

# **Fundamentals of Theoretical Organic Chemistry**

## **Lecture 8**

## Preamble

Imagine an other civilization on some distant planet in a faraway corner of the Universe, where the scientific community had a rather sophisticated knowledge of physics but chemistry has not been studied as yet. One day the physicist decided to start investigating chemical phenomena in order to discover the laws of chemistry. So they drafted a grant application in which they outlined the philosophy of their research. They proposed to study reactions first in the gas phase so that solvent effect, diffusion and other disturbing phenomena would not influence their observation. Subsequently, they will carry out the same reactions in solution to observe the influence of the environment.

The situation on our planet was directly the opposite. Reactions were studied for centuries in solution before gas phase investigation could have started. Consequently mechanistic conclusions were dramatically influenced by the environment so it was hard to know if an observation was an intrinsic property or something due to the environment. Another disturbing factor was the absence of a rigorous computable theory. Reactions were investigated before the French Revolution, i.e. in the 18<sup>th</sup> Century. Mechanistic investigation started here and there in the 19<sup>th</sup> Century (**the mutarotation of glucose in 18... and the Walden inversion in 1893**). However, systematic study in the field of physical organic chemistry did not begin until the early 1900s. An understanding of nucleophile substitution started to unfold in the 1930s as the result of the work of Hughes and Ingold which was fully formulated in Ingold's book in 1953. This about half a Century was necessary to gain an acceptable understanding. Such an understanding was achieved between the period of 1900 and 1950 without the utilization of computable theory because a general theory was not formulated until 1926 by Schrödinger and the theory did not become computable until the 1960s. Of course at that time the computational capabilities were very marginal. Even today, when we are able to compute in a far more sophisticated way we still have not produced potential energy surfaces (PES) or potential energy hypersurfaces (PEHS) for such simple mechanism of S<sub>N</sub>2 and S<sub>N</sub>1. Mostly critical points of the PES were computed but some surfaces were also generated for the gas phase reaction. However, no PES was computed for the reaction in aqueous solution.

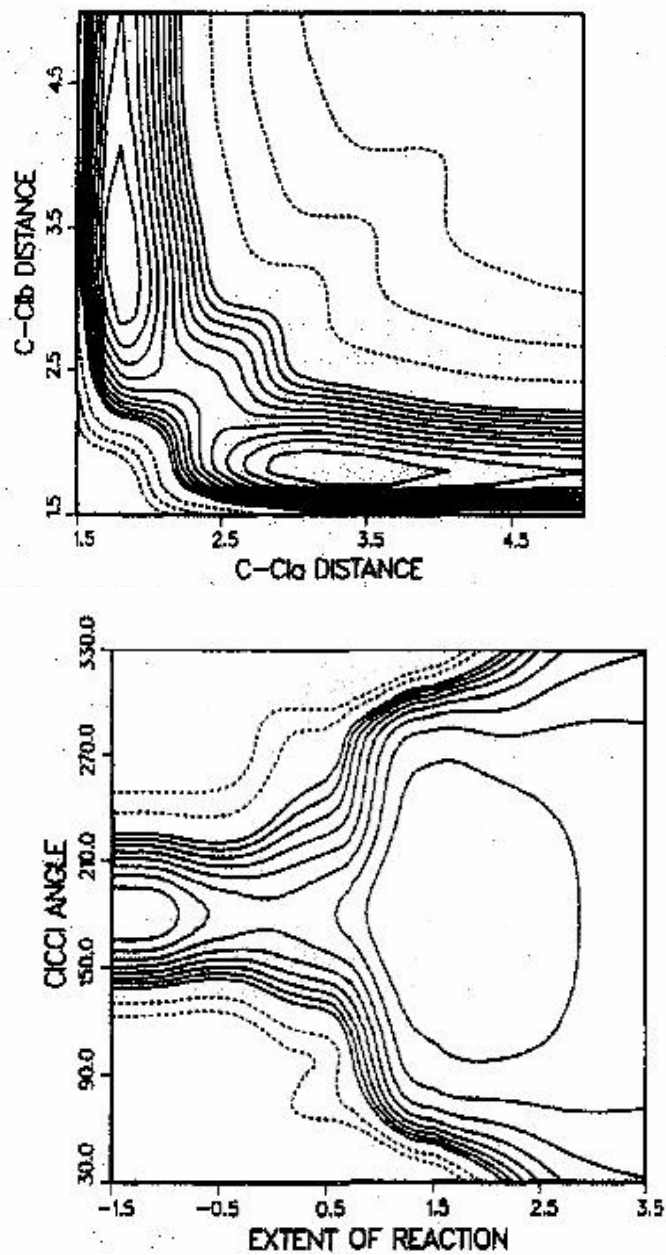
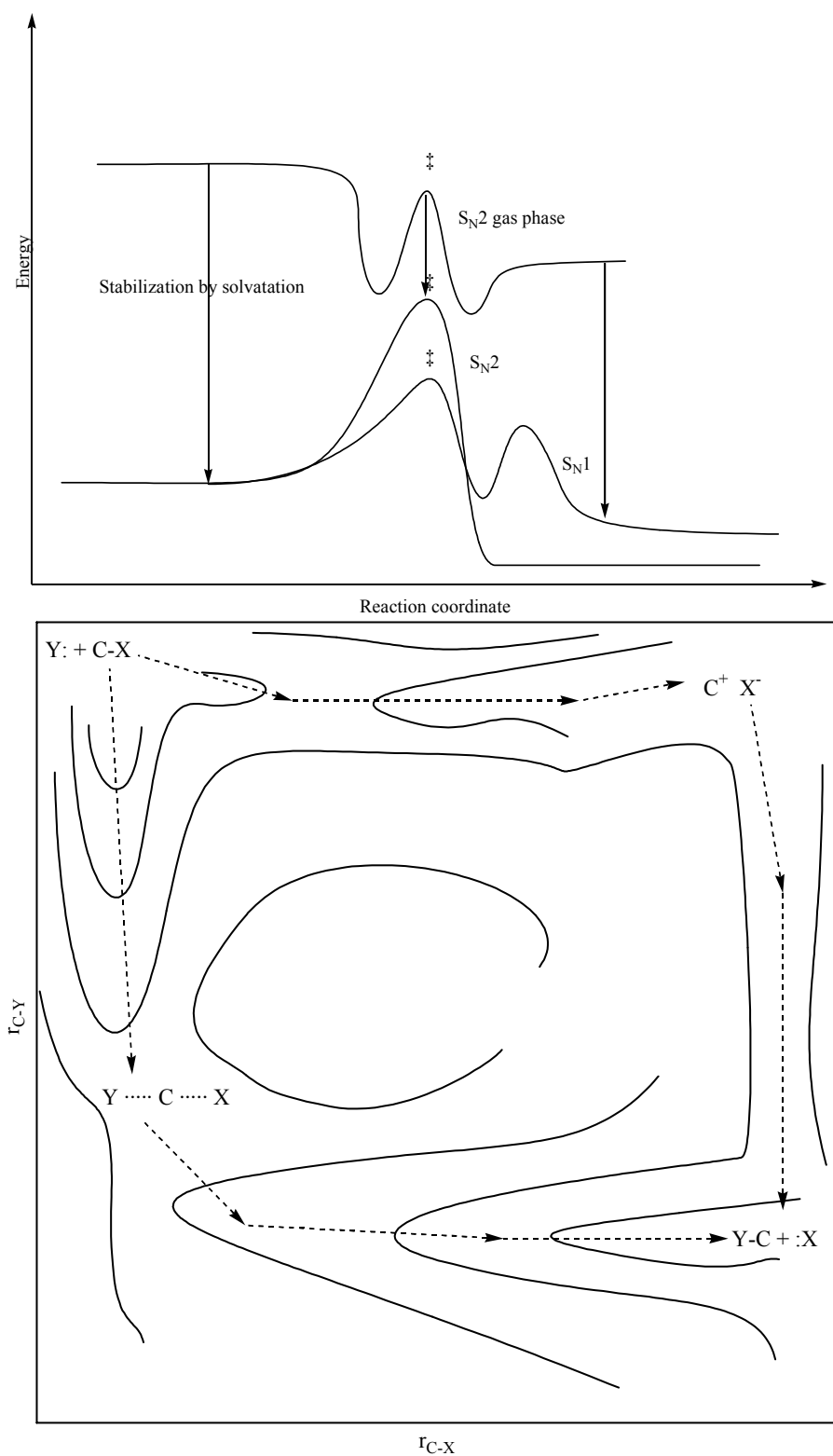


Figure 2.1.2-1. The PES for aqueous solution is expected to look like on the picture.



**Figure 2.1.2-2. PES of the S<sub>N</sub>2 and S<sub>N</sub>1 mechanism.**

If the concept of such a surface even if this sketchy form was available in 1900 the discovery of the S<sub>N</sub>2 and S<sub>N</sub>1 mechanism would have been instantaneous. It would have been

also clear that there are always so many competing mechanisms as many paths there are on the PES.

Clearly such a line of thought is anachronistic. However, the conclusion is inexorable; with the help of theoretical results the experimental research can be accelerated.

## 2.1 Substitution

### 2.1.2 Nucleophil substitution

In 1893 Walden presented evidence that D-malic acid (hydroxyl succinic acid) can be converted to L-malic acid via L-chloro succinic acid intermediate using  $\text{PCl}_5$  for the first and  $\text{AgOH}$  for the second step. Subsequently, this is called the Walden inversion. Similarly L-Malic acid can be converted to D-malic acid via D-chloro succinic acid with the same pair of reagents. The two alternative Walden inversions are summarized in the figure below. This figure also shows that either enantiomers of the optically active chloro succinic acid is hydrolyzed by inversion of configuration if  $\text{KOH}$  is used as reagent by the process has occurred by retention of configuration if  $\text{AgOH}$  is used as reagent.

Today, with considerable oversimplification, only the step which proceeds with inversion of configuration is called the “Walden inversion”.

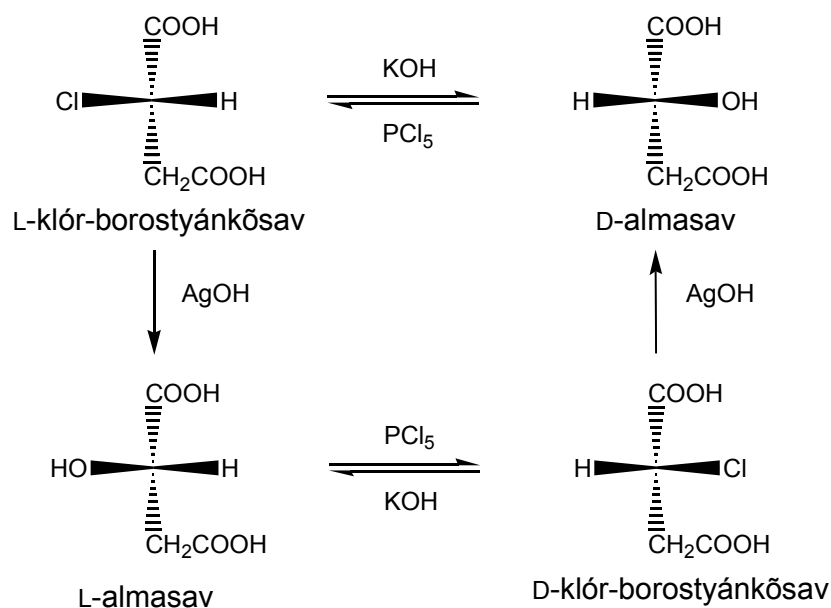
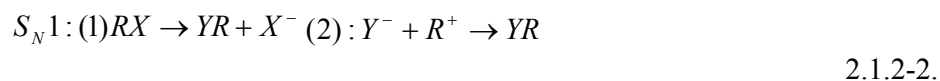


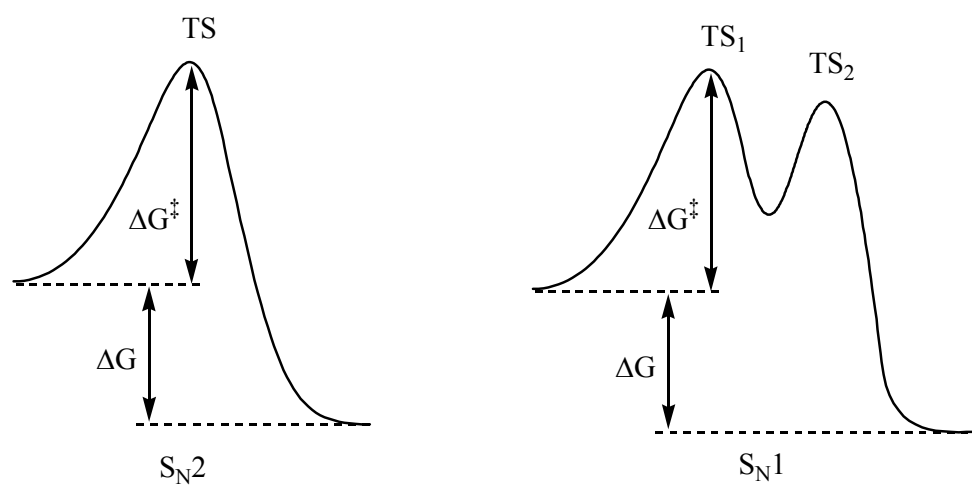
Figure 2.1.2-1. Walden inversion of L-Malic acid to D-malic acid via D-chloro succinic acid.

Hughes and Ingold initiated reactionkinetic studies on nucleophilic substitution in the 1930s which matured to a grand-scale understanding of S<sub>N</sub>1 and S<sub>N</sub>2 reaction mechanisms in 1953 when Ingold published his classic book on “Structure and Mechanism in Organic Chemistry”.

The two mechanism were represented by the following equations:



At that stage the potential energy profile for S<sub>N</sub>2 was considered a one-step reaction with a single transition state (TS) In contrast to that the S<sub>N</sub>1 reaction had two transition states (TS<sub>1</sub> and TS<sub>2</sub>)

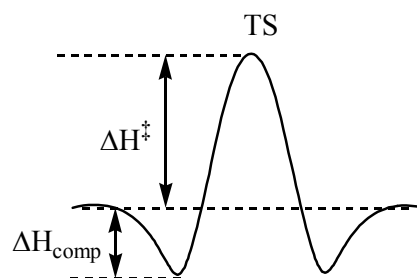


**Figure 2.1.2-2. Potential energy profile for S<sub>N</sub>2 and S<sub>N</sub>1 reaction**

Almost a quarter of a century has passed by, after Ingold’s book has been published, when Olmstead and Brauman has shaken the chemical community with their double-well potential for gas-phase S<sub>N</sub>2 reaction. For a symmetric arrangement:

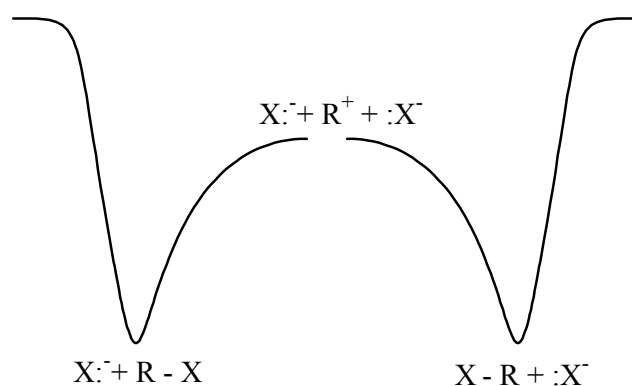


potential had the following shape:



**Figure 2.1.2-3. Double-well potential for gas-phase S<sub>N</sub>2 reaction.**

Also there was no evidence for S<sub>N</sub>1 mechanism occurring in the gas-phase. This is understandable since the dissociation and the recombination can only be described by the lower-end of the corresponding Morse potential and the ionic dissociation limits are much higher than the radical dissociation limits ( $R - Y \rightarrow R \bullet + \bullet Y$ )



**Figure 2.1.2-4.**

An attempt was made by Shaik, Schlegel and Wolff to overcome the gulf that existed by the last decade of the 20<sup>th</sup> century by publishing in 1992 their classic book entitled “Theoretical Aspects of Physical Organic Chemistry: The S<sub>N</sub>2 Reaction”. In spite of their brave attempt the schism between solution physical organic chemists on the one hand and gas phase physical chemists and computational theoretical chemist on the other hand has been carried over to the 21<sup>st</sup> century. A recent review, published in the International Journal of Mass Spectrometry (2002) is still critical of the physical organic chemists, who collect information about reaction mechanisms.

The concepts and language of physical organic chemistry used to describe reactivity often confuse rather than clarify. Interesting, but a timeless discussion is a part of the somewhat dubious reputation of physical organic chemistry. We hope that the present review

has taken away some of the misconceptions introduced in this way. It should be evident that simplified models based on accumulated knowledge in the field of gas phase chemistry is a rich and inspiring source of ideas and information to the rest of chemistry and science, and all signs point towards a future where this will continue to be so.



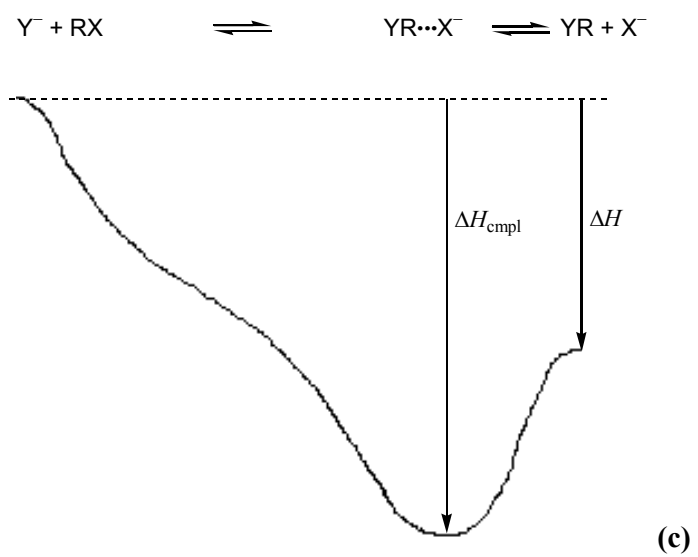
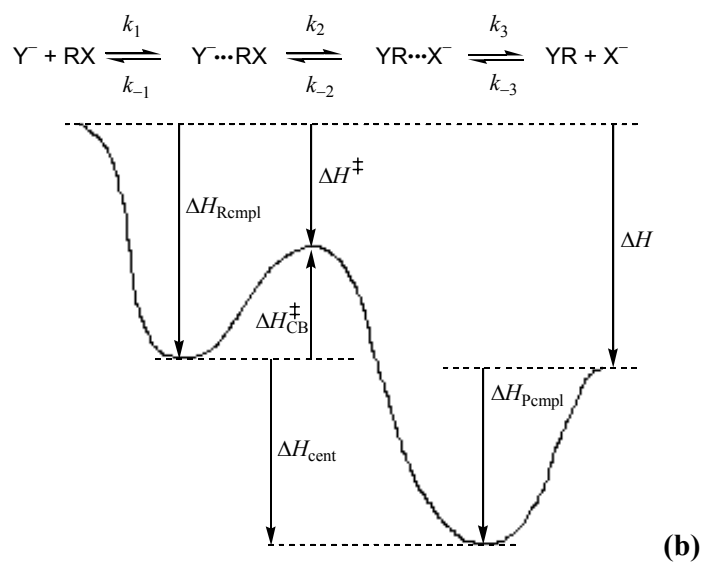
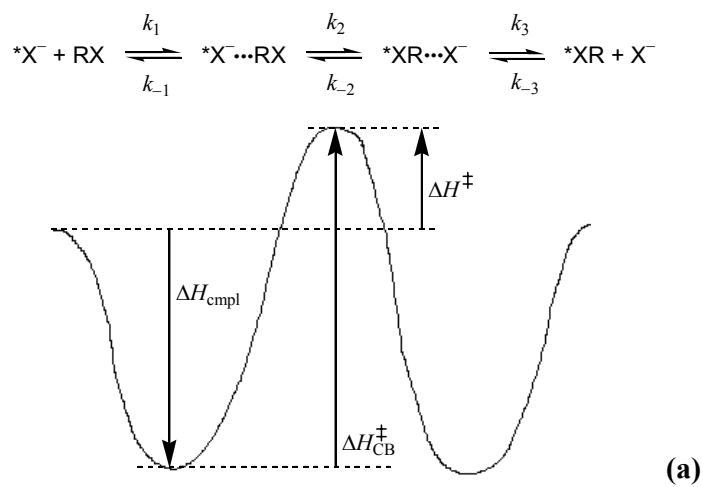
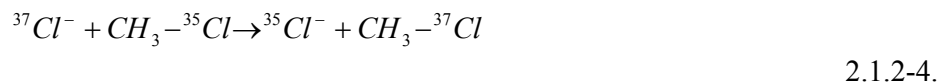


Figure 2.1.2-5.

**Potential energy curves (Figure 2.1.2-5. a)**

The simplest reaction for anionic nucleophile and neutral reactant:



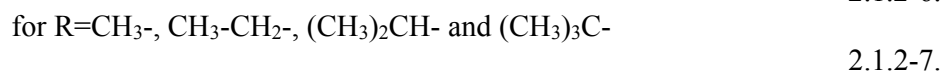
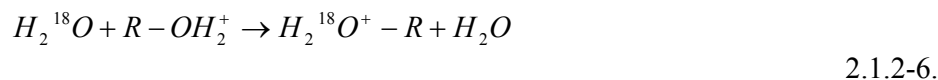
is expected to be thermoneutral thus it is expected to be slow in following the top energy-profile of Figure 2.1.2-5.(a). (Publication: S.E. Barlow J.Am.Che.Soc. 1988, 110, 7240.)

The mixed halide reaction



is, however, exothermic.(Publication: W.L. Hase Science 1994, 226, 998.) Dynamics on the PES are shown in the following Figure

Perhaps the simplest reaction for neutral nucleophilic and cationic reactants



have been reported by (E. Uggerud ... Chem. Eur. J. 1999, 5, 1917.).

Shi and Boyd studied S<sub>N</sub>2 reactions with the inclusion of electron correlation via MP2 computations. No major difference was observed between HF and MP2 results in the relative energies (barriers) but the HF method overestimated charge separations by placing excessive negative charge on both the incoming nucleophile and the leaving group. (J. Am. Chem. Soc. ... 1990, 112, 6789-6796.)

Nucleophilic substitution on allylic chlorides of various substitution H<sub>2</sub>C=CHCH<sub>2</sub>Cl, MeCH=CHCH<sub>2</sub>Cl and Me<sub>2</sub>C=CHCH<sub>2</sub>Cl has been studied with the inclusion of solvent effects. (Kormos and Cramer, J. Org. Chem. 2003, 68, 6375-6386.) In addition to regular S<sub>N</sub>1 and S<sub>N</sub>2 mechanism S<sub>N</sub>2' mechanisms have also been studied in which the incoming nucleophile (Cl<sup>-</sup>) attacks the far-end of the olefinic moiety.

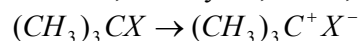
Microsolvation, including up to 4 water molecules for the



system has been studied by A.A. Mohamed et al. (J. Phys. Chem. A 2001, 105, 3259-3268.)

### Aliphatic S<sub>N</sub>1 mechanism

J.R. Mathis, H.J. Kim, J.T. Hynes, JACS, 1993, 115, 8248



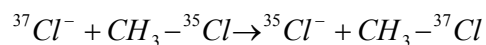
2.1.2-9.

**Table 2.1.2-1. Theoretical and experimental rate constants of reaction in different solvent.**

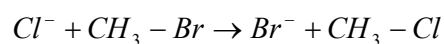
Solvent	C <sub>6</sub> H <sub>5</sub> Cl	CH <sub>2</sub> Cl <sub>2</sub>	(CH <sub>3</sub> ) <sub>2</sub> CO	CH <sub>3</sub> CN
tBuCl	10,7	9,5	8,7	8,4
exp.	11,3	9,5	9,6	8,6
tBuBr	7,5	6,5	5,7	5,5
exp.		7,2	7,1	5,9
tBuI	5,9	5,1	4,5	4,4
exp.	6,6	6,1	5,2	4,3

-log k, k in s<sup>-1</sup>. Experimental values taken from Dvorko, G. F.; Ponomareva, E. A.; Kulik, N. I. Russ. Chem. Rev. 1984,53, 547. (b) Kulik, N. I.; Dvorko, G. F. Org. React. (Tartu) 1974, 1 1 ,333. (c) Abraham, M.H.; Doherty, R.M.; Kamlet, M. J.; Harris, J.M.; Taft, R. W. J. Chem. SOC., Perkin Trans. II 1987, 913. (d) Abraham, M. H.; Grellier, P. L.; Nasehzadeh, A.; Walker, R. A. C. J. Chem. SOC., Perkin Trans. II 1988, 1717.

### Aliphatic S<sub>N</sub>2 mechanism



2.1.2-10.



2.1.2-11.

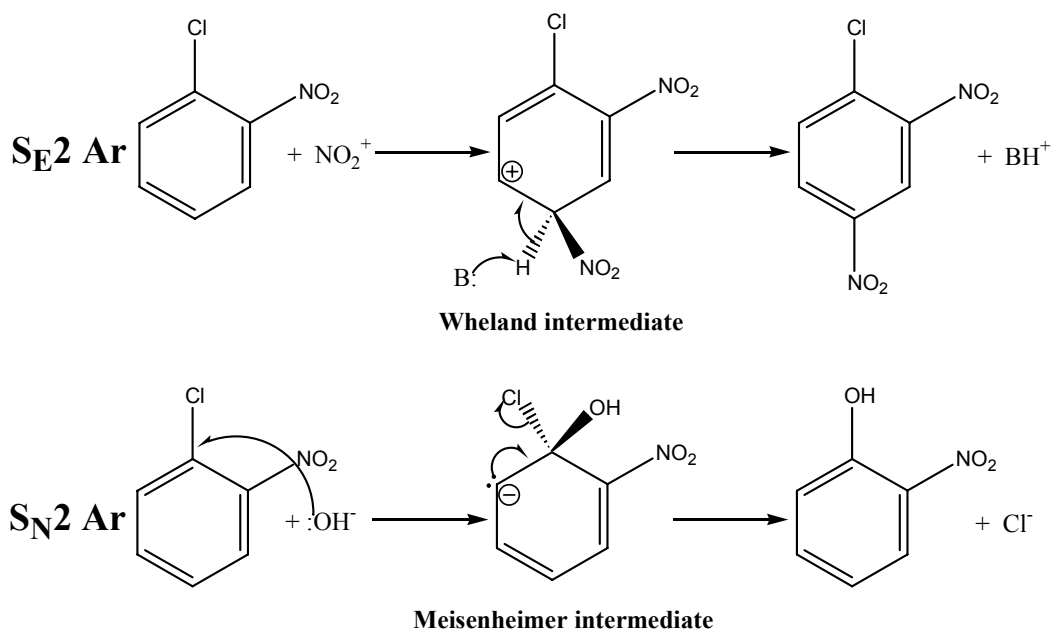
**Table 2.1.2-2.**

S <sub>N</sub> 2 Reaction Mechanism	ΔH <sup>‡</sup> in kJ/mol [Year] (Ref.)	
	Exp	THO
<sup>37</sup> Cl <sup>-</sup> + CH <sub>3</sub> <sup>35</sup> Cl → CH <sub>3</sub> <sup>37</sup> Cl + <sup>35</sup> Cl	4±4 [1988] (1.)	11,2~11,5 [1995] (2.) /[1998] (3.)
Cl <sup>-</sup> + CH <sub>3</sub> Br → CH <sub>3</sub> Cl + Br <sup>-</sup>	-8,2±1,5 [1988] (1.)	-6,8~-8,9 [1996] (2.) /[1998] (4.)

1. S.E. Barlow, J.M. Van Doren, et al. J. Am. Chem. Soc., 1988, 110, 7240
2. Glukhovtsev et al., JACS, 1995 // G2(+)
3. Botschwina, Theor. Chem Acc., 1998 // CCSD(T)
4. Schmatz et al., Int. J. Mass Spect., 1998 // CCSD(T)

### Aromatic S<sub>N</sub>2 mechanism.

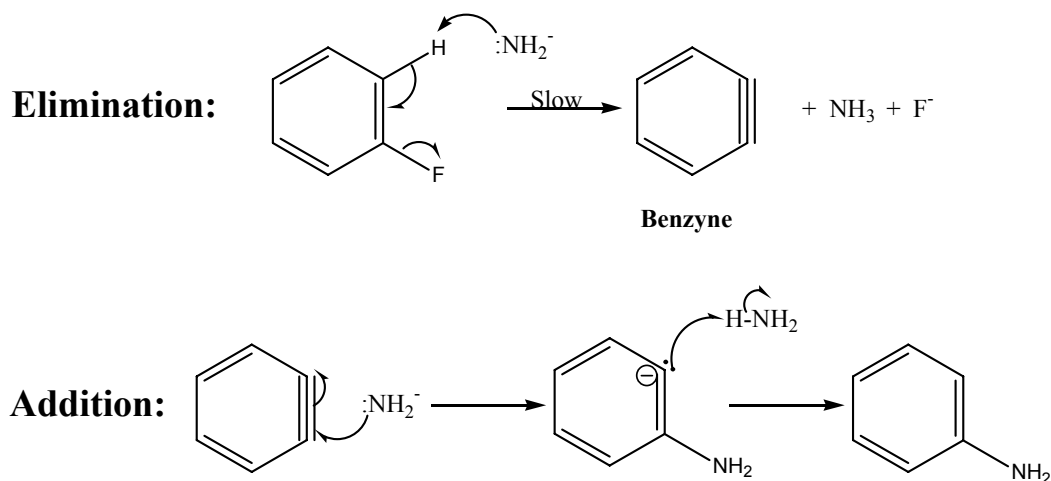
There is some difference between the aromatic nucleophilic substitution (S<sub>N</sub>2<sub>ar</sub>) and the aromatic electrophilic substitution (S<sub>E</sub>2<sub>ar</sub>) even though at first glance they appear to be quiet similar of we consider the bimolecular mechanisms.



what is common in the above pair of mechanism that the actual substitution involves addition to the π-system first which is followed by elimination.

Unlike in the electrophilic substitution in the nucleophilic the alternate mechanism, elimination followed by addition may also occur if the structure of reactant will allow that.

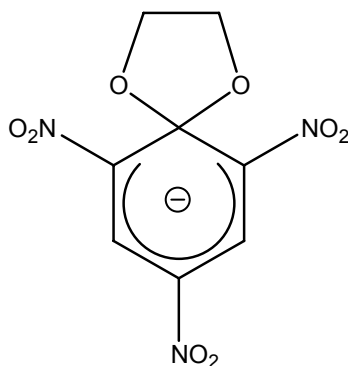
Such a mechanism involves not a Meisenheimer intermediate but a Benzyne intermediate. For example, fluorobenzene and NaNH<sub>2</sub> may react via such a mechanism.



Consequently, the study of nucleophilic substitution involves the study of the structure and reactivity of the two key intermediate the Meisenheimer complex and the Benzene.

***Examination of Meisenheimer complex X-ray crystallography and quantum chemical computations.***

Borbulevych et al, J. Phys. Chem.A., 2002,106, 8109



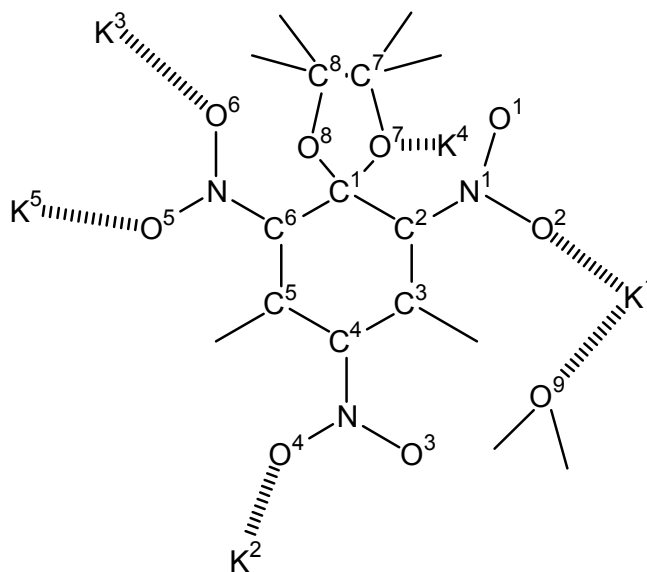
2',4',6'-trinitro-3',5'-dihidrospiro(1,3-dioxolán-2,8'-ciklohexadienid)

The calculations do not reflect the assymetry of the Meisenheimer complex determined by X-ray diffraction.

HF/6-31+G\*

B3LYP/6-31+G\*

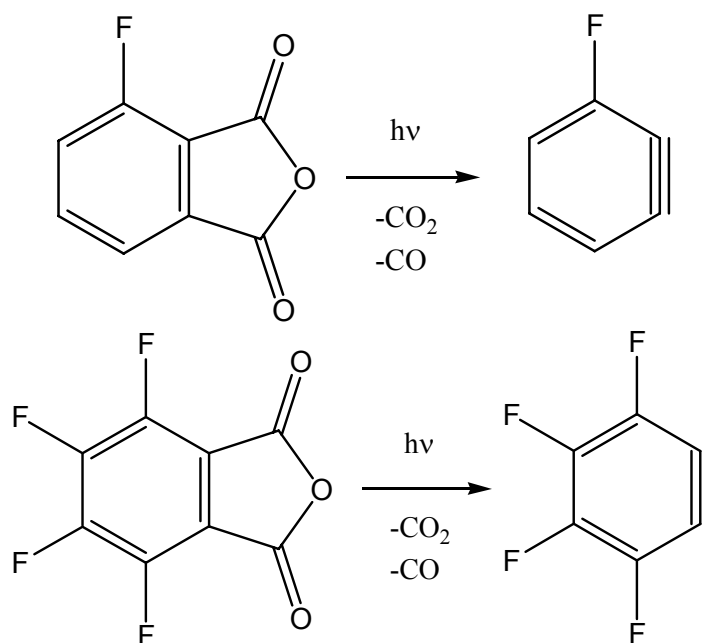
B3LYP/6-311++G\*\*



### *Study of Benzyne structures*

o-Benzyne derivatives originated from photochemical reactions and examined by high resolution IR spectroscopy in noble gas matrix. The results was compared with results of theoretical computations.

Radziszewski et al, J. Phys. Chem. A, 2002, 106, 6730



### Similar reactions of fluorised ftalanhydride derivates (Not an S<sub>N</sub> reaction)

The assignation of IR peaks were supported by B3LYP/cc-pVDZ computations. Differences between the stretching frequency of triple bond of mono-(1866  $\text{cm}^{-1}$ ) or perfluoro(1878  $\text{cm}^{-1}$ ) o-benzyn were well approximated by computation. Nevertheless the absolute frequencies (2007 ill. 2031  $\text{cm}^{-1}$ ,  $n_{\text{experimental}}=0,9671n_{\text{DFT}}$ ) and intensities were strongly overestimated.

The MP2/6-311G\*\* computation is better fitted to experimental values of frequencies and intensities, but the difference in frequency is not so punctual.

