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Quantum Chemical Study of the Thermodynamic and Kinetic Aspects of the S_N2 Reaction in Gas Phase and Solution Using a DFT Interpretation

B. Safi, K. Choho, and P. Geerlings*

Eenheid Algemene Chemie, Faculteit Wetenschappen, Free University of Brussels (VUB), Pleinlaan 2, 1050 Brussels, Belgium

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The S_N2 reactions $X^- + CH_3Y \rightarrow Y^- + CH_3X$ have been investigated in the gas phase and in solution using the Hartree−Fock level with 6-31+G* and 3-21G* bases, respectively. In the gas phase the interpretation has been done in the context of the HSAB principle using Gázquez's formalism using the polarizability (proportional to softness) of the two minima corresponding to the two ion−molecule complexes, and the TS, the softness of the nucleophile and the charge on the leaving group. The thermodynamic study shows that the reaction energy, ΔE_{r-p} and the energy differences between the two ion−molecule complexes, ΔE_m, are close to the experimental data available. The application of the MHP indicates that in these reactions the molecules arrange themselves to be as hard as possible. The polarizable continuum model (PCM) has been used to study the influence of the solvent on the kinetics of the S_N2 reaction. The application of Gázquez's formula provides fundamental information in a case study, with X = Cl and Y = I: the activation energy calculated with the PCM model yields a very good correlation with the values obtained with Gázquez's formula. Finally, we concentrate on the influence of solvation on the nucleophilicity and the kinetics using the (PCM) model with X = F, I and Y = Br and compare the results with the gas phase. The order of reactivity in the gas phase is $F^- > I^-$, which is the same order as in the solvent using the polarizable continuum model, but opposed to experiment. If, however, we take into consideration the interaction energy caused by the hydrogen bond, the order of reactivity in solution is reversed yielding the same results as experiment.

I. Introduction

The development of density functional theory from the Hohenberg−Kohn theorems, which show that the electron density contains the necessary information to describe all properties of a system, has been of great interest in the evolution of quantum chemistry from both computational and conceptual points of view.[1]

Because of the partial inclusion of electron correlation, DFT computational techniques allow computations comparable with the "beyond SCF" level at lower computational cost thus pervading organic, inorganic and biochemistry. Furthermore, a series of quantities, which are readily used when considering chemical reactivity, appear in a most natural way within the framework of density functional theory (conceptual DFT). For example, a sound theoretical basis was established for the frontier molecular orbital (FMO) HOMO and LUMO reactivity indices as introduced by Fukui.[2] These FMO indices, which are used in the study of site selectivity of a reaction, can be seen as an approximation to the Fukui functions introduced in DFT. Other basic concepts in this theory are the chemical hardness and softness which can be used as reactivity index both in their global and local forms. Two important principles have been formulated, involving these quantities: the hard and soft acids and bases principle (HSAB)[3] and the maximum hardness principle (MHP).[4,5]

For some years our group has been involved in both computational and conceptual aspects of DFT and several studies in which the two previous principles have been studied and have been published.[6−14] In particular, some important group properties have been calculated such as the softness, the hardness, and also the electronegativity both in gas phase[15] and in different solvents,[16] thereby paving the way to study solvent effects on reactions via conceptual DFT.

Parker[17] divided solvents into two groups, the first one being dipolar aprotic solvents, and the second one being dipolar protic solvents; the difference between these two categories resides in the ability to form hydrogen bonds. Dipolar aprotic solvents are characterized by a large dielectric constant, a sizable dipole moment, and the inability to act as a hydrogen-bond donor since their C−H bonds are not strongly enough polarized. Protic solvents contain hydrogen atoms bound to electronegative elements and are, therefore, hydrogen bond donors.

A change in solvent can considerably change both the rate and order of homogeneous chemical reactions. Already in 1890, Menschutkin demonstrated that the rate of reaction depends on the choice of the solvent.[18] The reaction rates of homogeneous chemical reactions can be affected via electrostatic effects, due to the solvent. When the reactants and the transition state are solvated, the solvent can modify the rate of the chemical reaction by changing the Gibbs energy of activation.[19,20]

Since the 1970s, much work has been delivered on both gas phase and solution reactions[21,22] in order to understand the energetic evolution related to the electronic and nuclear rearrangements along the reaction path, with the nucleophilic substitution reaction as a prominent example.

In this paper, DFT concepts are used to study the influence of the solvent on the S_N2 reaction of alkyl halides. Bimolecular

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* Corresponding author. E-mail: pgeerlin@vub.ac.be. Tel: 00 32 2 629 33 14. Fax: 00 32 2 629 33 17.

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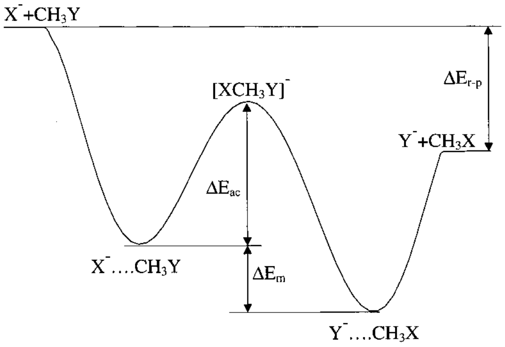

Figure 1. Reaction profile for an S_N2 reaction in the gas phase.

nucleophilic substitution reactions at tetrahedral carbon centers represent one of the most basic chemical transformations. Over the past 20 years, research efforts have focused on simple S_N2 reactions in order to explore the intrinsic chemical behavior of the reactants in gas phase and on the solvent effects in the corresponding condensed phase systems.

The S_N2 reaction considered in this work is the result of an interaction between an anion X^- and a neutral molecule CH_3Y

$$X^- + CH_3Y \rightarrow Y^- + CH_3Y \qquad (1)$$

Generally, in solution this reaction is considered to unroll in one step, in particular in protic solvents.[23,24] However, many studies show that the S_N2 reaction pathway can be subdivided in three steps, in the gas phase and in aprotic solvents.[23−25]

$$X^- + CH_3Y \leftrightarrow X^-\cdots CH_3Y \leftrightarrow Y^-\cdots CH_3X \leftrightarrow Y^- + CH_3X \qquad (2)$$

This is ascribed to the formation of two potentieal-wells, $X^-\cdots CH_3Y$ for the reactants, and $Y^-\cdots CH_3X$ for the products.

The presence of the double-well potential surface as schematically presented below in Figure 1 is probably due to the ion−dipole interactions[26−29] between the anion X^- and the neutral molecule CH_3Y. The depth of these minima was supposed to be governed by properties of the neutral systems such as the polarizability and dipole moment.[30] In a lot of work the height of the central barrier, localized between the transition state (TS) and the two ion−molecule complexes, is considered to be the activation energy ΔE_{ac}.[21,23] The central barrier values have been calculated using some statistical theories,[31,32] in particular the Rice−Ramsperger−Kassel−Marcus (RRKM) theory.[31]

DFT concepts remain poorly explored in studies along the reaction pathway. In this context we recently concentrated on the investigation of the reaction path in gas phase, using the HSAB and MHP principles. In the case of cycloaddition reactions the HSAB and MHP principles provide an interpretation of the evolution of the complexes between reactants and products through the transition state.[33,34] In the present work we will extend these studies to the bimolecular nucleophilic substitution (S_N2) reaction in gas phase and in solution,[21,22] using DFT concepts, as in Pearson's[35] and Gázquez's works.[23]

Our objective is the investigation of some sets of S_N2 reactions (vide supra) in gas phase and in solution with X^- equal F^-, H^-, OH^-, NH_2^-, HCC^-, CN^-, I^-, Cl^-, Br^-, and SH^-, and Y^- equal to F^-, Cl^-, and Br^- with the calculation of quantities like local and global softness, polarizability, and the charges (related to local hardness) and their relationship to both the kinetic and thermodynamic aspects of the reaction. We will first calculate the energy of all critical points such as the reagent complex, $X^-\cdots CH_3Y$, the transition state $[XCH_3Y]^-$, the product complex $Y^-\cdots CH_3X$, the reactants $X^- + CH_3Y$, and the products $Y^- + CH_3X$. These energies will be used to calculate the reaction energies (ΔE_{r-p} between the reactants and products and ΔE_m between the two complexes) in a thermodynamic study in the gas phase. For a kinetic investigation we will calculate the central barrier energies ΔE_{ac} which are associated with the activation energy (vide supra). All these values will be correlated with the experimental data available.

As a second objective, these reaction energies will be interpreted using quantities such as the polarizability of the two minima and the TS, the softness of the nucleophilic group X^- and the charges in the leaving group Y in the $X^-\cdots CH_3Y$ complexes. The polarizability is introduced based on Gázquez's works[23] instead of the softness, due to computational problems when evaluating softness values for anionic species in the finite difference approximation.[7] Gázquez developed a formalism to relate the reaction energy and the activation energy to differences of the hardness between the reagent, products and TS. Thus, the reaction energy has been formulated as a function of the softness (the inverse of the hardness) of the reactants, S_r, and of the products, S_p

$$\Delta E_{r-p} \sim \frac{1}{\sum S_r} - \frac{1}{\sum S_p} \qquad (3)$$

When the sum of the product softnesses is higher than the reactant softnesses, it is seen via (3) that $\Delta E_{r-p} > 0$, i.e., the reaction is endothermic; in the opposite case, ΔE_{r-p} is smaller than zero and the reaction is exothermic. These interpretations are in good agreement with experimental evidence, which shows that in the majority of cases reactions proceed into the direction which produces the hardest molecule, or the products of highest average hardness.[36,37]

The activation energy ΔE_{act} mainly depends on the difference between the hardness[38] of the initial state of a reaction and the hardness of the transition state. These two quantities can be related to the softness of the reacting molecules and the softness of the molecular fragments that characterize the transition state, by making use of the additivity properties of the softness;[39] so the activation energy can be written as a function of the reactant and TS softnesses.

$$\Delta E_{ac} \sim -\frac{1}{2}(\eta_{TS} - \eta_i) = -\frac{1}{2}\left(\frac{1}{S_{TS}} - \frac{1}{S_i}\right) \qquad (4)$$

Various theoretical results,[40−42] which show that the TS is softer than any other state of a system, are in line with the positive ΔE_{ac} values (TS higher in energy than reactants). The same equations have been applied to the study of S_N2 reactions in solution; in the gas phase, however, the softness has been replaced by the polarizability, α[43,44] of the complexes ($X^-\cdots CH_3Y$ and $Y^-\cdots CH_3X$) and the TS ($[XCH_3Y]^-$).

Specially in the solvent we will apply Gázquez's approach to investigate the effect of the nucleophile involved in the S_N2 reaction, and to describe trends in the kinetic aspects of reactions of this type.

Many properties have an influence on nucleophilicity. Those generally considered to be most significant are the solvation energy of the nucleophile, the strength of its bond with carbon, and the electronegativity of the attacking atom. A high solvation energy lowers the ground state energy relative to the transition state, characterized by a more diffuse charge distribution, leading to a decrease in ΔG^*. A stronger bond between the nucleophilic atom and the carbon will be reflected in a more stable transition state and therefore in a reduced activation energy; finally, a more electronegative atom binds its electrons more tightly than a less electronegative one.

There is clearly a conceptual relationship between the properties called nucleophilicity and basicity, the most useful qualitative approach for making predictions of this type being the hard and soft acids and bases (HSAB)[3] concept. This concept proposes that reactions will occur most readily between species that are matching in hardness or softness. Hard nucleophiles prefer hard electrophiles, while soft nucleophiles prefer soft electrophiles. (For a recent review on the use of the HSAB principle at global and local level, see ref 45.) A soft anion will preferentially interact with a sp^3 carbon as a nucleophile yielding substitution while a hard anion is more likely to abstract a proton giving the elemination products.

Considering the literature about the S_N2 reaction until now, the following aspects about the S_N2 reaction discussed in this paper received little attention: in the first place the application of the MHP principle in the gas phase to investigate the evolution of the stabilization of the complexes for this reaction, and in the second place the use of Gázquez's formula to study the S_N2 reaction in different solvents.

In the gas phase we will investigate both thermodynamic and kinetic aspects. Thermodynamic quantities involved are ΔE_{r-p} (the difference in energy between the products and the reactants) and ΔE_m (the difference in energy between the two complexes). A correlation between these two quantities and the experimental values will be investigated together with the effect of the nuclueophile and the leaving group. The results are interpreted involving the HSAB principle by correlating ΔE_m with the group hardness difference between X and Y. Gázquez's work was then used to calculate the softness-dependent factor in the reaction energy (by replacing softness by polarizability) between the ion complexes ($X^-\cdots CH_3Y$ and $Y^-\cdots CH_3X$) and to compare it with ΔE_m. Finally, the charge on Y in the ion−molecule complexes, $X^-\cdots CH_3Y$, will be correlated with the reaction energies.

For the kinetic study we will consider ΔE_{ac}, the energetic barrier between the ion−molecule complexes $X^-\cdots CH_3Y$ and $Y^-\cdots CH_3X$ and the transition state (TS), as the central quantity. We will investigate the effect of the leaving group and the nucleophile on the kinetics of this reaction, and just as in the thermodynamical study we will calculate the softness-dependent factor in the activation energy (using polarizability instead of softness) and correlate it with ΔE_{ac}; the charges in the Y part of the ion−molecule complexes $X^-\cdots CH_3Y$ will be correlated with the energetic barrier ΔE_{ac}. Finally, we will apply the MHP principle to investigate the evolution of the stabilization of the complexes when going from $X^-\cdots CH_3Y$ to $Y^-\cdots CH_3X$.

The polarized continuum model (PCM),[46−48] proposed by Tomasi and co-workers, in combination with Gázquez's approach, will be used to study the effect of protic and dipolar aprotic solvents on the kinetics of a reaction of type $Cl^- + CH_3I \rightarrow I^- + CH_3Cl$. Finally, we will concentrate on the influence of the nucleophile both in the gas phase and in solvent for the reaction of the type (1) with X = F, I , and Y = Br.

II. Methodology

In this work, the polarizability, α, is calculated according to eq 5, as the arithmetic average of the three diagonal elements of the polarizability tensor

$$\alpha = \frac{\alpha_{xx} + \alpha_{yy} + \alpha_{zz}}{3} \qquad (5)$$

where the α_{xx}, α_{yy} and α_{zz} values are obtained through the finite field method.[49]

Starting from Gázquez's equations in which the softness was replaced by the polarizability due to computational problems when evaluating softness values for anionic species in the finite difference approximation,[7] we have considered the following proportionality for the reaction energy ΔE_m as well as for the activation energy ΔE_{ac}

$$\Delta E_m \sim \left(\frac{1}{\alpha_{X^-\cdots CH_3Y}} - \frac{1}{\alpha_{Y^-\cdots CH_3X}}\right) \qquad (6)$$

$$\Delta E_{ac} \sim -\frac{1}{2}\left(\frac{1}{\alpha_{TS}} - \frac{1}{\alpha_{X^-\cdots CH_3Y}}\right) \qquad (7)$$

where the factors involving the polarizability will be denoted as α_m^{-1} and α_{ac}^{-1}, respectively. The electronegativity χ, identified by Parr et al. with the negative of the chemical potential μ, is defined as[50]

$$\mu = -\chi = \left(\frac{\partial E}{\partial N}\right)_{\upsilon(r)} \qquad (8)$$

with E the energy of the system, N the number of electrons, and $\upsilon(r)$ the external (i.e., due to the nuclei) potential. The hardness, defined by Parr and Pearson,[51] is given by

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial^2 N}\right)_{\upsilon(r)} \qquad (9)$$

Finally, the global softness is defined as[52]

$$S = \frac{1}{2\eta} \qquad (10)$$

Assuming a quadratic relationship between the energy and the number of electrons, one obtains from (6) Mulliken's formula[53] for the electronegativity

$$\chi = \frac{\mathrm{IE} + \mathrm{EA}}{2} \qquad (11)$$

with IE and EA the vertical ionization energy and electron affinity, respectively.

Upon the introduction of a SCRF model the energy of the neutral system, cation and anion will become a function of the dielectric constant ϵ of the solvent so that (9) can be generalized to

$$\chi(\epsilon) = \frac{\mathrm{IE}(\epsilon) + \mathrm{EA}(\epsilon)}{2} \qquad (12)$$

with its obvious counterparts

$$\eta(\epsilon) = \frac{\mathrm{IE}(\epsilon) - \mathrm{EA}(\epsilon)}{2} \qquad (13)$$

$$S(\epsilon) = \frac{1}{\mathrm{IE}(\epsilon) - \mathrm{EA}(\epsilon)} \qquad (14)$$

where IE(ϵ) and EA(ϵ) are the vertical ionization energy and electron affinity in a dielectric medium characterized by a dielectric constant ϵ, yielding solvent-dependent group properties.

We propose to use expressions (13) and (14) as working equations to calculate the group hardness and softness in a solvent. Following our previously designed methodology,[6] this

TABLE 1: Calculated Polarizability, α, of $X^-\cdots CH_3Y$ (min1), the Transition State (TS) and $Y^-\cdots CH_3X$ (min2) and the Factor Combination Proportion to the Reaction Energy, α_m^{-1}, Calculated from Eq 6 (in a_B^{-3})[a]

X^-	CH_3Y	α(min1)	α(TS)	α(min2)	α_m^{-1}	ΔE_m	ΔE_{r-p}	ΔH
F^-	CH_3F	18.40	21.80	18.40	0.0	0.0	0.0	0.0
H^-		28.56	31.01	17.84	−0.0210	−57.76	−92.65	−57.0
OH^-		23.30	27.99	21.51	−0.0036	−18.07	−24.42	−14.0
NH_2^-		32.62	37.00	26.26	−0.0074	−42.38	−44.23	−37.0
HCC^-		45.20	46.72	37.70	−0.0044	−23.01	−21.08	−24.0
CN^-		34.62	37.30	30.58	−0.0038	−3.57	5.86	−5.0
Cl^-		28.72	34.30	28.94	0.0003	38.19	44.66	28.0
Br^-		40.43	43.49	38.11	−0.0015	42.97	51.69	37.0
SH^-		42.51	49.45	35.75	−0.0044	18.32	19.61	9.0
F^-	CH_3Cl	28.94	34.30	28.72	−0.0003	−38.19	−44.66	−28.0
H^-		45.70	47.51	27.36	−0.0147	−94.86	−137.31	−86.0
OH^-		35.60	41.25	32.08	−0.0031	−59.28	−69.08	−47.5
$NH2^-$		44.18	51.63	36.19	−0.0050	−76.63	−88.89	−66.1
HCC^-		56.23	64.67	48.35	−0.0029	−61.13	−65.74	−51.0
CN^-		45.05	54.36	42.36	−0.0014	−42.13	−38.80	−32.0
Cl^-		39.79	53.29	39.79	0.0	0.0	0.0	0.0
Br^-		51.83	65.16	48.12	−0.0015	4.51	7.03	8.0
SH^-		54.16	71.33	46.50	−0.00304	−24.72	−25.05	
F^-	CH_3Br	38.11	43.49	40.43	0.00150	−42.97	−51.69	−36.7
H^-							−144.34	
OH^-		42.49	50.46	44.07	0.00084	−62.45	−76.12	−55.7
$NH2^-$		54.07	60.89	48.11	−0.00229	−78.46	−95.91	
HCC^-		65.48	75.65	60.80	−0.00117	−63.34	−72.77	
CN^-		53.63	65.21	54.43	0.00027	−45.41	−45.83	−35.4
Cl^-		48.12	65.16	51.83	0.00149	−4.51	−7.03	−8.2
Br^-		60.28	78.06	60.28	0.0	0.0	0	0
SH^-		58.84	83.91	58.82	−0.00000	−26.44	−32.08	

[a] The reaction energy, ΔE_m, calculated between the ion−molecule complexes, and the reaction energy, ΔE_{r-p}, calculated between the reagents and products and the experimental heat of the reaction ΔH are also tabulated (in kcal/mol).

necessitates the calculation of the energies of the neutral (N_0 electron system), cationic ($N_0 - 1$ electron system), and anionic ($N_0 + 1$ electron system) for a group, taken as the corresponding radical at the geometry the group usually adopts in a molecule. In order to avoid the multiplicity problems in calculations involving some system cations and anions, it was necessary to approximate IE and EA by the energy of the highest occupied molecular orbital (HOMO), ϵ_{HOMO}, and the energy of the lowest unoccupied molecular orbital (LUMO), ϵ_{LUMO}, according to Koopmans' theorem.[54] This approximation leads to the current working equation for the global hardness

$$\eta(\epsilon) = \left(\frac{\epsilon_{LUMO} - \epsilon_{HOMO}}{2}\right) \tag{15}$$

The charges considered are electrostatic potential driven, according to the Merz−Singh−Kollman scheme (mk).[55,56]

In the case of the gas phase, all structures were optimized with the 6-31+G* basis set at Hartree−Fock level using the GAUSSIAN 94[57] and GAUSSIAN 98[58] programs.

In this paper we have used the polarizable continuum model (PCM) developed by Tomasi and co-workers[46−48] to study the solvent effects on the energetics of the S_N2 reaction, using the 3-21G* basis set (cf. the absence of the 6-31+G* basis for I) with GAUSSIAN 98,[58] programs, on the CRAY J-916 and ORCA computers of the Free University of Brussels.

III. Results and Discussion

IIIA. Gas Phase Investigation. As mentioned above, a first step involves the calculation of the electronic energies in each of the critical points along the reaction path (the reactants, the reactants complex, the transition state, the products complex, and the products) with a 6-31+G* basis set at the HF level. In a second step the trends in the previous quantities have been interpreted using calculated molecular properties such as the polarizability, the softness of the X group and atomic charges.

*IIIA.1. Thermodynamic Study***.** The thermodynamic quantities such as the reaction energy, ΔE_{r-p} ($[E_{Y^-} + E_{CH_3X}] - [E_{X^-} + E_{CH_3Y}]$) and the energy differences between the two ion−molecule complexes, ΔE_m ($\Delta E_m = [E_{Y^-\cdots CH_3X}] - [E_{X^-\cdots CH_3Y}]$) have been calculated, as shown in Table 1, for $Y^- = F^-$, Cl^-, and Br^-, respectively. These values were correlated with the experimental data, ΔH[22,59] available for all X^- in the three cases, $Y^- = F^-$, Cl^-, and Br^-. High correlation coefficients are obtained ($r^2 = 0.978$ in the three cases of Y^- for ΔE_{r-p}, and $r^2 = 0.995$ for ΔE_m). The analysis of these energies shows that the values obtained with ΔE_m (reaction energy calculated between the double-well potential surface energy) are close to the experimental data available, better than ΔE_{r-p} values. As indicated previously and confirmed by this result, the intermediate step involving the two complexes and the TS of the S_N2 reaction in gas phase can be seen as the most relevant step of the reaction, although not directly experimentally observable.

On this basis, our thermodynamic investigation will be focused on the properties of the reactants and products and the ion−molecule complexes, $E_{X^-\cdots CH_3X}$ and $E_{Y^-\cdots CH_3X}$.

As shown in previous work,[59] the exothermicity of the reactions of nucleophiles with a single substrate reflect; the thermodynamic affinity of the nucleophile. Following this idea, the exothermicity trend, in this work, is given by the following sequences of ΔE_m as a function of the nucleophile X^-.

With methyl fluoride (CH_3F) these data follow the order (see Table 1):

$$H^- > NH_2 > HCC^- > OH^- > CN^- > F^- > SH^- > Cl^- > Br^-$$

With methyl chloride (CH_3Cl) the same order is obtained (see Table 1):

$$H^- > NH_2 > HCC^- > OH^- > CN^- > F^- > SH^- > Cl^- > Br^-$$

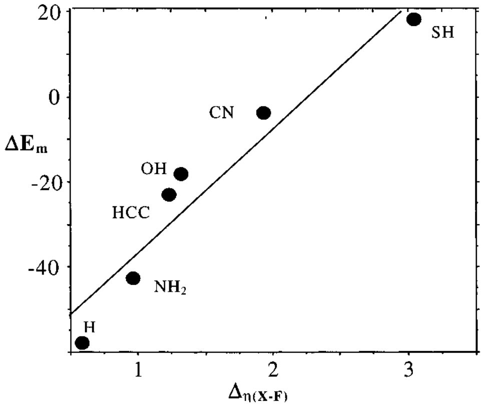

Figure 2. Calculated reaction energy, ΔE_m (in kcal/mol) (see text), as a function of the group hardness difference between the X group and fluorine, $\Delta\eta_{X-F}$ (in eV).

whereas with methyl bromide (CH_3Br) all the reactions are exothermic, the order being still the same as in the previous case.

The three sequences are in good agreement with the experimental[22,59] and theoretical[22] heat of reaction sequences. This exothermicity can be clearly related to the nucleophilicity[22,59] of X^- which follows the same trend.

On the other hand, the global comparison of the ΔE_m values in Table 1 when going from Y = F to Br clearly shows that the exothermicity of this reaction increases in this direction. This is certainly related to the leaving group ability which increases in the order F < Cl < Br in gas phase.[59] These results confirm that there is some complicity between the nucleophile and the leaving group during the reaction.

Following this principle, our results are compared to the hardness of the X and Y groups as calculated by us in the past.[16] The group hardness difference between X and Y gives a good correlation with the reaction energy ΔE_m ($r^2 = 0.928$), as shown in Figure 2 for CH_3F, except for X = F and Cl. This result shows that when the difference of the hardness between X and Y increases the exothermicity decreases. This result is in line with the HSAB principle as proved by Pearson et al.[35] in the case of S$_N$2 reactions, stating that when the nucleophile and the leaving group have similar hardness, the reaction rates are relatively high, and can be interpreted as follows: increasing hardness of Y also hardens the neighboring C atom of the CH_3 group, thereby favoring the attack of a harder nucleophile. In the case of CH_3Cl the correlation analysis yields a correlation coefficient of 0.941; in the case of CH_3Br the analogous trend is respected the correlation being however less outspoken.

In view of the definition of isodesmic reactions (number of formal identical bond types conserved),[60] these S$_N$2 reactions can be considered as anionic isodesmic reactions. As shown by Hehre et al.,[61] in the case of benzene and confirmed by us in the hydrofullerenes,[62] isodesmic reactions can be used to investigate the stabilizing effect of the substitutient. In this work the energy of the S$_N$2 reaction can be considered as a measure of the stabilizing effect of the substitution of Y by X in CH_3Y. Following the reaction energies in Table 1 for Y = F, Cl, and Br, respectively, we see that the reactions are more exothermic in the case of Y = Br as compared to Y = Cl and F. This explains the stability sequence $CH_3F > CH_3Cl > CH_3Br$. This trend is the same as given by the hardness sequence $CH_3F > CH_3Cl > CH_3Br$. On the other hand, this explains the leaving group ability (F has lower leaving group capacities than Cl and Br) which is in good agreement with the hardness sequence (F > Cl > Br). This shows that the softer group has the higher leaving group ability, influencing the stability of the neutral molecule.

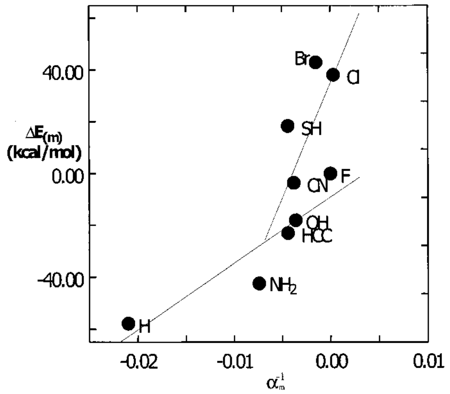

Figure 3. Calculated reaction energy, ΔE_m (in kcal/mol) (see text), as a function of the quantity α_m^{-1} (in a_B^{-3}) obtained via the Gázquez approach Separate linear functions for hard (X = H, NH$_2$, OH, F) and soft (X = HCC, CN, SH, Cl) nucleophiles are shown.

This discussion can still be applied when the two ion–molecule complexes are considered, thereby explaining the stability of one complex toward an other. Indeed, the exothermic reaction energies in Table 1 show that the second complex, $Y^-\cdots CH_3X$, is more stable than the first one, $X^-\cdots CH_3Y$. This can be explained, as above, by the hardness of the nucleophilic group, X^-, for constant softness of the leaving group. For a given Y, the exothermicity increases when the X^- hardness increases, whereas for a given nucleophile X^-, the exothermicity increases when the softness of the leaving group, Y, increases.

As indicated above, this exothermicity can be interpreted in terms of the polarizability (or softness) of ion–molecule complexes for the reactants $X^-\cdots CH_3Y$ and the products $Y^-\cdots CH_3X$ and also by the charge upon Y in the first complex $X^-\cdots CH_3Y$ which is the initial complex of all exothermic reactions. These polarizability values which are calculated by eq 5, have been used to calculate α_m^{-1} using eq 6 following Gázquez's work.[23] Figure 3 shows that in the case of Y = F, the values of the reaction energies ΔE_m and reaction energies α_m^{-1} obtained via Gázquez's approach yield fair but separate correlations for hard and soft nucleophiles X.

The range of values α_m^{-1} is, however, not large enough to account for the experimental ΔH sequence. However, the systematic negative values of α_m^{-1} indicate that the product complex $Y^-\cdots CH_3X$ has a lower polarizability (higher hardness) than the reagent complex $X^-\cdots CH_3Y$ (see Table 1). Following these trends we can assert that the exothermicity of the reaction is in the direction of forming systems with smaller polarizability. As, in general, the polarizability shows a fair correlation with the softness, the previous results are in line with the experimental data which show that the reaction always evolves in the direction of harder compounds or groups of compounds.[36,37]

Moreover, the calculations of the charges (vide supra) on Y in the ion–molecule complexes, $X^-\cdots CH_3Y$ for Y = F, Cl, and Br, as indicated in Table 2, show a good correlation with the reaction energies ($r^2 = 0.958$, 0.977, and 0.909 for F, Cl, and Br respectively) (Figures 4 and 5). The analysis of these values shows that the charge upon Y, in the complex, increases progressively when the exothermicity of the reaction increases too. The increase of the negative charge on Y when the exothermicity of the reaction increases is governed by the electronegativity difference between the nucleophile X and the leaving group Y. The relation between charges and reaction

TABLE 2: Calculated Charge *q* (in atomic units) on the Y Atom of the Complex $X^-\cdots CH_3Y$ (min1) According to the Merz−Singh−Kollman Scheme, Calculated Group Properties of the Nucleophile, X^- (for the Corresponding Radical Species), Such as the Electronegativity (χ_X) and the Softness (S_X) (in eV), the Activation Energy (ΔE_{ac}) (Calculated and Experimental) and the Calculated Reaction Enthalpy ΔH (in kcal/mol)

X^-	CH_3Y	q_Y	χ_X	S_X, 10^{-2}	ΔE_{ac}	ΔH	ΔE_{ac}(exp)
F^-	CH_3F	−0.4091	10.01	7.04	18.55	0.0	26.2
H^-		−0.4860			9.85	−57.0	16.0
OH^-		−0.4273	6.95	8.79	16.74	−14.0	9.1
$NH2^-$		−0.4449	6.16	8.28	15.13	−37.0	
HCC^-		−0.4321	8.21	8.67	25.06	−24.0	22.8
CN^-		−0.3857	8.63	9.86	30.64	−5.0	26.6
Cl^-		−0.3767	7.65	10.89	41.18	28.0	
Br^-		−0.3705			44.09	37.0	
SH^-			5.69	12.62	34.32	9.0	
F^-	CH_3Cl	−0.3888	10.01	7.04	2.99	−28.0	6.9
H^-		−0.5262			.01	−86.0	2.7
OH^-		−0.4097	6.95	8.79	1.38	−47.5	-
$NH2^-$		−0.4079	6.16	8.28	2.07	−66.1	-
HCC^-		−0.3646	8.21	8.67	7.54	−51.0	6.2
CN^-		−0.3323	8.63	9.86	11.52	−32.0	9.4
Cl^-		−0.3108	7.65	10.89	15.47	0.0	10.2
Br^-		−0.3014			16.40	8.0	15.1
SH^-		−0.3449	5.69	12.62	11.82		
F^-	CH_3Br	−0.3974	10.01	7.04	1.12	−36.7	4.8
H^-							1.9
OH^-			6.95	8.79	1.06	−55.7	
$NH2^-$		−0.4129	6.16	8.28	.50		
HCC^-		−0.3361	8.21	8.67	4.38		5.0
CN^-		−0.2946	8.63	9.86	8.19	−35.4	7.4
Cl^-		−0.3001	7.65	10.89	11.89	−8.2	9.0
Br^-		−0.2793	-	-	13.49	0	11.2
SH^-		−0.2847	5.69	12.62	8.59		

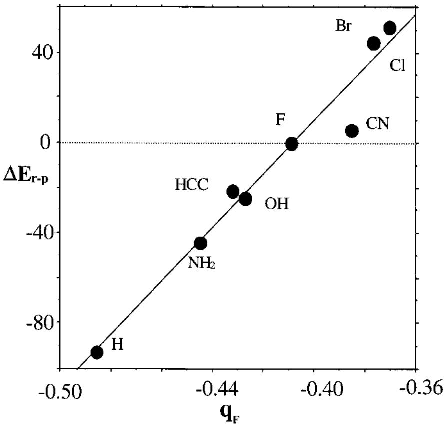

Figure 4. Calculated values of the reaction energy, ΔE_{r-p} (in kcal/mol) (see text), as a function of the charge q_F (in au) on fluorine in the ion−molecule complex, $X^-\cdots CH_3F$.

energies can be interpreted by the fact that the leaving group Y tries to increase its electronic population in order to leave the starting molecule and quickly reach its anionic form Y^- at the end of the reaction.

Thus, in general, the evolution upon reaction can be interpreted by the difference in the polarizability (softness) between the reactant and the product complexes (or between the reactants and the products) and also by the charge on the leaving group.

IIIA.2. Kinetic Study. In the gas phase the most important energetic barrier is localized between the ion−molecule complexes, $X^-\cdots CH_3Y$ and $Y^-\cdots CH_3X$, and the transition state (TS), which is known as the central barrier. As the reaction rate is determined by the step with the larger energy barrier to overcome, the central barrier height can be considered as the activation energy. This idea is supported by previous works.[22−24]

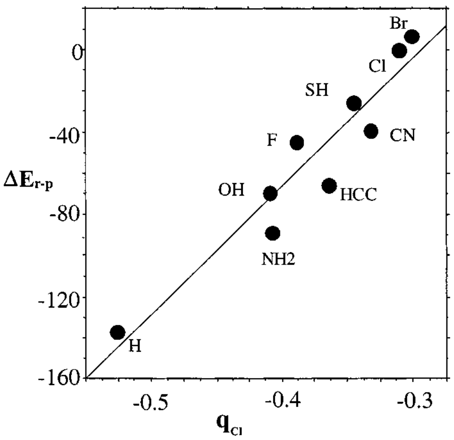

Figure 5. Calculated values of the reaction energy, ΔE_{r-p} (in kcal/mol) (see text), as a function of the charge q_{Cl} (in au) on chlorine in the ion−molecule complex, $X^-\cdots CH_3Cl$.

TABLE 3: Calculated Activation Energy (ΔE_{ac}), (in kcal/mol), the Factor Combination Proportional to the Activation Energy Calculated Using the Polarizability of the Complexes from Eq 5, α_{ac}^{-1} (in a_B^{-3}), and the Experimental Data Available for the Activation ΔE_{ac}(exp) (in kcal/mol)

X^-	CH_3Y	ΔE_{ac}	α_{ac}^{-1}	ΔE_{ac} (exp)
F^-	CH_3F	18.55	0.004238	26.2
H^-		9.85	0.001382	16.0
OH^-		16.74	0.003590	9.1
$NH2^-$		15.13	0.001842	
HCC^-		25.06	0.000358	22.8
CN^-		30.64	0.001037	26.6
Cl^-		41.18	0.002831	
Br^-		44.09	0.000870	
SH^-		34.32	0.001648	
F^-	CH_3Cl	2.99	0.002698	6.9
H^-		0.01	0.000416	2.7
OH^-		1.38	0.001926	
$NH2^-$		2.07	0.001633	
HCC^-		7.54	0.001160	6.2
CN^-		11.52	0.001900	9.4
Cl^-		15.47	0.003182	10.2
Br^-		16.40	0.001972	
SH^-		11.82	0.002222	
F^-	CH_3Br	1.12	0.001621	4.8
H^-				1.9
OH^-			0.001859	
$NH2^-$		0.50	0.001034	
HCC^-		4.38	0.001026	5.0
CN^-		8.19	0.001656	7.4
Cl^-		11.89	0.002716	9.0
Br^-		13.49	0.001888	11.2
SH^-		8.59	0.002539	

The analysis of these central barrier values, ΔE_{ac}, as indicated in Table 3 for Y = F, Cl, and Br respectively, shows a fair correlation with the experimental data available.[22] This is a reason why we did not proceed to beyond SCF (including DFT) calculations.

The sequences given by ΔE_{ac} in the case of methyl floride (CH_3F) show the following decreasing order (see Table 3):

$$Br^- > Cl^- > SH^- > CN^- > HCC^- > F^- > OH^- > NH_2^- > H^-$$

which is also the order for methyl chloride (CH_3Cl).

Finally for methyl bromide (CH_3Br) an inversion between OH and NH_2 occurs

$$Br^- > Cl^- > SH^- > CN^- > HCC^- > F^- > NH_2^- > OH^- > H^-$$

These results are in good agreement with the exothermicity of the reactions given in IIIA.1, showing that when the energetic

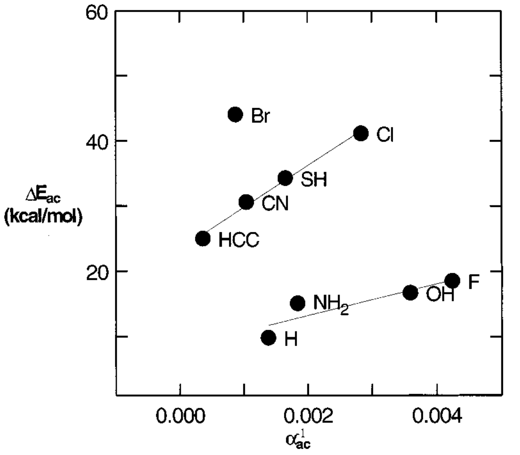

Figure 6. Calculated values of the energy of the central barrier, ΔE_{ac} (in kcal/mol), as a function of the central barrier α_{ac}^{-1} (in a_B^{-3}.) obtained via the Gázquez approach. Separate linear correlations for hard (X = H, NH_2, OH, F) and soft (X = HCC, CN, SH, Cl) nucleophiles are shown as in Figure 3.

barrier decreases the exothermicity of the reactions increases. These trends are in line with the Hammond postulate[63,64] which states that in exothermic reactions the transition state (TS) is closer to the reagents than the products, whereas in endothermic reactions the TS is closer to the products. What is more, for a given nucleophile, X^-, the calculated energetic barrier, ΔE_{ac}, decreases when going from Y = F to Br (see Table 3). Once more, these results confirm that the leaving group ability is related to softness: the softer a given leaving group the lower the energetic barrier, ΔE_{ac}.

Combining the results of kinetic and thermodynamic investigations, one arrives at the following picture on the influence of the hardness of X^- and Y on the reaction profile. The harder the X^-, the smaller the energetic barrier, the more the reaction is exothermic; for a given nucleophile, X^-, the softer the Y, the smaller the energetic barrier and the more exothermic the reaction. These trends are in good agreement with data available for nucleophilicity and leaving group ability.[26]

As was also the case for thermodynamic aspects, the kinetic results can also be interpreted in terms of the polarizability of the TS ($[XCH_3Y]^-$) and the complex ($X^-\cdots CH_3Y$) and also via the charge upon the leaving group, Y of $X^-\cdots CH_3Y$.

Again, separating hard and soft groups as in the thermodynamical discussion of the α_m^{-1} obtained via the Gázquez approach (Figure 3), we see that the values given by α_{ac}^{-1} show in general a good trend with the calculated barrier, ΔE_{ac} (Figure 6 with again Y = F). The positive values α_{ac}^{-1} of all indicate that the transition state (TS), $[XCH_3Y]^{-1}$, has always a higher polarizability (lower hardness) than the reagent complex $X^-\cdots CH_3Y$ (see Table 1).

As indicated above, the polarizability follows the same trend than the softness (inverse of the hardness), Consequently, the previous results are in good agreement with theoretical evidence showing that the transition state is the softer complex along the reaction pathway.[33,34] Following the α_{ac}^{-1} values, the lower the difference between the softnesses of the reagent complex and the TS, the smaller the energetic barrier. As the polarizability (or softness) is related to the structure of complex, these results are also in good agreement with Hammond's postulate which predicts a correlation between the structure of the reagent complex and the TS on the one hand, and the energetic barrier and the exothermicity of the reaction on the other hand.

Moreover, the calculations of the charges (vide supra) in the Y part of the ion−molecule complexes, $X^-\cdots CH_3Y$ for Y = F, Cl, and Br, given in Table 2, show a good correlation with the barrier energy (around 0.90 in the cases F and Cl, as seen in Figures 7 and 8 (cf. the thermodynamic part). The analysis of these values shows that the charge upon a given leaving group, Y, increases progressively when the energy barrier decreases. The increase of the negative charge upon Y when the energy barrier, ΔE_{ac}, decreases is governed by the electronegativity difference between the nucleophile X and the leaving group Y. The relation between charge and reaction energy can also be interpreted, as in the thermodynamic part, by the fact that the leaving group Y tries to increase its electronic population in order to leave the mother molecule and reach its anionic form Y^- at the end of the reaction.

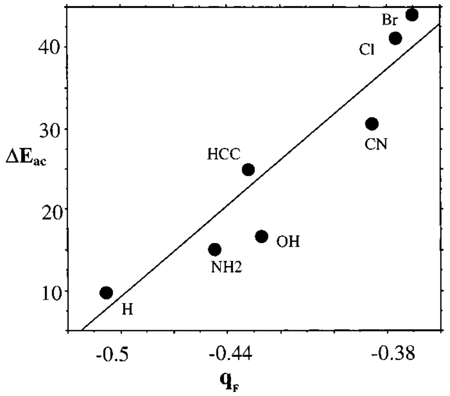

Figure 7. Calculated values of the energy of the central barrier, ΔE_{ac} (in kcal/mol), as a function of the charges q_F (in au) on fluorine in the ion−molecule complex, $X^-\cdots CH_3F$.

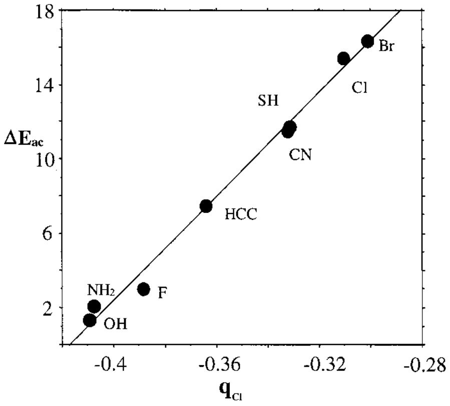

Figure 8. Calculated values of the energy of the central barrier, ΔE_{ac} (in kcal/mol), as a function of the charges q_{Cl} (in au) on chlorine in the ion−molecule complex, $X^-\cdots CH_3Cl$.

All results discussed so far show illuminating trends between the polarizability and energy-related quantities of the complexes both from the thermodynamic and kinetic point of view. There is also a good agreement between the exothermicity of the reaction (thermodynamic aspect) and the energy barrier (kinetic aspect) as shown by Hammond's postulate. The evolution of polarizability along the reaction path can finally be casted into the framework of the maximum hardness principle (MHP)

Suppose, as also done in numerous other studies,[23] that for a given ion−molecule complex the variation of chemical potential is slow as compared to the variation of its chemical hardness along the reaction pathway. Within the requirement that the external potential, $v(r)$, is also constant along this pathway, the MHP can then be applied following Gázquez's work.[23] In this sense, the MHP can used to investigate the evolution of the stabilization of the complexes when going from $X^-\cdots CH_3Y$ to $Y^-\cdots CH_3X$.

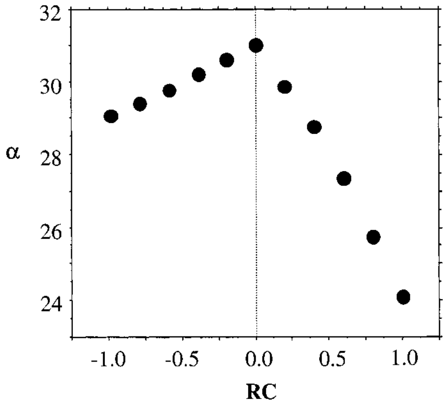

Figure 9. Polarizability, α (in au), of the complex $[H\cdots CH_3\cdots F]^-$ when going from reactants to products versus the reaction coordinate, RC. (RC range considered is between the two minima corresponding to the two ion−molecule complexes.)

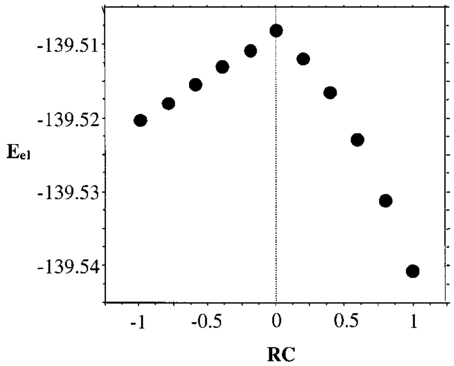

Figure 10. Electronic energy, E_{el} (in au), of the complex $[H\cdots CH_3\cdots F]^-$ when going from reactants to products versus the reaction coordinate, RC. (RC range considered is between the two minima corresponding to the two ion−molecule complexes.)

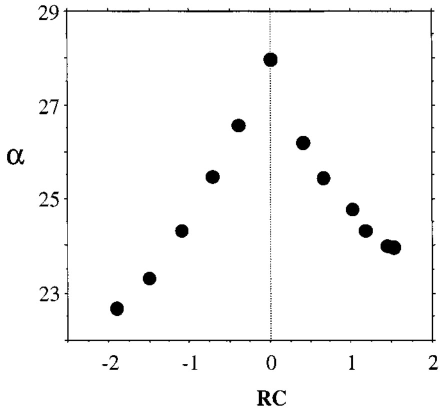

Figure 11. Polarizability, α (in au), of the complex $[F\cdots CH_3\cdots OH]^-$ when going from reactants to products versus the reaction coordinate, RC. (RC range considered is between the two minima corresponding to the two ion−molecule complexes.)

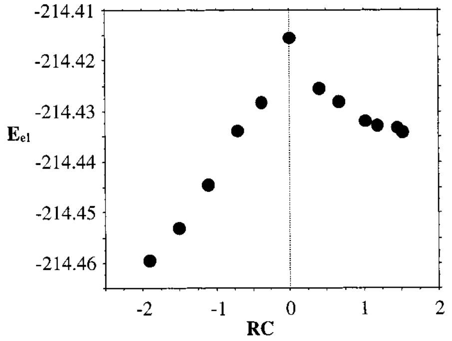

Figure 12. Electronic energy, E_{el} (in au), of the complex $[HO\cdots CH_3\cdots F]^-$ when going from reactants to products versus the reaction coordinate, RC. (RC range considered is between the two minima corresponding to the two ion−molecule complexes.)

In view of the relation between the polarizability and the softness[43] and as softness calculations for the complexes might be much more difficult than the polarizabilty evaluation (cf. section IIIA.1), we have chosen to use the polarizability instead of the softness (hardness) to apply the MHP, thereby reducing MHP to a "minimum polarizabilty principle" as was done by us in our previous work on cycloaddition reactions.[33,34]

The calculation of the polarizabilty along the reaction path as indicated in Figure 9 shows that the TS always has a maximum polarizability. The analysis of this figure for the most exothermic reaction, ($H^-\cdots CH_3F \rightarrow F^-\cdots CH_4$) shows that polarizability (softness) decreases more sharply when going from the transition state (TS) to the ion−product complexes than to the ion−reactant complexes. Following the MHP the ion−molecule complex stability is more important when going from TS to the products than to the reagents. This means that when the nucleophile approaches the carbon atom of the methyl group and simultaneously the leaving group F moves away, this complex is more stabilized than in the opposite case. This stabilization trend is supported by the energy of the complexes which gives the same trend along the reaction coordinate as shown in Figure 10.

In the same way, if we consider an endothermic reaction ($F^-\cdots CH_3OH \rightarrow OH^-\cdots CH_3F$), as shown in Figure 11, the polarizability (softness) decreases more sharply when going from TS to the reactants than in the exothermic direction in which the complex becomes more and more stable as indicated by the MHP. This trend is also supported by the stabilization energy as shown in Figure 12. This result is confirmed for all reactions investigated in this work, except for some complexes with Br and SH.

From Gázquez's formula we can deduce an important result: $\alpha_m{}^{-1}$ is negative if the polarizability of the reactants is larger than the polarizability of the products. If the products are harder than the reactants, the reaction follows the direction in which the products will be as hard as possible following the idea of the MHP principle. For example, the reaction $H^-\cdots CH_3F \rightarrow F^-\cdots CH_4$ is exothermic (experimental value $\Delta G_R = -57$ kcal/mol). Figure 9 clearly indicates that the polarizability of the reactants is superior to that of the products, yielding via Gázquez's equation $\alpha_m{}^{-1} < 0$.

Figure 11 on the other hand gives the hardness profile of the endothermic reaction ($F^-\cdots CH_3OH \rightarrow OH^-\cdots CH_3F$) ($\Delta H = 14$ kcal/mol). From this figure we can deduce that the polarizability of the products is superior to that of the reactants and from Gázquez's formula we obtain that the reaction is thermodynamically favorable in the opposite direction.

In conclusion, the hardness profile turns out to be a very important tool to describe both thermodynamic and kinetic aspects of the S_N2 reaction.

IIIB. Solvent Effects. *IIIB.1. Protic and Dipolar Aprotic Solvent Effects on Reaction Rates of* S_N2 *Reactions of the Type* $Cl^- + CH_3I \rightarrow I^- + CH_3Cl$. For S_N2 reactions involving anionic nucleophiles a change from protic to aprotic solvent causes an increase in rate constant. The typical example is the reaction

$$Cl^- + CH_3I \rightarrow I^- + CH_3Cl \tag{16}$$

for which the experimental[65] and calculated activation energy in several solvents are reported in Table 4.

TABLE 4: Calculated Activation Energies ΔG^*(TS) and the Experimental Relative Rates[65] in Different Solvents for the Reaction $CH_3I + Cl^- \rightarrow I^- + CH_3Cl$[a]

solvent	ϵ_r	ΔG^*(TS) (kcal/mol)	ln ($k^{solvent}/k^{MeOH}$)
acetone	20.56	28.77	6.2
DMSO	46.45	30.40	4.6
methanol	32.66	33.24	0
water	78.30	34.12	0.08

[a] ϵ_r is the dielectric constant for the pure liquid at 25 °C.

TABLE 5: Softness for CH_3, I^-, and Cl^- Calculated in Various Solvents (All Values in eV) (I^- and Cl^- Are Taken as the Neutral Radical Values[37])[a]

solvent	ϵ_r	$S(CH_3)$	$S(Cl^-)$	$S(I^-)$
acetone	20.56	0.1474	0.1483	0.2121
DMSO	46.45	0.1509	0.1521	0.2190
methanol	32.66	0.1647	0.1734	0.2567
water	78.30	0.1679	0.1776	0.2652

[a] ϵ_r is the dielectric constant for the pure liquid at 25 °C.

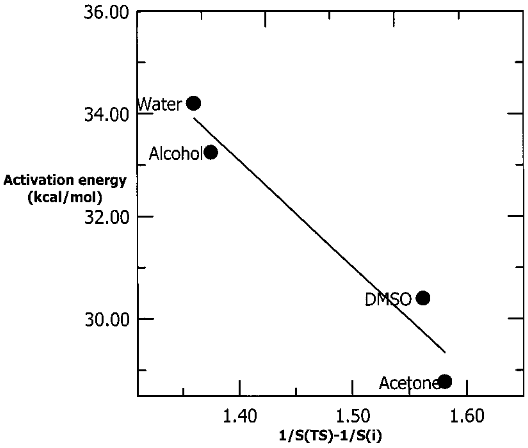

Figure 13. Correlation between the activation energy ΔE_{ac} (in kcal/mol) given in Table 4 and the "hardness difference term" (eq 4).

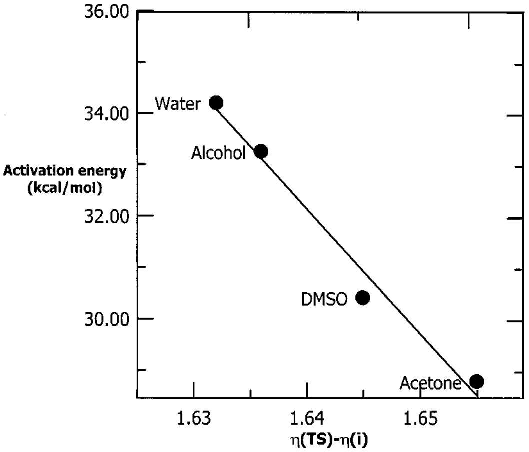

Figure 14. Correlation between the activation energy ΔE_{ac} (in kcal/mol) given in Table 4 and the "softness difference term" using the frontier orbitals (HOMO and LUMO) (eq 17).

In this table it can be seen that the effects when passing from a protic solvent to an aprotic solvent are spectacular. S_N2 reactions in solvents like dimethyl sulfoxide or acetone go faster than in an alcohol. Solvation of the anion is of overriding importance: the more strongly it is solvated relative to the transition state the slower the reaction. The strongest solvation of anions, we know, is through hydrogen bonding which is possible for protic solvents but not for aprotic solvents; they leave the anion relatively free and highly reactive. In our case the nucleophile Cl^- is more solvated by water and alcohol than acetone and DMSO leading to a decrease in the rate of reaction in protic solvents.

In this paper we will show that the activation energy in different solvents depends on the difference between the hardness of the reactants and the hardness of the transition state. To make use of eq 4, we suppose that the softness values for the reactants and for the molecular fragments in the transition state can be determined using the methodology described in our earlier work.[16] Using eq 14 we calculated the softness of the halide groups in different solvents with varying dielectric constant ϵ and with IE(ϵ) and EA(ϵ) respectively the ionization energy and the electron affinity of the corresponding radicals, as suggested by Pearson[37] (see Table 5).

As an example, we take reaction 16 which is of the type (1) with X = I and Y = Cl. In this case the reactants are Cl^- and CH_3I and the molecular fragments in the transition state are Cl^-, CH_3, and I^-; the softness of the group CH_3 is taken from ref 16; the softness of Cl^- and I^- are evaluated with the same methodology in ref 16.

Figure 13 gives the correlation between the activation energy in different solvents reported in Table 4 and the difference between the softness of reactants and the transition state, according to eq 4. We clearly see that the activation energy decreases when changing from a protic solvent such as water and alcohol to an aprotic solvent as acetone and DMSO.

The correlation between the activation energy and the "softness difference term" in Figure 13 points to the same direction as the HSAB principle.[3] In our case we know that protic solvents such as water and alcohol are very hard because they contain acidic, highly positive hydrogen atoms. Using the HSAB principle, hard anions are better solvated by hard (hydrogen bonding) solvents and soft anions have strong interactions with soft solvents (dipolar, non hydrogen bonding donors). The Cl^- anion will thus be more solvated in water and alcohol than in acetone and DMSO, yielding an increase of the activation energy and decreasing reactivity of the anion when passing from dipolar aprotic to dipolar protic solvents.

We know that the hardness can be calculated approximately by using the values of the highest occupied (HOMO) and the lowest unoccupied molecular orbitals (LUMO), eq 4 then can be written as

$$\Delta E_{ac} = \frac{1}{2}((\epsilon^{TS}_{LUMO} - \epsilon^{TS}_{HOMO}) - (\epsilon^{i}_{LUMO} - \epsilon^{i}_{HOMO})) \quad (17)$$

Figure 14 gives the correlation between the activation energy and the eigenvalues of the highest occupied (HOMO) and the lowest unoccupied molecular orbitals (LUMO) in different solvents for reaction 16.

A very good correlation is observed confirming that the activation energy increases when passing from an aprotic solvent to a protic one. In conclusion, the frontier orbitals play a crucial role to describe reactivity. Equation 17 shows that for all solvents the lowest value of the HOMO−LUMO gap occurs at the transition state, pointing into the same direction as the MHP.

IIIB.2. Comparing the Effect of the Nucleophile in the Gas Phase and in Solvent. We now concentrate on the influence of solvation on the nucleophilicity and so on the kinetics of the S_N2 reaction in the gas phase and in solution with X = F, I, and Y = Br. Table 6 gives the activation energy for this reaction with various halide ions $X^-$and in water calculated with the PCM model using the Hartree−Fock level.

TABLE 6: Calculated Activation Energies ΔG*(TS) in Water for the Reaction $X^- + CH_3 \rightarrow Y^- + CH_3X$ with X = F, I and Y = Br

nucleophile	ΔG*(TS)[a] (kcal/mol)	ΔG*(TS)[b] (kcal/mol)
F^-	7.35	58.10
I^-	38.47	23.76

[a] Calculated using the PCM model. [b] Calculated using the PCM model and using eq 18.

In the gas phase, the reactivity of halide ions is $F^- > I^-$, reflecting the strength of the C−X bond being formed. Yet experimentally, one finds in water and methanol[66] that the order of reactivity is reversed.

In Table 6 it can be seen that we do not obtain the same sequence as in the experimental one. This has been explained by the fact that reaction field theory is appropriate only for solvents which do not lead to specific interactions, such as hydrogen bonding, with the solute. Thus, it is not surprising that the effect of water is not reproduced. Indeed, liquids possessing hydroxyl groups or other groups with a hydrogen atom bound to an electronegative atom are strongly associated.

Hydrogen bonding plays a crucial role in the interactions between ions and HBD solvents. Hence HBD solvents are good anions solvators. Because of the small size of the atom, small anions like F^- and Cl^- are more solvated by such solvents than the larger ones, e.g., I^-. This is also the reason why the Gibbs energy of hydration, ΔG_{solv}, of the halide ions increases in the series $F^- > I^-$.

Our calculation of the activation energy in water for the reaction (X = F, I, and $Y = Br^-$) does not agree with experiment. To solve this problem, we must take into consideration the interaction energy caused by the hydrogen bond.

We recalculated the activation energy in water according to the following procedure.

$$\Delta G^* = G[\mathrm{TS}]_W + 4G[\mathrm{H_2O}]_W - G[\mathrm{I^-(H_2O)_4}]_W - G[\mathrm{CH_3Br}]_W \quad (18)$$

where $G[X]_W$ denotes the calculated free energy of formation for the species X (TS, ion water complex $I^-(H_2O)_4$, a water molecule, and the reactant CH_3Br) in the aqueous medium. The stoichiometry of this complexation reaction has been chosen in this way on the basis of the results in ref 67.

Table 6 gives the final activation energy for the reactions (X = F, I, and Y = Br) obtained via eq 18. The order of reactivity is now reversed and becomes $I^- > F^-$.

So, whereas the self-consistent reaction field theory provides a useful and computationally efficient model for the study of solvent effects, the model should be corrected for solvents giving hydrogen bonding with the reactant.

When explaining the inversion when we go from the gas phase to a protic solvent, we must as always compare the reactant with the transition state, including the effect of the solvent in the protic solvent case. In the rate-determining step of an S_N2 reaction we must take into account the two reactants, the alkyl halide and the halide ion; the latter carries a full negative charge, and binds to the solvent; the alkyl halide has a dipole moment and interacts via a dipole−dipole mechanism with the solvent. The transition state carries a full negative charge too, but the charge is very dispersed. Bonding of the solvent to this dispersed charge carrier is much weaker than to the concentrated charge of the small halide ion. Table 7 gives the calculated solvation energy for the halide ions and for the transition states. In this table, one can see that the solvatation energy for the transition state is much weaker than that for the halide ions.

The strength of solvation varies from one anion to another. Fluoride is the smallest halide, with the most concentrated charge; as we can see in Table 7, it forms the strongest ion−dipole bonds hydrogen bond in water and methanol. I^- is the biggest of these halides, with a dispersed charge leading to the smallest solvation.

IV. Conclusions

In the gas phase the reaction energies, ΔE_m and ΔE_{r-p}, and the central barrier energies (involving the ion molecule complexes) ΔE_{ac}, for the reaction $X^- + CH_3Y \rightarrow Y^- + CH_3X$ with $X^- = F^-, H^-, OH^-, NH_2^-, HCC^-, CN^-, I^-, Cl^-, Br^-$, and SH^- and $Y^- = F^-, Cl^-$, and Br^-, calculated at the Hartree−Fock level using the 6-31+G* basis set, show the same trend as the experimental data available. In general the reaction energies, and the same trend as the experimental data available. In general, the reaction energies α_m^{-1} and the central barrier α_{ac}^{-1} calculated using Gázquez's equations with polarizability instead of softness, reproduce the ab initio calculated values.

The variation of the exothermicity and the central barrier of the reaction with X and Y can be interpreted in terms of the hard and soft acids and bases principle (HSAB). The leaving group ability parallels its polarizability (softness); the more the leaving group is soft, the more its ability to leave the mother molecule increases. The charges, which are a measure of the electronegativity of Y, in the complexes, increase progressively when the exothermicity of the reaction increases and the central barrier energy decreases. The maximum hardness principle, MHP, applied in the gas phase, and with replacement of the softness by the polarizability, yields a firm basis to discuss the energy stabilization and the determining role of the ion−molecule complexes along the reaction pathway.

The polarizable continuum model (PCM) has been used to study the influence of the solvent on the kinetics of the S_N2 reaction. The application of Gázquez's formula provides fundamental information in a case study, with X = Cl and Y = I: the activation energy yields a very good correlation with the values obtained with Gázquez's formula. The influence of solvation on the nucleophilicity and the kinetics using the (PCM) model with (X = F, I and Y = Br) is compared with the results in the gas phase. The order of reactivity is $F^- > I^-$, which is the same order as in the solvent using the polarizable continuum model but opposed to experiment. If however we take into consideration the interaction energy caused by the hydrogen bond the order of reactivity in solution is reversed yielding the same results as experiment.

TABLE 7: Solvation Energy for the Nucleophile and the TS Calculated in Different Solvents (All Values in kcal /mol)

solvent	F^-	Cl^-	I^-	$Br\cdots CH_3\cdots F$	$Br\cdots CH_3\cdots Cl$	$Br\cdots CH_3\cdots I$
acetone	−93.64	−67.33	−56.76	−57.13	−52.53	−48.34
DMSO	−96.20	−69.07	−58.46	−58.05	−53.62	−49.43
alcohol	−111.28	−78.95	−66.36	−73.38	−53.53	−41.77
water	−112.93	−79.76	−66.81	−69.15	−44.16	−41.16

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