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Modeling Protic to Dipolar Aprotic Solvent Rate Acceleration and Leaving Group Effects in S_N2 Reactions: A Theoretical Study of the Reaction of Acetate Ion with Ethyl Halides in Aqueous and Dimethyl Sulfoxide Solutions

Daniel W. Tondo and Josefredo R. Pliego, Jr.*

Departamento de Química, Universidade Federal de Santa Catarina, CEP 88040-900 Florianópolis, SC, Brazil

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The S_N2 reactions between acetate ions and ethyl chloride, ethyl bromide, and ethyl iodide in aqueous and dimethyl sulfoxide (DMSO) solutions were theoretically investigated at an ab initio second-order Møller−Plesset perturbation level of theory for geometry optimizations and at a fourth-order Møller−Plesset perturbation level for energy calculations. The solvent effect was included by the polarizable continuum model using the Pliego and Riveros parametrization for DMSO and the Luque et al. scale factor for the water solution. The calculated $\Delta G^{\ddagger}$ values of 24.9, 20.0, and 18.5 kcal mol^{-1} in a DMSO solution for ethyl chloride, ethyl bromide, and ethyl iodide are in good agreement with the estimated experimental values of 22.3, 20.0, and 16.6 kcal mol^{-1}, respectively. In an aqueous solution, the theoretical $\Delta G^{\ddagger}$ barriers of 26.9, 23.1, and 22.1 kcal mol^{-1} are also in good agreement with the estimated experimental values of 26.1, 25.2, and 24.7 kcal mol^{-1}, respectively. The present ab initio calculations are reliable to predict the absolute and relative reactivities of ethyl halides in a DMSO solution, but in the aqueous phase, the results are less accurate. The protic to dipolar aprotic solvent rate acceleration is theoretically predicted, although this effect is underestimated. We suggest that further improvement of the present results could be obtained by including liquid-phase optimization in both solvents and treating specific solvation by water molecules for the reaction in the aqueous phase.

1. Introduction

Prediction of the kinetics of chemical reactions in different solvents is a very important problem for theoretical chemistry. Despite the fact that pioneer theoretical studies date from almost 20 years ago,[1−3] the ability to predict accurate chemical reaction rates remains a very difficult task. The major problem is the calculation of a reliable solvation free energy of the system for any configuration of the atoms of the reactant system. At room temperature, an error of ±1 kcal mol^{-1} in the activation barrier translates to an increase in error by a factor of 5 in the rate constant. In addition, the target chemical accuracy of ±1 kcal mol^{-1} for the process in solution is very hard to attain.

Continuum solvation models have become the most usual approach for including solvent effects in the theoretical studies of chemical reactions.[4−14] Solvation in aqueous media has received a great amount of attention, but it has become evident that this approach can be flawed in situations where there are strong and specific solute−solvent interactions.[15] In these cases, the use of a discrete-continuum approach can lead to a substantial improvement of the solvation model.[15−22] Whereas the performance of pure continuum models for solvation of ions in aqueous media presents problems, the polarizable continuum model (PCM) works very well for solvation in a dimethyl sulfoxide (DMSO) solvent. Indeed, in a recent study, Pliego and Riveros have reported the first parametrization of a continuum model for describing anions in DMSO.[23,24] In a later study by Pliego and co-workers,[25] this parametrization was tested in the calculation of pK_a values of over 41 organic acids having diverse functional groups. The method has worked very well, with an average error of only 2.2 pK_a units. A similar and independent study by Liu et al.[18] was reported almost simultaneously, where the pK_a values of a set of 105 organic acids in DMSO were investigated. These authors also calculated the pK_a values of cations, using the hybrid cluster-continuum model to account for the strong interactions present in these cases. Even more interesting was the observation that some neutral molecules, such as the CH_3SO_3H acid, were able to form very strong hydrogen bonds with the DMSO species. These strong and specific interactions were not adequately described by the pure continuum model, and in these cases, the hybrid cluster-continuum model was able to predict more-accurate pK_a values. These results have indicated that, for modeling chemical reactions in solution, pure continuum solvation models are adequate in many situations. However, in several cases, the inclusion of explicit solvent molecules can become very important for an accurate treatment.

One of the most well-known effects of solvation on chemical reactions is the classic rate acceleration observed for anion−molecule S_N2 reactions when going from protic to dipolar aprotic solvents.[26−28] This effect has very useful synthetic applications and is currently widely used in the industrial synthesis of fine chemicals. Evidently, the ability of modeling these reactions in aprotic solvents could be an important tool in the design of chemical reactions relevant to process chemistry. On the theoretical side, S_N2 reactions have received a great deal of attention for processes both in the gas phase and in solution.[3,29−50] The majority of these theoretical studies have concentrated on the exchange reactions of halide ions with alkyl halides. In the case of the reaction of carboxylate ions with alkyl halides, only recently have some studies been published.[32,51,52] Gronert et al. have investigated the importance of the S_N2 and

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* To whom correspondence should be addressed. E-mail: josef@qmc.ufsc.br.

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E2 reaction pathways involving acetate and *β*-substituted ethyl bromides in the gas phase.[32] The role of some substituent groups on the branching ratio was analyzed. A study of the inverse reaction of fluoride and chloride ions with methyl formate in the gas phase was reported by Pliego and Riveros,[52] in which an extensive analysis of the reaction pathways was done. More recently, a liquid-phase study of the S_N2 reactions of formate, acetate, and propionate ions with methyl chloride and 1,2-dichloroethane was reported by Kahn and Bruice.[51]

The esterification of carboxylic salts with alkyl halides is of great interest because of the relevance of the ester groups in bulk and fine chemistry. In the present work, we have reported a theoretical study of the S_N2 reaction of acetate ions and ethyl halides (Cl, Br, and I) in aqueous and DMSO solutions, which is as follows:

$$\mathrm{CH_3COO^-} + \mathrm{CH_3CH_2X} \xrightarrow{\mathrm{S_N2}} \mathrm{CH_3COOCH_2CH_3} + \mathrm{X^-}$$

Our aim is to theoretically determine the solvent and leaving group effects on the activation free-energy barrier as well as to verify the reliability of our predictions by comparison with available experimental data. A related study involving OH^- + $CH_3COOCH_2CH_3$ in aqueous and DMSO solutions has been published recently.[53] It is important to emphasize that the usual parametrizations of continuum solvation models are not able to predict the rate acceleration on the transfer from protic to dipolar aprotic solvents because they define the same cavity for both solvents. An adequate definition of the cavities, different for each solvent, similar to those reported by Pliego and Riveros[24] for DMSO and Luque et al. for octanol,[54] chloroform,[55] carbon tetrachloride,[56] and water,[57] is needed for a reliable model.

2. Theoretical Calculations

Because the present study deals with heavy atoms such as Br and I, the ab initio calculations were carried out using effective core potentials (ECP). We have used the ECP of Stevens et al.[58,59] for all of the atoms but hydrogen. The valence electrons, including that of hydrogen, were treated using the 31G basis set designed for this specific ECP. We have also included sp-diffuse and d polarization functions on the heavy atoms. This basis set will be referred to as CEP-31+G(d). The geometry optimizations and harmonic frequencies were obtained at the Hartree−Fock (HF) and second-order Møller−Plesset perturbation theory (MP2) levels. To obtain reliable activation barriers, electron correlation was included up to a fourth-order Møller−Plesset perturbation theory (MP4) level using the CEP-31+G(d) basis set.

The solvent effect was included through the PCM[6,11] for both aqueous and DMSO solutions through the integral equation formalism routines. We have used the default atomic radii stored in the general atomic and molecular electronic structure system (Gamess) for solvation in a water solution (1.50 for O, 1.70 for C, 1.20 for H, 1.81 for Cl, 1.95 for Br, and 2.15 for I), and the scale factor was set to 1.10. Although a scale factor of 1.20 is usually recommended for water, Orozco and Luque[57] have shown that a scale factor of 1.10 is more reliable for ions in a water solution. Despite the fact that our atomic radii present some differences to those of Luque et al., we have found that this scale factor is very adequate and predicts solvation free energies of CH_3COO^-, Cl^-, Br^-, and I^- ions in very good agreement with the experimental data.[23] For the DMSO solution, we have adopted the atomic radii reported by Pliego and Riveros[24] (1.50 for O, 1.70 for C, 1.20 for H, 1.81 for Cl, 1.88 for Br, and 2.05 for I) and a scale factor of 1.35. Considering that the electrostatic contribution of the solvation free energy (ΔG_{el}) is the main term and nonelectrostatic solvation plays a minor role, this last term was not included. Thus, the final activation (and reaction) free energy is calculated by the equation

$$\Delta G^{\ddagger}_{sol} = \Delta G^{\ddagger}_{g} + \Delta\Delta G^{\ddagger}_{solv} \tag{1}$$

TABLE 1: Electrostatic Contribution to the Solvation Free Energy in DMSO and Aqueous Solutions Calculated by the PCM Method

	ΔG_{solv}(DMSO)	ΔG_{solv}(H_2O)
CH_3COO^-	−64.11	−75.87
Cl^-	−64.21	−73.58
CH_3CH_2Cl	−1.91	−3.40
TS−Cl	−50.63	−61.87
Br^-	−61.10	−67.79
CH_3CH_2Br	−1.99	−3.42
TS−Br	−49.30	−59.46
I^-	−55.75	−60.86
CH_3CH_2I	−1.87	−3.27
TS−I	−47.15	−56.76
$CH_3COOCH_2CH_3$	−4.05	−8.16

[a] Units of kcal mol^{-1}, standard state of 1 mol L^{-1}.

All of the ab initio and PCM calculations were done with the Gamess[60] and the PC Gamess[61] versions of the Gamess United States Quantum Chemistry Program.

3. Results and Discussion

Values for the calculated electrostatic contribution to the solvation free energy (ΔG_{solv}) for every species studied are presented in Table 1, and these values can be directly compared with the experimental[23] ΔG_{solv} values. In the cases of the ions AcO^-, Cl^-, Br^-, and I^- in aqueous solutions, our calculated ΔG_{solv} values of −75.9, −73.6, −67.8, and −60.9 kcal mol^{-1} are in very good agreement with the available experimental values[23] of −77.3, −74.6, −68.6, and −59.9 kcal mol^{-1}, respectively. Similarly, in a DMSO solution, the respective theoretical ΔG_{solv} values are −64.1, −64.2, −61.1, and −55.8 kcal mol^{-1}, while the respective experimental[23] ΔG_{solv} values are −62.7, −65.0, −62.1, and −57.4 kcal mol^{-1}. Thus, in both solvents, these parametrizations of the PCM method are able to provide reliable solvation data of ions, which is a critical property for modeling ion−molecule reactions in the liquid phase.

The gas-phase activation and reaction energies for the S_N2 reactions between acetate ions and ethyl halides are displayed in Table 2, and the respective structures of the transition states are shown in Figure 1. The geometries of the transition states obtained at the HF level present X−C and C−O bond distances that are too long by 0.1 Å when compared to the MP2 values. As a result, the energy barrier drops by ∼1.5 kcal mol^{-1} when using the MP2 geometries instead of the HF structures. On the other hand, the reaction energies do not differ by more than 0.5 kcal mol^{-1} when using the HF and MP2 geometries.

It can be noted that a high level of electron correlation is important for an accurate computation of the activation barrier, which decreases by 1.5−2.5 kcal mol^{-1} upon going from an MP2 level to an MP4 level of theory. This sensibility has been reported for other studies of S_N2 reactions, and calculations indicate that density functional theory is not accurate for this kind of reaction.[62] In the computation of the thermodynamic properties, we have used the MP2-optimized geometries and frequencies. By comparing the gas-phase activation free energies, we can observe the considerably greater reactivity of ethyl

TABLE 2: Calculated Activation and Reaction Thermodynamic Properties for the S_N2 Reaction CH_3COO^- + CH_3CH_2X in the Gas Phase[a]

Activation	Cl	Br	I
MP2/CEP-31+G(d)//HF	4.50	−2.16	−5.67
MP4/CEP-31+G(d)//HF	1.97	−4.28	−7.66
MP2/CEP-31+G(d)//MP2	2.62	−3.92	−7.44
MP4/CEP-31+G(d)//MP2	0.50	−5.66	−9.10
$\Delta E^{\ddagger b}$	1.06	−4.99	−8.38
$\Delta H^{\ddagger}_{g}$	1.73	−4.28	−7.65
$\Delta G^{\ddagger}_{g}$	9.47	3.23	−0.31

Reaction	Cl	Br	I
MP2/CEP-31+G(d)//HF	−14.89	−26.06	−35.13
MP4/CEP-31+G(d)//HF	−15.08	−25.77	−34.46
MP2/CEP-31+G(d)//MP2	−15.19	−26.34	−35.40
MP4/CEP-31+G(d)//MP2	−15.38	−26.01	−34.70
ΔE^{b}	−13.46	−23.61	−31.95
ΔH_{g}	−13.20	−23.43	−31.84
ΔG_{g}	−9.38	−19.50	−27.75

[a] Units of kcal mol^{-1}, 298.15 K, standard state of 1 mol L^{-1}. The symmetry factor was included to account for the two isomeric transition states. [b] MP4//MP2 energy plus zero-point vibrational energy contribution.

TABLE 3: Calculated Activation and Reaction Free Energies for the S_N2 Reaction CH_3COO^- + CH_3CH_2X in DMSO and Aqueous Solutions[a]

Activation	DMSO		H_2O	
X	$\Delta\Delta G^{\ddagger}_{solv}$	$\Delta G^{\ddagger}_{sol}$	$\Delta\Delta G^{\ddagger}_{solv}$	$\Delta G^{\ddagger}_{sol}$
Cl	15.39	24.86	17.40	26.86
Br	16.80	20.03	19.84	23.07
I	18.83	18.52	22.38	22.06

Reaction	DMSO		H_2O	
X	$\Delta\Delta G_{solv}$	ΔG_{sol}	$\Delta\Delta G_{solv}$	ΔG_{sol}
Cl	−2.24	−11.62	−2.47	−11.85
Br	0.94	−18.56	3.35	−16.15
I	6.18	−21.57	10.13	−17.62

[a] Units of kcal mol^{-1}, 298.15 K, standard state of 1 mol L^{-1}.

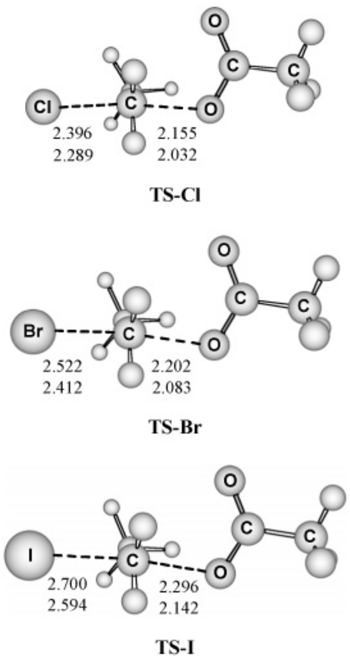

Figure 1. Transition states for the S_N2 reaction of CH_3COO^- with CH_3CH_2Cl (TS−Cl), CH_3CH_2Br (TS−Br), and CH_3CH_2I (TS−I). The geometries at HF/CEP-31+G(d) (upper numbers) and MP2/CEP-31+G-(d) (lower numbers) levels are given.

iodide, which has an activation barrier lower than those of ethyl bromide and ethyl chloride by 3.5 and 9.8 kcal mol^{-1}, respectively. When the values for the reaction free energy are compared, the difference increases considerably, reaching 18.4 kcal mol^{-1} between those of iodide and chloride. However, by transferring the reaction to a DMSO solution, this greater reactivity of ethyl iodide is considerably reduced, which can be observed in Table 3. Indeed, our calculations indicated that, in a DMSO solution, ethyl iodide is more reactive than bromide and chloride by 1.5 and 6.3 kcal mol^{-1}, respectively. Such an effect is also observed for the reaction free energy.

In an aqueous solution, the solvent effect is more accentuated and the different reactivities among the alkyl halides are further reduced. Iodide is still more reactive ($\Delta G^{\ddagger}$) than bromide and chloride, with an activation barrier lower by 1.0 and 4.8 kcal mol^{-1}, respectively. A similar trend is observed for the reaction free energy, and the ethyl iodide reaction is more negative than that of ethyl chloride by only 6 kcal mol^{-1}.

When we analyze the solvent rate acceleration effect (from water to DMSO) for each reaction, we note a moderate effect on the ethyl chloride reaction: the barrier decreases by 2.0 kcal mol^{-1}. For bromide and iodide, the effect is more pronounced and the barrier decreases by 3.0 and 3.5 kcal mol^{-1}, respectively. These values translate to a rate acceleration by factors in the range of 30−370.

Values for the heat of formation of reactants and products in the gas phase are available from the NIST database.[63] We have used these values for the species studied in this work in order to compare them with our ab initio results. For the reaction of acetate with ethyl chloride, ethyl bromide, and ethyl iodide, the respective $\Delta H°$ values from NIST are −13.4, −21.5, and −29.2 kcal mol^{-1}, respectively. These values are in very good agreement with our theoretical values (see Table 2) of −13.2, −23.4, and −31.8 kcal mol^{-1}, respectively, and they support the quality of our gas-phase calculations.

No kinetics data on the reaction of acetate ions with ethyl halides in aqueous and DMSO solutions are available for direct comparison. However, some kinetics data are available for the reaction of alkyl halides with carboxylate ions,[64,65] and we have used these values for comparison purposes. These data are given in Table 4, in which some details of the compilation of the activation free energy values are presented. We have also included, in parentheses, values that we think are less reliable, for comparison. In a DMSO solution, our theoretical $\Delta G^{\ddagger}$ value for ethyl chloride is 2.6 kcal mol^{-1} higher than the experimental value. A more-accurate result is observed for the reactions with ethyl bromide and ethyl iodide, with deviations of 0.0 and 1.9 kcal mol^{-1}, respectively. Nevertheless, in these cases, the rate constants were obtained through an extrapolation procedure, and thus they are probably subject to a much larger degree of uncertainty.

The agreement between theoretical and experimental results is very good. In fact, the deviation in the values of the activation barriers is within the uncertainty range of the solvation model tested in the calculation of pK_a by Pliego et al.[25] Nevertheless, it would be interesting to examine the possible source of error. We have used a modest basis set, and it can decrease the accuracy of the gas-phase energies. However, in the case of ethyl chloride, a calculation with the extended 6-311+G(2df,-2p) basis set does not lead to an important variation from the

TABLE 4: Comparison of Theoretical and Experimental Activation Free-Energy Barrier Values for the S_N2 Reaction $RCOO^-$ + R−X in Aqueous and DMSO Solutions[a]

	DMSO			H_2O		
	$\Delta G^‡$(theor)	$\Delta G^‡$(exp)	deviation	$\Delta G^‡$(theor)	$\Delta G^‡$(exp)	deviation
R−Cl	24.9	22.3[b]	2.6	26.9	(26.1)[d]	0.8
R−Br	20.0	(20.0)[c]	0.0	23.1	25.2[e]	−2.1
R−I	18.5	(16.6)[c]	1.9	22.1	24.7[e]	−2.6

[a] Units of kcal mol^{-1}, 298.15 K, standard state of 1 mol L^{-1}. [b] Measured for propanoate + 1-chlorohexane at 60 °C and corrected to 25 °C assuming $\Delta S^‡ = -23$ cal K^{-1} mol^{-1}. See ref 65. [c] Based on measurements in an ethanol + HMPA mixture, extrapolated to pure HMPA, and using the different reactivities between alkyl halides in pure HMPA plus the rate constant for alkyl chloride in DMSO. These are estimated values at 25 °C. See ref 65. [d] Based on measurements for formate + methyl chloride in a 50% aqueous solution + acetone mixture at 120 °C corrected to 25 °C using $\Delta S^‡ = -23$ cal K^{-1} mol^{-1}. See ref 64. [e] Values measured for 2-methyl-2-propylpentanoate + 1-bromopentane (1-iodopentane) in pure ethanol at 60 °C and corrected to 25 °C. See ref 65.

present value, which increases by only 0.8 kcal mol^{-1}. Yet, the use of gas-phase-optimized geometry could be a relevant point to analyze. Kormos and Cramer[31] recently investigated the S_N2 reaction between allyl chloride and chloride ions in the aqueous phase. The activation free-energy barrier was calculated utilizing gas-phase- and solution-phase-optimized geometries, and the authors found that solution optimization decreases the barrier by 1.5 kcal mol^{-1}. In the other cases investigated, the decrease was even greater. These results suggest that a probable source of overestimation of our calculated barriers in a DMSO solution is the lack of liquid-phase optimization. However, the DMSO solvent has a smaller interaction with the solute than the water solvent does, and as a consequence, liquid-phase optimization should be less important in the DMSO solvent.

In the aqueous solution, the agreement between theoretical and experimental results is good, although in this situation, the activation barriers are underestimated on the average. The major deviation occurs for ethyl iodide, −2.6 kcal mol^{-1}. It should be observed that we are using the kinetics data obtained in an ethanol solution as a reference for the aqueous-phase reaction. Likewise, liquid-phase optimization for an aqueous solution should decrease the barrier. However, in this case, using this procedure, the results would be worse. Therefore, we think that, in the aqueous solution, specific solvation is probably the main source of error. If we consider the solvations of the acetate ion and the transition state with explicit water molecules, the acetate ion is expected to be more stabilized, thus leading to an increase in the activation barrier. The cluster-continuum model[15−17,22] could be an interesting alternative in which to include explicit solvation, and this issue will be addressed in a future work.

Another issue to analyze concerns the differences in reactivities of the ethyl halides in the same solvent. Our theoretical calculations are in good agreement with the experimental data in the DMSO solution, showing that the reactivity order is I > Br > Cl, with relative free-energy barriers of 0.0, 1.5, and 6.4 kcal mol^{-1}, respectively, while the respective experimental values are 0.0, 3.4, and 5.7 kcal mol^{-1}. In the aqueous solution, the respective theoretical relative barriers of 0.0, 1.0, and 4.8 kcal mol^{-1} can be compared with the respective experimental values of 0.0, 0.5, and 1.4 kcal mol^{-1}. It must be mentioned that, for the ethyl chloride case, the experimental data are probably underestimated because they are based on a formate−methyl chloride reaction.

4. Conclusion

The difference in reactivities of alkyl halides with acetate ions in aqueous and DMSO solutions was predicted by the present theoretical study, although our calculations underestimate this effect. The variations in $\Delta G^‡$ for ethyl chloride, ethyl bromide, and ethyl iodide, on going from a DMSO solution to a water solution, are 2.0, 3.1, and 3.6 kcal mol^{-1} at the theoretical level, respectively, whereas the experimental values are 3.8, 5.2, and 8.1 kcal mol^{-1}, respectively. Possible sources of error are the lack of liquid-phase optimization and the inclusion of explicit water molecules for the reactions in the aqueous phase. The absolute and relative reactivities of ethyl halides in the same solvent are well-predicted in the DMSO solution, but the deviation increases in the aqueous phase.

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