is based on the relationship of molecular structure and properties. Chemists realize that molecules are not flat, they move, collide, and react in three-dimensional (3D) space. Furthermore, 3D molecular structure is considered as an important factor to study chemical reactions. The scientific field focusing on the relationship between 3D molecular structure and chemical processes is called stereochemistry (Padalkar and Hegeraty, 2013; Cody *et al.*, 1990; Morisson and Boyd, 1990; Pribly and Bodner, 1987).

Generally, the topics studied in stereochemistry include chirality and nomenclature, conformational stability, racemization, stereoselectivity, etc. (Battle, 2010; Kurbanoglu *et al.*, 2006; Barta and Stille, 1994). On the topic of conformational stability, students will be taught that a molecule can adopt various Newmans' conformations. Moreover, they will be explained that those conformations have different energies and stability based on qualitative reasons, mainly steric effects (Hounshel *et al.*, 1978). As an example: butane adopt three different conformations i.e. *anti*, *gauche*, *eclipsed* which the last is the most unstable conformation caused by steric reasons. However, learning this topic by qualitative explanation causes students to become passive, bored, and leads to a reduction of cognitive and psychomotoric activities (Wingfield and Black, 2005). Students should be guided to discover concepts through investigation of phenomena from a small experiment in the classroom. Parrill and Gervay (1997) stated that discovery-based tutorials are better statistically compared to conventional instruction in teaching stereochemistry.

Additionally, another issue that should be clarified is manyorganic chemistry textbooks generalized *anti*, *gauche*, *eclipsed* as a common order of conformational stability for acyclic organic molecules (McMurry, 2008; Narain, 2008; Hart *et al.*, 1999). This issue arises because often only non-polar molecules (such as ethane, propane, butane, cyclohexane) are used to explain this topic while notes regarding polar molecules are often missing. Is the stability order for non-polar molecules similar to that for polar ones? How to explain the energy profile for polar molecules? These questions are still mystery for most of students and chemistry teachers. Based on the description above, studying conformational

stability should be designed to become a student's project using computer experiment in the classroom (Stieff *et al.*, 2005; Starkey, 2001).

Some researchers have studied the use of computational chemistry packages in teaching stereochemistry and found that this strategy is effective to enhance spatial ability (Pribly and Bodner, 1987), cognitive models of visualization (Stieff *et al.*, 2005), student' visualization skills (Starkey, 2001). This research proposes a simple procedure to explore conformational stability of all acyclic organic molecules using an open-source and user-friendly computational chemistry package.

## MATERIALS AND METHODS

This research utilizes open-source software, namely Avogadro v1.1.1 (Hanwell *et al.*, 2012), ORCA Quantum Chemistry Package v3.0.3 (Neese, 2012), and Molden (Schafteenaar & Noordik, 2000). All the calculation processes have been run on a personal computer with an Intel® Pentium® 4 CPU 3,00 GHz (2 cores), 2GB RAM, and operating system Windows-7 64 bit. Molecular modeling on this research was conducted by following this procedure:

1. Design a molecular structure, optimize its geometry and generate ORCA input file (\*.inp) using Avogadro. The input file contains information about the level of theory applied for the quantum calculations, basis set, convergence, commands for scanning the potential energy surface (PES), and the coordinates of the atoms. A detailed description of the input files is shown in Figure 1.
2. Quantum geometry optimization is then performed using the ORCA quantum chemistry package. ORCA binaries were executed using Windows PowerShell or Command Prompt by simply typing "*orca.exe \*.inp*" on the active background.
3. The optimized structure generated resulting from the second step (\*.xyz file) is visualized using Avogadro, also preparing an input file for the PES scan. After executing the scan, a bunch of output files is produced including a trajectory file (\*.trj) which is used for the next step. A \*.trj file contains sets of molecular coordinates with its related energy which has been generated for 100 times of dihedral

atoms changes.

- After the calculation is finished, a \*.trj file is visualized and interpreted using Molden by simply typing "gmolden.exe \*.trj" on the active Windows PowerShell background. The profile of the potential energy versus dihedral atoms changes at each point (See Supplementary Material) can be visualized by simply pressing the "Geom. Conv." button and clicking on the "Movie" button for a dynamic moving.

## RESULTS AND DISCUSSION

Molecules studied in this research are eight disubstituted ethane (R1-CH<sub>2</sub>-CH<sub>2</sub>-R2) with the division of R1 and R2 in 3 groups i.e (a) alkyl groups, (b) polar groups with non-hydrogen interaction, and (c) polar groups with intramolecular hydrogen bond. It was believed that most of chemistry students would spontaneously argue *anti*, *gauche*, *eclipsed* as a correct conformational stability order for those molecules. However, exploring PES of molecules in this research found that the stability order highly depends on the interaction between substituents as shown in table 1.

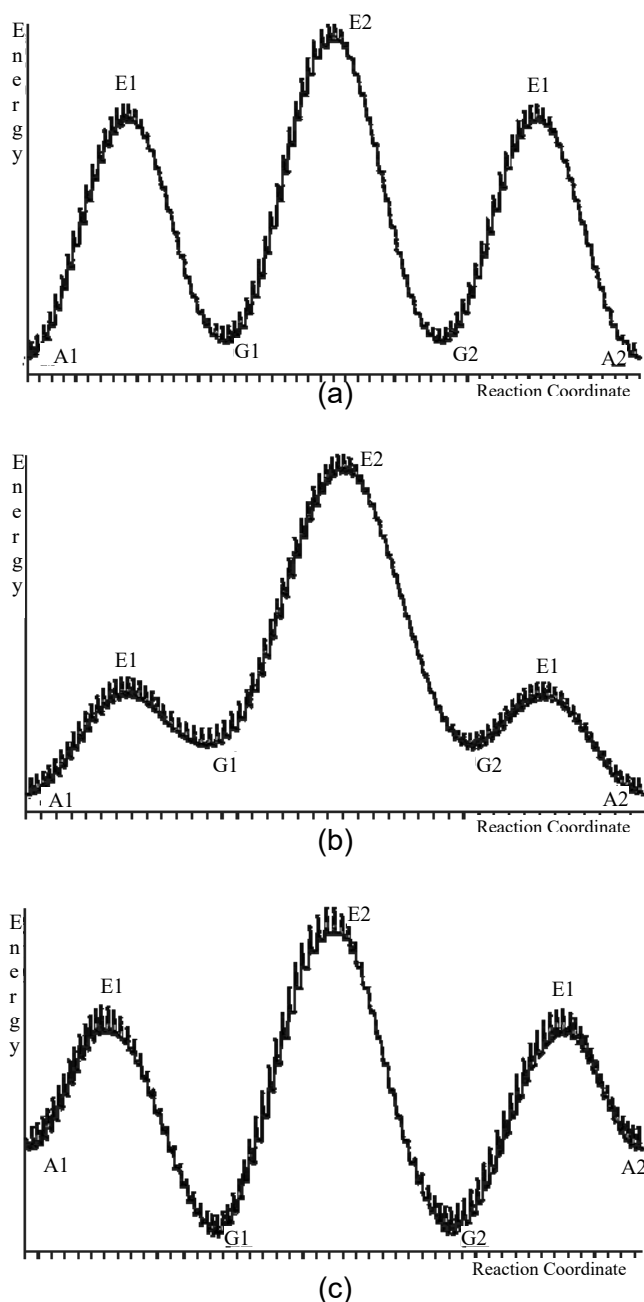
**Table 1.** Conformational stability order of molecules (R1-CH<sub>2</sub>-CH<sub>2</sub>-R2)

Groups	R1	R2	Stability order
Alkyl	CH <sub>3</sub>	CH <sub>3</sub>	A → G → E1 → E2
polar groups with no intramolecular hydrogen bond	F	F	A → G → E1 → E2
	F	Cl	A → G → E1 → E2
polar groups with intramolecular hydrogen bond	Cl	Br	A → G → E1 → E2
	OH	OH	G → A → E2 → E1
	OH	OMe	G → A → E2 → E1
polar groups with intramolecular hydrogen bond	OH	F	G → A → E1 → E2
	OH	CN	G → A → E1 → E2

A = Anti, G = Gauche, E1 = Hydrogen-Substituent Eclipsed, E2 = Substituent-Substituent Eclipsed

Table 1 shows that alkyl and polar groups with no intramolecular hydrogen bond have the same stability order i.e *anti*, *gauche*, and then

*eclipsed* conformations which commonly understood as steric reasons for the first and dipole-dipole repulsion for the other. However, the third group showed a different pattern with *gauche* as the minimum. Although a *gauche* conformation also has a steric problem, an attractive interaction in the form of hydrogen bonding is established lead to increasing molecular stability. The PES graph for one molecule of (a) alkyl group, (b) polar groups with no intramolecular hydrogen bond, (c) polar groups with intramolecular hydrogen bond, is depicted in Figure 2.



**Figure 2.** PES graph for (a) R1 = CH<sub>3</sub>; R2 = CH<sub>3</sub>, (b) R1 = F; R2 = F, (c) R1 = HO; R2 = F

## CONCLUSIONS

The findings show that the stability order of conformers strongly depends on the interaction occurring between substituents. Substituents' interactions with intramolecular hydrogen bonds leads to reduced molecular energy so that a *gauche* conformation is more stable than *anti*. This study finds: (1) alkyl groups, the *anti* conformation is always more stable than *gauche* for steric reasons; (2) polar groups with no intramolecular hydrogen bonds such as F, Cl, Br, I, or Sr also *anti* conformer is more stable than *gauche* for dipole-dipole repulsion; (3) polar groups with intramolecular hydrogen bond such as the interaction of OH–OH, OH–F, OH–OMe, OH–CN showed the *gauche* conformer is the minimum. Hence, a simple computer technique provided in this paper is very recommended as a students' project in learning stereochemistry at Universities.

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```
! HF-3c OPT TightSCF
%geom scan
D 4 0 1 5 = 180, -180, 100 end
end
```

```
*xyz 0 1
C -6.23307 1.53825 -0.01761
C -4.67612 1.53257 -0.01330
H -6.58561 2.35848 -0.63726
H -6.59247 1.71652 0.99238
C -6.80545 0.19216 -0.55028
C -4.10374 2.87847 0.51984
H -4.31672 1.35465 -1.02335
H -4.32358 0.71212 0.60606
H -4.44052 3.70285 -0.10336
H -3.01656 2.86452 0.51858
H -4.44692 3.05630 1.53572
H -6.46168 0.01362 -1.56584
H -7.89262 0.20638 -0.54972
H -6.46927 -0.63192 0.07363
*
```

**Figure 1.** Example ORCA input file for Buthane generated by Avogadro

## Supplementary Material

### A. Example input file for Buthane

```
! HF-3c OPT TightSCF
%geom scan
D 4 0 1 5 = 180, -180, 100 end
end
*xyz 0 1
C -6.23307 1.53825 -0.01761
C -4.67612 1.53257 -0.01330
H -6.58561 2.35848 -0.63726
H -6.59247 1.71652 0.99238
C -6.80545 0.19216 -0.55028
C -4.10374 2.87847 0.51984
H -4.31672 1.35465 -1.02335
H -4.32358 0.71212 0.60606
H -4.44052 3.70285 -0.10336
H -3.01656 2.86452 0.51858
H -4.44692 3.05630 1.53572
H -6.46168 0.01362 -1.56584
H -7.89262 0.20638 -0.54972
H -6.46927 -0.63192 0.07363
*
```

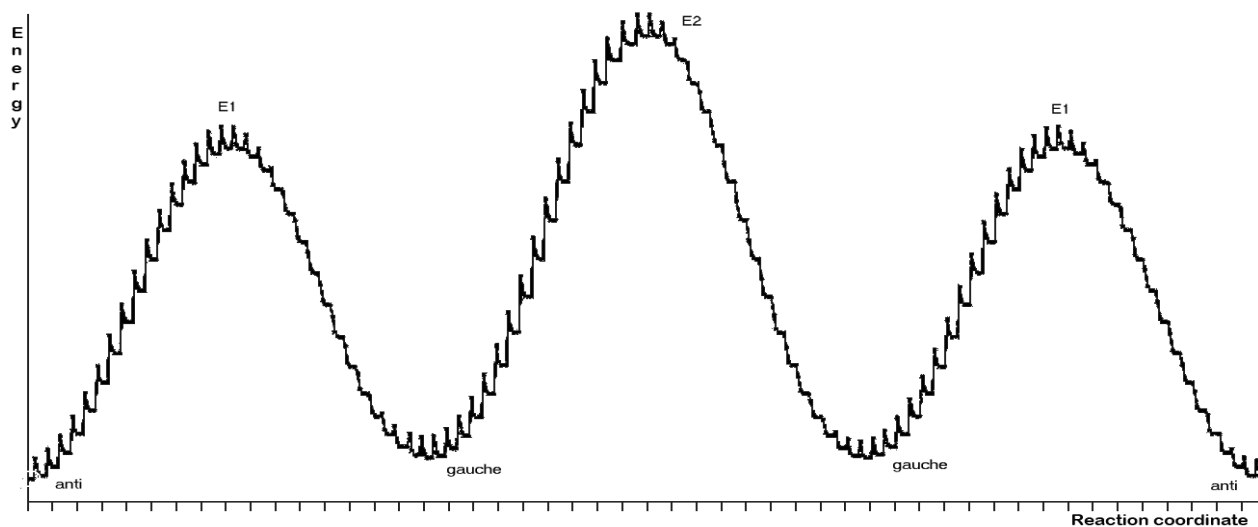
Command for level of quantum calculation, optimization, and type of SCF iteration

Command for scanning PES which is relative to the 100 point of the dihedral angle changes from 180 to -180 degree for atomic number 4 0 1 5.

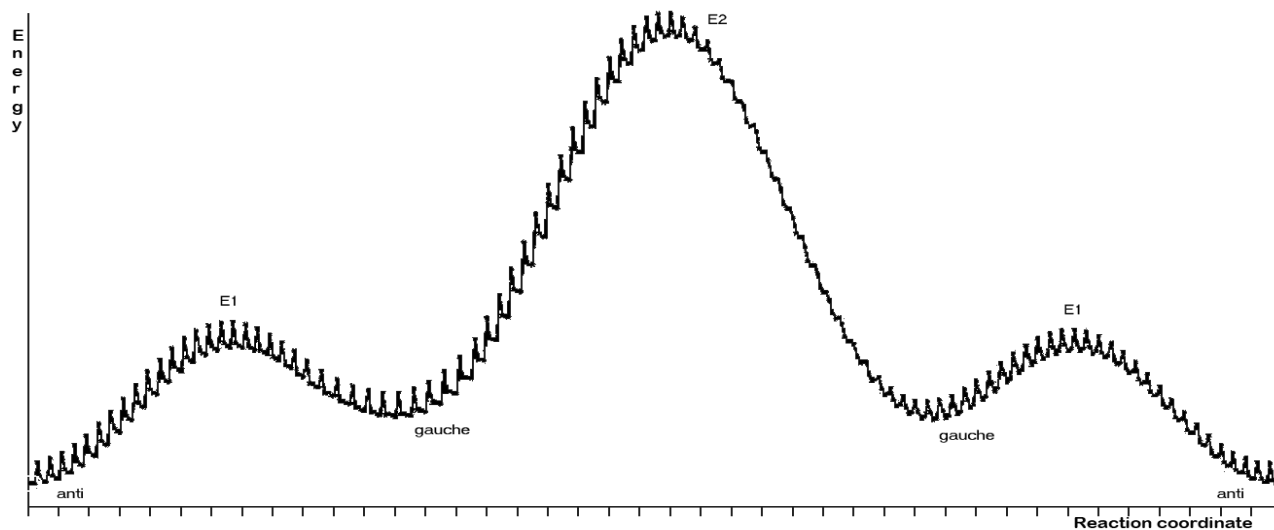
Coordinate for all atoms in Buthane. Numbering of atom was started from 0.

### B. Potential Energy Surface

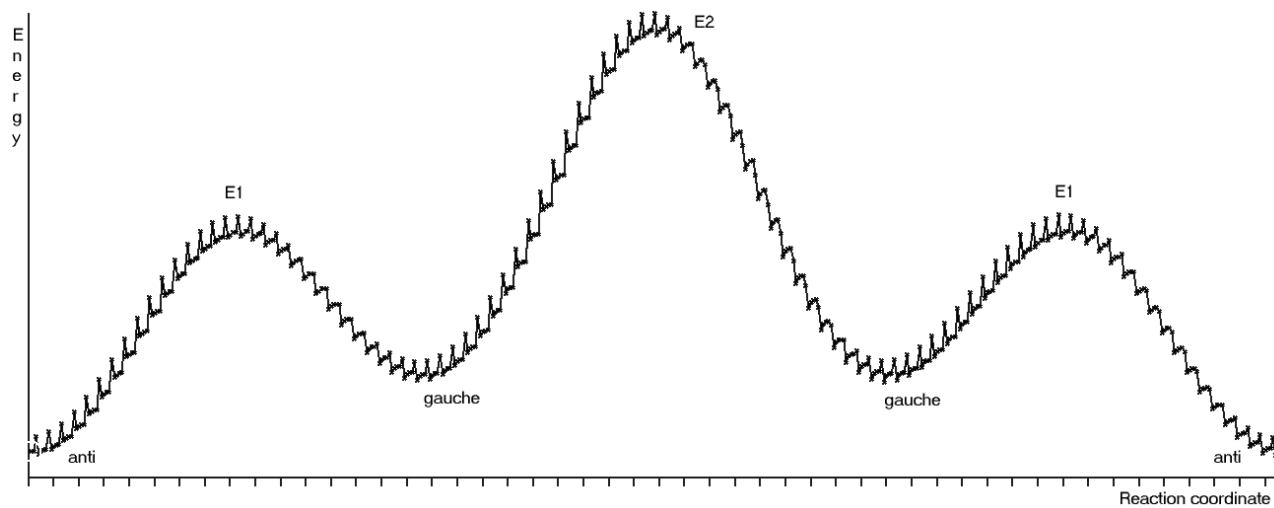
#### 1) $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_3$



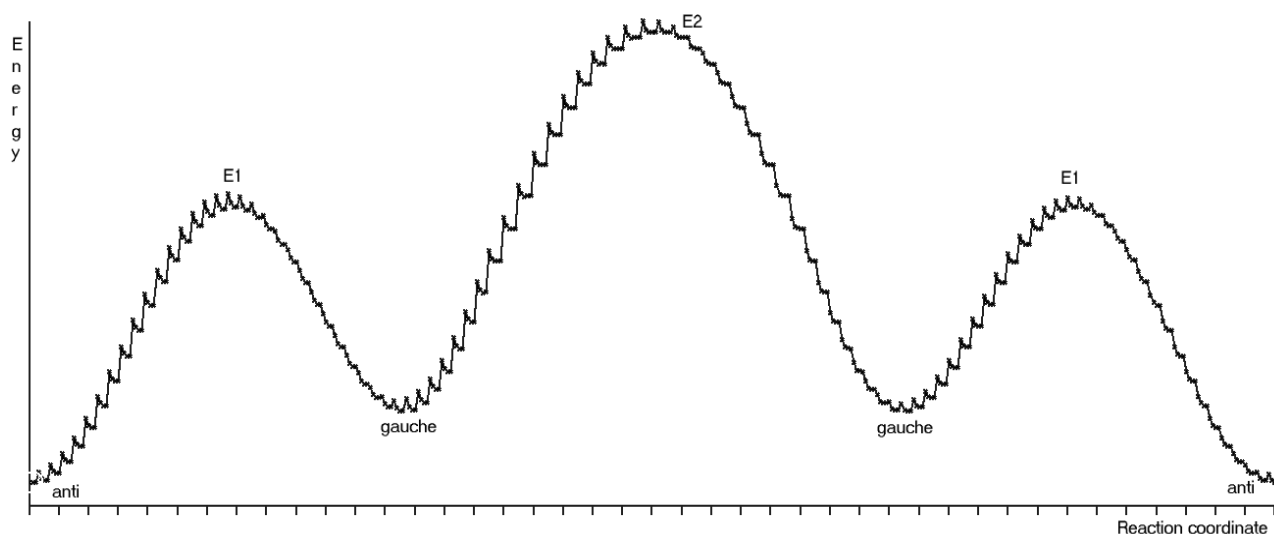
2) F-CH<sub>2</sub>-CH<sub>2</sub>-F



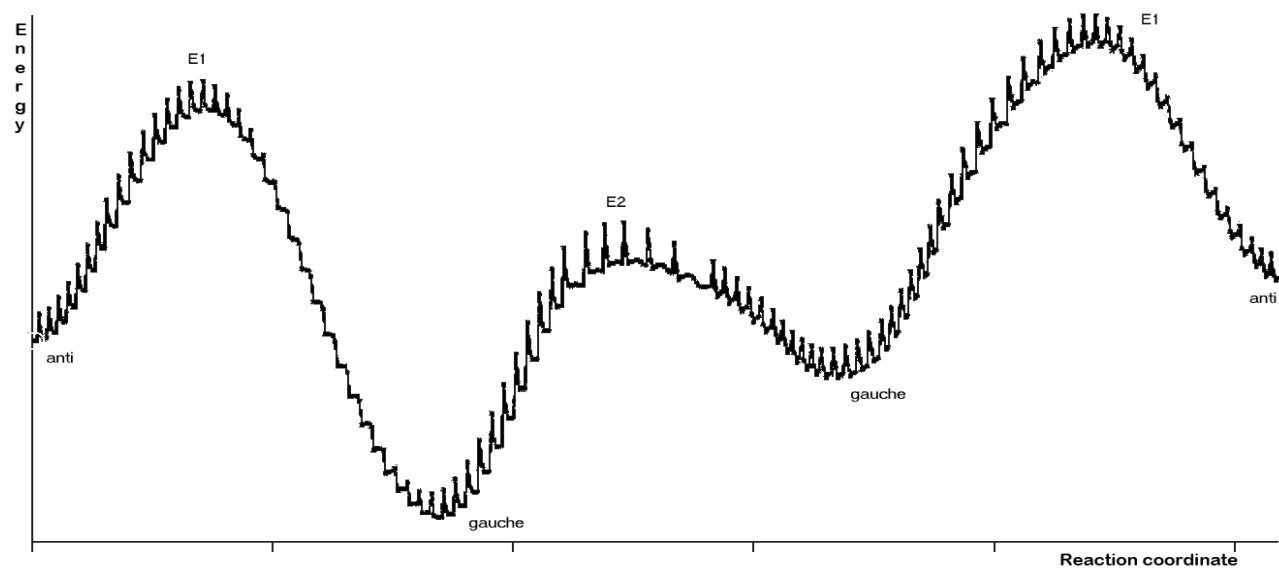
3) F-CH<sub>2</sub>-CH<sub>2</sub>-Cl



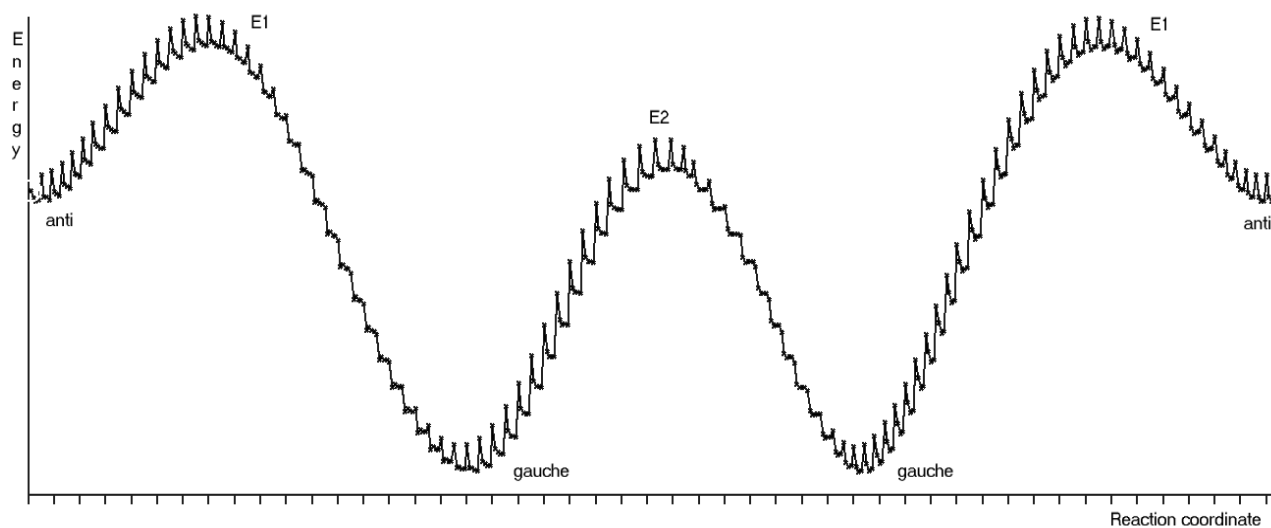
4) Br-CH<sub>2</sub>-CH<sub>2</sub>-Cl



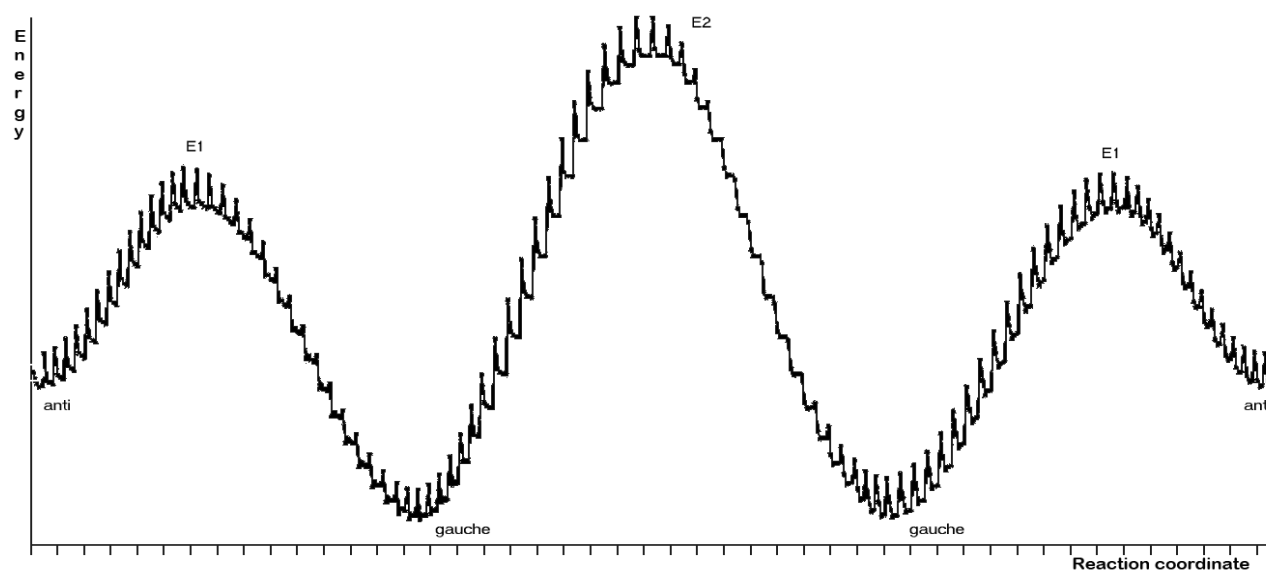
5) HO-CH<sub>2</sub>-CH<sub>2</sub>-OH



6) HO-CH<sub>2</sub>-CH<sub>2</sub>-OCH<sub>3</sub>



7) HO-CH<sub>2</sub>-CH<sub>2</sub>-F





8) HO-CH<sub>2</sub>-CH<sub>2</sub>-CN

