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ANALYSIS OF SOLVENT EFFECT ON S_N2 REACTIONS BY DIFFERENT THEORETICAL MODELS

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ABSTRACT

The solvent effect on two S_N2 reactions was evaluated by discrete, continuum and discrete–continuum models. The potential energy profiles were found to change dramatically on introduction of the solvent effect. The double-well shape which characterizes the $F^- + CH_3F \rightarrow FCH_3 + F^-$ reaction in the gas phase becomes unimodal when the solvent is introduced, in good agreement with experimental data. The solvation parameters are found to intervene in the reaction coordinate. Recent Monte Carlo and molecular dynamics calculations are discussed.

INTRODUCTION

The S_N2 nucleophilic substitution reaction is one of the central reactions of organic chemistry. It is well known experimentally that this process is very sensitive to solvent effects. In fact, the behaviour it exhibits when it is carried out in the gas phase is completely different from that in solution. The solvent is found to change both the reaction rate and the mechanism. In solution, the rate constant decreases by up to 20 orders of magnitude and the energetic profile, which has a double-well shape in the gas phase, becomes unimodal.[1–8]

Analysis of the different factors that determine the effect of the solvent on chemical reactions has been one of the leading goals of physical organic chemistry. However, the theoretical modelling of the solvent has presented (and still presents) many difficulties. Several models have been proposed that correspond fundamentally to two options: a discrete representation of the solvent, the molecules of which are each treated as an entity,[9] and a continuum representation of the solvent, which is characterized by macroscopic magnitudes.[10] For a long time discrete models were restricted to include a very limited number of solvent molecules,[9] but more recently Monte Carlo and molecular dynamics techniques allow a fairly large number of molecules to be considered.[11] In continuum models the initial treatment in which solute polarization was not taken into account has been modified and now the reaction field feedback effect is often introduced.[10]

Owing to the dramatic effect of the solvent on S_N2 reactions, these processes have been the most often studied with different theoretical methods. In pioneering work, Ingold[12,13] interpreted the increase in the reaction barrier in solution starting from qualitative considerations by using a continuum model for the solvent. He stated that when ionic species

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intervene in an S_N2 reaction, one of the reactants has a localized charge, whereas the transition state exhibits a diffuse charge distribution. Thus, a polar solvent causes greater stabilization of the reactants, leading to a barrier increase. Later, Parker[14] pointed out that specific interactions, such as hydrogen bonding or the solvent reorganization energy, are of great importance when the reaction takes place in strongly structured solvents. Initial desolvation of the nucleophile has also been invoked as one of the factors that account for the barrier.[15]

Carrion and Dewar[16] stressed two other points. On the one hand, intermediate and transition state formation is unfavoured from an entropic point of view, since there is cancellation between the ΔH and $-T\Delta S$ terms, so the double-well profile disappears and a free-energy unimodal shape is obtained. On the other hand, the ion–dipole stabilization of the reactant system in strongly polar solvents is compensated for by the energy loss associated with the ion–solvent complex cleavage. Shaik[17,18] remarked that the S_N2 reaction is a charge-transfer process, and that the charge migration during the reaction must be accompanied by a large solvent reorganization.

Using the discrete model for the solvent, the S_N2 reaction has recently been the subject of a variety of more quantitative studies. Several calculations with a reduced number of solvent water molecules have been carried out.[19–21] However, they represent the experimental situation of a gas-phase cluster reaction rather than a process in solution. Further, the contribution to the activation barrier of the bulk solvent reorganization has not been taken into account. In a series of recent studies,[22–30] a large number of water molecules have been incorporated and the effect of solvent reorganization has been evaluated. The main magnitude calculated was the variation in free energy of activation within the framework of the activated complex theory, where the hypothesis that the solvent is in equilibrium with the reactants and activated complex has been implicitly assumed. In particular, the work by Jorgensen and co-workers[26–29] is especially relevant. Through *ab initio* calculations, the interaction potential between one water molecule and the chemical system at every point of the reaction coordinate was computed. This allowed Monte Carlo simulations of 250 water molecules along different points of the reaction coordinate, using the characteristic pairwise approximation of this kind of calculation. A unimodal free-energy profile was obtained, whose barrier agrees well with experience. The barrier increase on going from the gas phase to solution was attributed to a larger solute–solvent interaction in reactants than in the transition state, partially compensated for by greater breakage of the solvent structure. According to that study, the differential solvation effect is caused by the decreased strength rather than the number of hydrogen bonds for the transition state as compared with the reactants. Finally, in a recent work by Bash *et al.*,[30] the reaction field feedback effect was included in the hamiltonian of the chemical system through use of semi-empirical methods. This allowed the study of the solvent effect in the charge-transfer process which characterizes this reaction.

Recent studies [31–33] have indicated a new aspect of solvent intervention in the S_N2 reaction. The fast charge transfer about the transition state produces a supplementary force owing to the absence of solvent relaxation, which opposes the advance of the reaction. Molecular dynamics calculations have shown that, in contrast to what happens in the gas phase, a large proportion of the trajectories recross the barrier in solution. This fact throws doubt on the application of the activated complex theory to the S_N2 reaction in solution. An interesting aspect of these results is the correlation between the trajectories which recross the barrier and the local configuration of the solvent.[31] More recently, Hwang *et al.*[34] examined and discussed in more detail the influence of solvent fluctuations in this kind of reaction.

In the above brief review of theoretical studies on the S_N2 reaction in solution, it appears that, to our knowledge, no accurate quantitative calculations that use a continuum model have

yet been made. The purpose of this work was to study the S_N2 reaction in solution through different representations of the solvent: discrete, continuum and discrete–continuum. Comparison of the results obtained with these theoretical models will allow a deeper insight into some of the aforementioned fundamental factors which determine the effect of the solvent. In particular, two different S_N2 reactions will be considered:

$$F^- + CH_3F \rightarrow FCH_3 + F^- \quad (1)$$

and

$$H_2O + CH_3OH_2^+ \rightarrow H_2OCH_3^+ + H_2O \quad (2)$$

The first process is a typical S_N2 reaction, in which the nucleophile is an anion, whereas the second is an example of a less usual S_N2 reaction, in which the nucleophile is a neutral molecule and the positive charge is supported by the attacked species.

METHODOLOGY

All calculations were carried out with an *ab initio* method at the RHF–SCF level. The diffuse function-augmented 3–21 + G basis set,[35] which has been shown to be necessary to describe anions adequately, was used for reaction (1), whereas the 3–21G basis set[36] was employed for reaction (2). The use of these basis sets allows the amount of computing time to be kept within reasonable limits.

For gas-phase and solvent discrete representation calculations, intermediates were located through full geometry optimization. Further, transition states were located in the full potential energy hypersurface and characterized by the existence of a single negative eigenvalue of the Hessian matrix.

For gas-phase structures of reaction (1), the Gibbs free energy was also evaluated. For this purpose, ΔH^0, ΔS^0 and ΔG^0 values, including zero-point energies, were calculated. The partition functions provided by the statistical thermodynamic equations within the ideal gas, rigid rotor and harmonic oscillator approximation were utilized. Harmonic vibrational frequencies were obtained by diagonalization of the mass-weighted second-derivative matrix. A pressure of 1 atm and a temperature of 298·15 K were assumed thoroughout.[37]

With respect to the discrete representation, the solvent was modelled by two water molecules, one solvating the entering nucleophile and the other solvating the leaving group. This is the simplest model that can be considered to introduce the solvent effect. Stationary points (intermediates, reactants and transition states) were relocated and correctly characterized in the new full potential energy hypersurface. It should be noted that for each stationary point, the positions of the entering and leaving group solvating molecules are optimized.

Regarding the continuum representation of the solvent, we applied it only to the stationary points (intermediates, reactants and transition states) obtained in gas-phase calculations. We chose the model of Tomasi and co-workers,[38,39] which represents the solvent by a continuous polarizable dielectric with permittivity ε (e.g. $\varepsilon = 80$ for water). In this model, the solute is placed inside a cavity accurately defined by its own geometry.[40] Dielectric polarization due to the solute is simulated by the creation of a system of virtual charges on the cavity surface. The charge distribution on the surface polarizes in turn the charge distribution in the solute. This process is iterated until self-consistency in the solute electron density is obtained. The electrostatic contribution to the solvation energy is obtained as the difference between the energies computed with the continuum model and without it. Moreover, the cavitation free energy is calculated with Pierotti's equation.[41]

Finally, the discrete–continuum model was taken into account by applying the continuum model to the stationary points found in the aforementioned discrete representation of the solvent with two water molecules.

RESULTS AND DISCUSSION

Since the ultimate goal of this work was to study the effect of the solvent on reactions (1) and (2), we have to investigate first how the basis sets employed describe the two-gas phase processes. Therefore in the first section we discuss the results obtained for the gas-phase reaction, in the second the results for the discrete representation of the solvent, in the third the results for the continuum model and in the fourth the discrete–continuum representation of the solvent.

Gas-phase study

The potential energy profile obtained for reaction (1) with the 3–21 + G basis set reproduces correctly the well known double-well shape (Figure 1a) with a symmetrical transition state whose imaginary frequency is 567 i cm^{-1}, very close to that obtained for a related reaction.[42] Use of this basis set decreases noticeably the well depth of the intermediate with respect to the 3–21G basis set.[21] However, the well depth is still overestimated, as can be seen if compared with high-level *ab initio* calculations.[43,44] In contrast, the energy barrier defined between the intermediate and the transition state is well described with respect to high-level results. Obviously, the excessive stabilization in the intermediate leads the transition state to lie below the separated reactants. The energetic profile for reaction (2) (Figure 1b) found with the 3–21G basis set also leads to a double-well shape. This reproduces previous studies with the same basis set.[45] Comparison with results obtained with a more extended basis set[46] shows an overestimation of the well depth by the 3–21G basis set, analogously to reaction (1).

To test if the double-well minimum disappears on calculation of the Gibbs free energy, as Dewar proposed owing to cancellation between energetic and entropic terms, the various components of ΔG^0_{298} for the gas-phase reaction (1) are collected in Table 1. No meaningful changes are found if ΔH^0 values are considered instead of ΔE, that is, if zero-point and thermal corrections are included. In contrast, incorporation of entropic contributions decreases the well depth of the intermediate by ca 7 kcal mol^{-1}. This result is in good agreement with

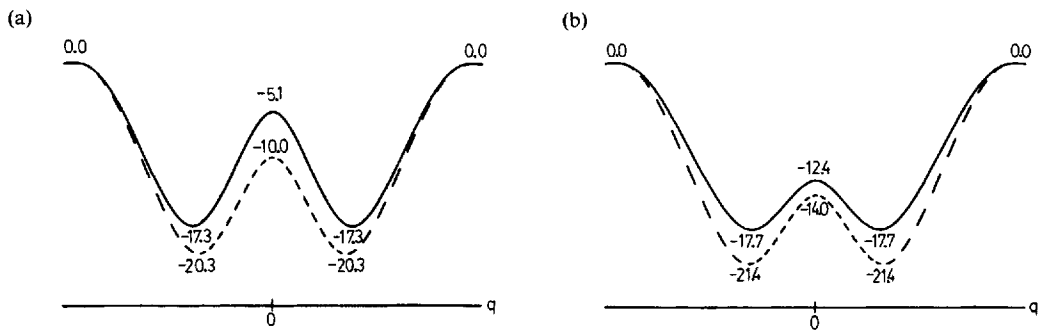

Figure 1. Potential energy profiles (kcal mol^{-1}) vs reaction coordinate q for (a) reaction (1) and (b) reaction (2). Continuous lines, gas-phase reactions; dashed lines, discrete representation for the solvent. For definition of q, see text. Energies relative to reactants are given in kcal mol^{-1}.

Table 1. Contributions to ΔG^0 relative to separated reactants for different species involved in the gas-phase reaction (1)

Species	ΔE^a	$\Delta E_t^{a,c}$	ΔH^a	ΔS^b	$-T\Delta S^a$	ΔG^a
Reactants	0	0	0	0	0	0
Intermediate	−17·3	1·7	−16·2	−22	6·6	−9·6
Transition state	−5·1	0·8	−4·9	−26	7·8	2·9

[a] In kcal mol^{-1}.
[b] In e.u.
[c] Thermal energies including zero-point energy and vibrational excited states and rotational contributions.

those of a similar study of the S_N2 reaction between ethyl fluoride and the fluoride anion.[42] Entropic terms do not change meaningfully the barrier between the intermediate and the transition state. There is partial compensation of enthalpic and entropic terms between the intermediate and reactants, but it is not strong enough to make the well disappear, even if one considers that the well depth is overestimated with our 3–21 + G calculations.

Discrete representation of the solvent

The energetic profiles for reactions (1) and (2) where one water molecule is attached to each fluorine are presented in Figure 1a and 1b (dashed lines). Comparison with the gas-phase profiles is different for each reaction: both cases exhibit an increase in the well depth of the intermediate, but the barrier between the intermediate and the transition state decreases for reaction (1) and increases for reaction (2). In both reactions the transition state is found to be even lower in energy with respect to reactants than in the gas-phase case. These results conflict with those found in a previous study of reaction (1),[21] where both the intermediate and the transition state were destabilized on introduction of two water molecules. We think that the difference may be due to the poor description of the fluoride anions provided by the 3–21G basis set. In the previous work,[21] the introduction of the two water molecules accounted for a pseudo-extension of the basis set, which caused a larger stabilization effect in the reactants than in the intermediates or the transition state.

To obtain a deeper insight into the different behaviour between reactions (1) and (2), Table 2 gives the main geometrical parameters of the stationary points (reactants, intermediates and transition state). The reaction coordinate q is defined as the difference between R_2 (leaving group–carbon distance) and R_1 (entering group–carbon distance). R_3 is a measure of the distance between the entering group and its solvating water molecule and R_4 similarly for the leaving group. Precise definitions and orientations of the water molecules are given in the representation of the transition states in Figure 2.

Considering the values for the intermediates, one can see that for reaction (1) the first intermediate is found later in the reaction coordinate with respect to the gas-phase case. In contrast, for reaction (2) the first intermediate is found earlier in the reaction coordinate. It is now possible to understand the different behaviours of the variations in the barriers between the intermediates and transition states on introduction of the water molecules: for reaction (1) the intermediate is found later in the reaction coordinate when two water molecules are included, so the barrier must decrease. In contrast, for reaction (2) the intermediate is found earlier in the reaction coordinate, hence the barrier must increase. The different displacement in q for the intermediates in reactions (1) and (2) may be found in the different solvations of

Table 2. Values of the four main interatomic distances (in Å) and the reaction coordinate q, as defined by $R_2 - R_1$ (see text), for reactions (1) and (2) in the gas phase and with a discrete representation for the solvent

Reaction and species	q	R_1	R_2	R_3	R_4
$F^- + CH_3F$ reaction:					
Reactants	$-\infty$	∞	1·434		
Intermediate	−1·091	2·575	1·484		
Transition state	0	1·872	1·872		
$OH_2 \cdot F^- + CH_3F \cdot H_2O$ reaction:					
Reactants	$-\infty$	∞	1·440	1·431	1·862
Intermediate	−1·012	2·507	1·495	1·481	1·759
Transition state	0	1·874	1·874	1·569	1·569
$H_2O + CH_3OH_2^+$ reaction:					
Reactants	$-\infty$	∞	1·540		
Intermediate	−0·891	2·474	1·583		
Transition state	0	1·941	1·941		
$H_2O \cdot H_2O + CH_3OH_2^+ \cdot OH_2$ reaction:					
Reactants	$-\infty$	∞	1·511	2·791	2·435
Intermediate	−0·939	2·490	1·551	2·687	2·476
Transition state	0	1·924	1·924	2·595	2·595

Figure 2. Structures of the transition states of (a) reaction (1) and (b) reaction (2) for the discrete representation of the solvent. Numbers indicate the main transition vector components for several internal coordinates, positive when the values increase (↔) and negative when they decrease (→ ←)

the entering and leaving groups: whereas for reaction (1) the arrangement of the hydrogen bond leads the water molecules to withdraw electron charge from the fluorine atom, in reaction (2) the water molecule releases electron charge to the nucleophile groups. Hence, in reaction (1) there is a decrease in the nucleophilic character of the entering fluoride, so the intermediate is found later in q. In contrast, in reaction (2) the nucleophilic character of the entering group is increased, so the intermediate is found earlier in the reaction coordinate. Finally, if we consider the R_1 and R_2 values in transition states, the difference in R_1 between the gas-phase and solvated cases for reaction (1) is very small. The very small increase (0·002 Å) can be compared with that found in a similar reaction.[29]

A surprising result found in our study of reactions (1) and (2) is that the introduction of two water molecules does not destabilize the intermediate and transition state with regard to reactants. Let us now analyse the hydrogen bond strength on each stationary point of reaction (1). The calculated stabilization of the fluoride anion solvated by one water molecule is 28·9 kcal mol^{-1}. This can be compared with the experimental value of 23 kcal mol^{-1}.[47,48] In the other reactant, methyl fluoride, the theoretical stabilization energy is calculated to be 6·5 kcal mol^{-1}. Hence the formation of the two hydrogen bonds in the reactants involves 35·4 kcal mol^{-1}. In the intermediate, the sum of the two hydrogen bonds is calculated to be 38·4 kcal mol^{-1}. Finally, in the transition state the value is 40·1 kcal mol^{-1}. Therefore, the increased stabilization due to hydrogen bonds on going from the reactants to the intermediates

and the transition state accounts for the increasing stabilization in this process. In the transition state, each hydrogen bond contributes 20·05 kcal mol^{-1} to the stabilization energy. One of them has decreased 8·85 kcal mol^{-1} from the reactants, but the other has increased 13·55 kcal mol^{-1}. Although these results may depend on the basis set employed, we think that the reduction in solvation energy on going from the reactants to the transition state, which has been found experimentally and theoretically calculated in various studies, cannot be attributed to a change in the strength of hydrogen bonds, but rather to a modification in their total number.

As seen in the preceding paragraph, the use of only two water molecules to model the solvent does not allow the experimental changes in the energy profile when solvent is introduced to be interpreted. However, it is especially suitable for investigating the participation of solvation parameters in the reaction coordinate. In a previous study of reaction (1) with the 3–21G basis set,[21] we found an important participation of solvation parameters in the reaction coordinate. One might think that such a study without diffuse basis functions to represent anions is questionable. If we consider Table 2, it can be seen that R_3 and R_4, which are the solvation parameters, have very different values in the reactants. Their values must obviously change in the final products. In fact, in Table 2 it can be seen that R_3 increases smoothly from the reactants to the transition state, whereas R_4 decreases. Hence there is an expansion of the first solvation shell in the entering group, with a simultaneous contraction of the first solvation shell in the leaving group, in parallel with the charge transfer from the entering group towards the leaving group. The participation of the solvation parameters in the reaction coordinate can also be observed from the main components of the transition vector depicted in Figure 2a. It can be seen that in addition to the components of the parameters adopted to define the reaction coordinate in the gas phase, the solvation parameters are also important components of the transition vector. For reaction (2), all of the aforementioned statements on solvation distances and solvent components in its transition vector (Figure 2b) are very similar. Therefore, in charge-transfer S_N2 reactions the solvation parameters are an important part of the reaction coordinate.

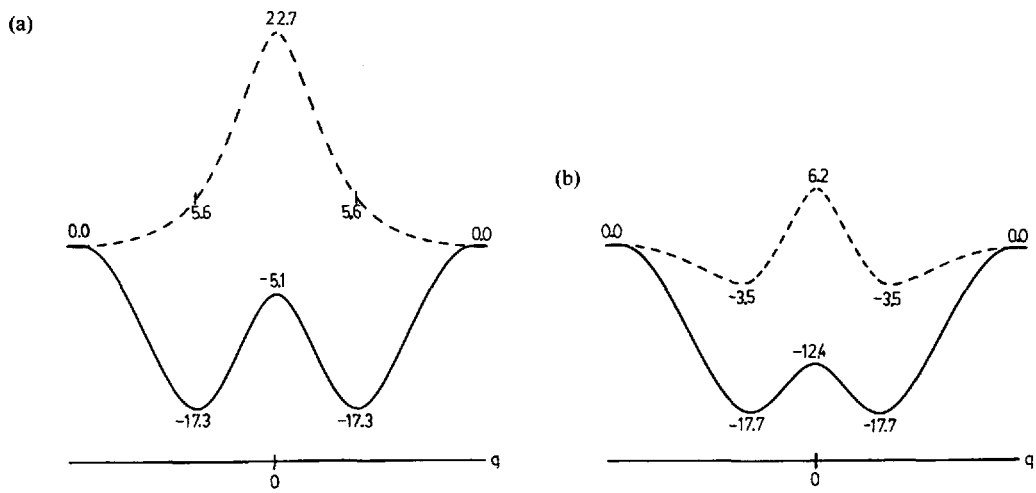

Figure 3. Potential energy profiles (kcal mol^{-1}) vs reaction coordinate q for (a) reaction (1) and (b) reaction (2). Continuous lines; gas-phase reactions; dashed lines, continuum representation for the solvent. For definition of q, see text. Energies relative to reactants are given in kcal mol^{-1}

Continuum representation of the solvent

Figure 3 shows the energetic profiles obtained on introduction of the solvent effect by the continuum model explained above on the stationary points of the gas-phase reactions (1) and (2). It should be noted that the reaction profile in solution was obtained by adding the electrostatic component of the solvation free energy to the gas-phase values. Obviously, other components exist that would contribute to the true ΔG^0 values. We calculated only the additional term related to the formation of the cavity in the bulk liquid, computed according to Pierotti's equation. All values obtained for reactions (1) and (2) are summarized in Table 3. It appears that the calculated $\Delta G'_{sol}$ and the experimental values agree fairly well. For instance, the calculated value of $\Delta G'_{sol}$ of the fluoride anion ($-93{\cdot}3$ kcal mol^{-1}) can be compared favourably with the experimental fluoride solvation free-energy values, which range between 81 and 128·7 kcal mol^{-1}.[49]

If we consider reaction (1) (Figure 3a), the decrease in free energy on going from the reactants to the intermediate and the transition state produces a dramatic change in the energy profile of the reaction. The double-well minimum shape becomes unimodal, in close agreement with experiment. These results can be compared with those obtained through Monte Carlo calculations.[26–29] In both our model and the Monte Carlo treatment it is assumed that the solvent is in equilibrium with the chemical system at each point along the reaction coordinate. The influence of the solvent is very similar in both cases with regard to the destabilization of the transition state. The main difference in the unimodal profiles in solution is that ours is broader whereas the Monte Carlo result is sharper. We must stress that, in contrast to our calculations with the continuum model, the Monte Carlo study does not introduce the solute polarization due to the solvent. Hence, it does not represent correctly the new charge

Table 3. Values of the electrostatic contribution to the free energy (ΔG_{el}), free energy of cavitation (G_{cav}) and their sum ($\Delta G'_{sol}$) (kcal mol^{-1}) for reactions (1) and (2) with a continuum and a discrete–continuum representation for the solvent

Reaction and species	ΔG_{el}	G_{cav}	$\Delta G'_{sol}$
$F^- + CH_3F$ reaction:			
F^-	−97·4	4·1	−93·3
CH_3F	− 6·8	7·3	0·5
Intermediate	−81·3	9·1	−72·2
Transition state	−76·4	9·1	−67·3
$OH_2 \cdot F^- + CH_3F \cdot H_2O$ reaction:			
$F^- \cdot H_2O$	−81·2	6·8	−74·4
$CH_3F \cdot H_2O$	−13·7	10·3	−3·4
Intermediate	−72·7	15·1	−57·6
Transition state	−69·1	14·5	−54·6
$H_2O + CH_3OH_2^+$ reaction:			
H_2O	− 8·3	5·2	−3·1
$CH_3OH_2^+$	−70·1	8·3	−61·8
Intermediate	−64·2	10·9	−53·3
Transition state	−59·7	11·1	−48·6
$H_2O \cdot H_2O + CH_3OH_2^+ \cdot OH_2$ reaction:			
$H_2O \cdot H_2O$	−13·0	8·2	−4·8
$CH_3OH_2^+ \cdot H_2O$	−60·2	11·0	−49·2
Intermediate	−54·6	16·3	−38·3
Transition state	−49·8	16·4	−33·4

distribution in the solute either. To consider this effect in more detail, Table 4 gives the charges of each meaningful group at every gas-phase located stationary point. It can be seen that the solvent always increases the negative charge on flourine atoms and the positive charges on the methyl group. In valence-bond language, the solvent augments the importance of ionic structures, as predicted by Shaik.[17,18] For instance, in the transition state the fluorine charges, which are 0·68 in the gas-phase, become 0·72 when the solvent is introduced through the continuum model. Another simultaneous effect worth noting is that in asymmetric structures

Table 4. Charges supported by the methyl group, the entering and leaving fluorines and both water solvating molecules (in atomic units) for the gas phase and the three representations of the solvent for reaction (1)

Phase/solvent representation	Species	Methyl	Entering F	Leaving F	EW[a]	LW[b]
Gas phase	Reactants	0·28	−1·00	−0·28		
	Intermediate	0·30	−0·94	−0·36		
	Transition state	0·37	−0·68	−0·68		
Discrete	Reactants	0·23	−0·90	−0·26	−0·10	0·02
	Intermediate	0·25	−0·88	−0·35	−0·04	0·02
	Transition state	0·34	−0·68	−0·68	0·01	0·01
Continuum	Reactants	0·34	−1·00	−0·34		
	Intermediate	0·33	−0·96	−0·37		
	Transition state	0·44	−0·72	−0·72		
Discrete–continuum	Reactants	0·27	−0·92	−0·29	−0·08	−0·10
	Intermediate	0·27	−0·90	−0·36	−0·04	−0·04
	Transition state	0·40	−0·71	−0·71	0·01	0·01

[a] Entering fluorine solvating water.
[b] Leaving fluorine solvating water.

Table 5. Charges supported by the methyl group, the entering and leaving nucleophile groups and both water solvating molecules (in atomtic units) for the gas phase and the three representations of the solvent for reaction (2)

Phase/solvent representation	Species	Methyl	Entering water	Leaving water	EW[a]	LW[b]
Gas phase	Reactants	0·63	0·00	0·37		
	Intermediate	0·62	0·05	0·32		
	Transition state	0·67	0·17	0·17		
Discrete	Reactants	0·60	−0·03	0·34	0·03	0·07
	Intermediate	0·58	0·02	0·30	0·06	0·04
	Transition state	0·64	0·13	0·13	0·05	0·05
Continuum	Reactants	0·61	0·00	0·38		
	Intermediate	0·60	0·05	0·35		
	Transition state	0·67	0·17	0·17		
Discrete–continuum	Reactants	0·59	−0·03	0·34	0·03	0·07
	Intermediate	0·57	0·01	0·32	0·04	0·06
	Transition state	0·65	0·13	0·13	0·05	0·05

[a] Entering water solvating water.
[b] Leaving water solvating water.

the solvent slows down the charge transfer from the entering group. This feedback effect on the charge distribution in a similar chemical system has been considered recently by Bash *et al.*[30]

Turning our attention to reaction (2), one can see from Table 3 that the free energy of solvation decreases on going from the reactants to the intermediates and the transition states. The main characteristic here is that the solvent is unable to eliminate the gas-phase double-well shape. However, the well depth of the intermediate is reduced, and the transition state lies over the reactants owing to the solvent effect. In a Monte Carlo study of the $Cl^- + CH_3$ reaction,[28] a similar effect was found when dimethylformamide was used as a solvent. Our results indicate that the energy profile shape depends not only on the solvent used, but also on the reaction itself. The feedback effect on the charge distribution (see Table 5) is not as noticeable as in reaction (1), but leads to analogous conclusions.

Discrete–continuum representation of the solvent

Figure 4 shows energy profiles for reactions (1) and (2), where the electrostatic contribution to the Gibbs free energy has been added to the values obtained for the discrete representation of the solvent. If we compare Figures 3 and 4, we can see that the profiles in solution (dashed lines) are not very different. Judging from Table 3, one can consider the reasons for this similarity in reaction (1): the negative species decrease their ΔG_{el} value on adding one discrete water molecule; this effect is more pronounced in the fluoride anion (from $-97{\cdot}4$ to $-81{\cdot}2$ kcal mol^{-1}) than in the intermediate ($-81{\cdot}3$ to $-72{\cdot}7$ kcal mol^{-1}); however, this is compensated for by the increase in ΔG_{el} in methyl fluoride on incorporation of one water molecule ($-6{\cdot}8$ to $-13{\cdot}7$ kcal mol^{-1}). This fact can be understood because in charged species the introduction of a discrete water molecule makes the charge more diffuse, so in a continuum model ΔG_{el} decreases. In contrast, in neutral species the introduction of a water molecule leads to a hydrogen bond, thus increasing the charge separation and augmenting ΔG_{el}.

If the free energies of cavitation were added to the continuum or discrete–continuum profiles, a stabilization of ca 2 kcal mol^{-1} would be found in the intermediates and transition

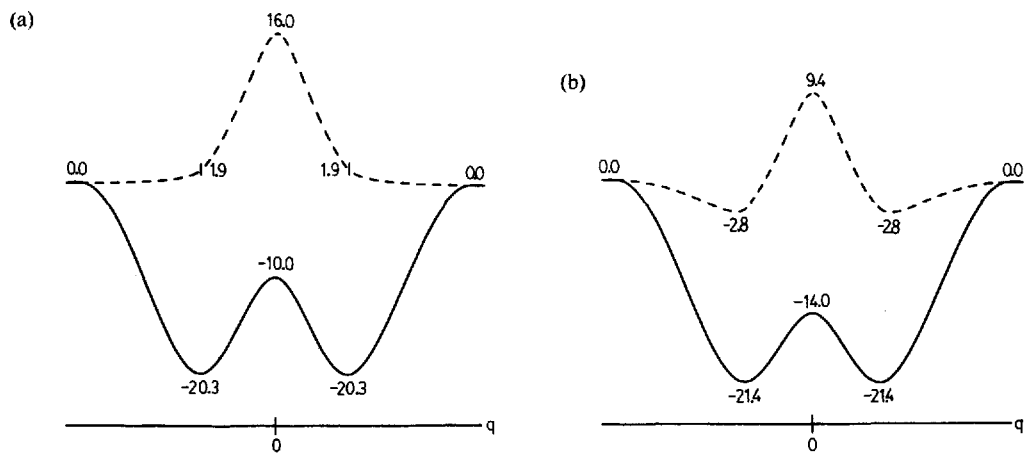

Figure 4. Potential energy profiles (kcal mol^{-1}) vs reaction coordinate q for (a) reaction (1) and (b) reaction (2). Continuous lines, discrete representation for the solvent; dashed lines, discrete–continuum representation for the solvent. For definition of q, see text. Energies relative to reactants are given in kcal mol^{-1}

states, thus only slightly modifying the energy shapes. Therefore, it is clear that reaction (1) has a unimodal shape in solution, whereas reaction (2) exhibits a double-well shape even in solution. As experimental results are lacking for reaction (2), it is difficult to assess the validity of the theoretical results for such a reaction.

Despite the similarities between the continuum and discrete–continuum models, the latter does not improve at all the energetic results compared with the former, as found in previous studies.[50,51] The main reason that has been invoked is that the continuum model does introduce a large part of the solvent effect for specific interactions such as hydrogen bonding, whose leading component is electrostatic.

CONCLUSIONS

We have demonstrated considerable similarity between our results obtained with a continuum representation of the solvent and those of previous Monte Carlo studies.[23,26–29] Two advantages of continuum models may be noted. On the one hand, almost the same quality of results as are obtained with Monte Carlo calculations may be achieved with a much cheaper continuum model. On the other hand, the feedback solvent effect is introduced in continuum models but not in Monte Carlo calculations. The agreement of the results shows that the main reason for the barrier may be attributed to the large reorganization of the solvent which parallels the charge transfer during the reaction. Obviously, in the solvent reorganization the reorganization of the first shell is a very important factor. This aspect is also considered in the continuum model to some extent. The main limitation of both models is that the solvent is assumed always to be in equilibrium with the chemical system. This may lead to two shortcomings: first, a time-scale problem, viz. the chemical reaction proceeds faster than solvent reorganization, so the solvent is not likely to be in equilibrium with the chemical system; second, use of the discrete model in this study has provided a more intrinsic reason for denying the equilibrium hypothesis, viz. the solvent parameters are themselves part of the reaction coordinate. The non-applicability of the activated complex theory to an S_N2 reaction in solution has been considered in recent molecular dynamics studies.[31–33] The transmission coefficient found in those studies was smaller than unity, since many trajectories recross the barrier owing to solvent configurations which are not adequate. However, the studies did not clarify enough how suitable solvent configurations starting from reactants may be achieved. In conclusion, although substantial advances have been made on elucidating how the solvent influences the S_N2 reaction, we are far from being close to fully understanding the solvent effect.

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