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Evidence for Different Types of Water Participation in the Solvolysis of 1-Adamantyl, *tert*-Butyl, and Methyl Chlorides from Density Functional Theory Computations

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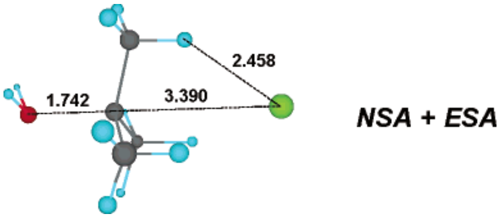

The activation energy in the gas phase ($\Delta E^{\ddagger}$) and the free energy of activation ($\Delta G^{\ddagger}$) in water solution for the hydrolysis of the monohydrates of methyl chloride (MeCl), *tert*-butyl chloride (*t*-BuCl), and 1-adamantyl chloride (AdCl) have been computed with the B3LYP/631-G(d) method and the polarizable continuum (PCM) solvation model. There is a fair agreement between the $\Delta G^{\ddagger}$ values computed by us and the experimental data. The mechanistic implications of our computations are in severe contradiction with conventional representations. Thus, the computed nucleophilic solvent assistance (NSA) for the backside attack of a water molecule in the hydrolysis of MeCl is slightly lower than the corresponding NSA for *t*-BuCl. Hence, the hydrolysis of both MeCl and *t*-BuCl takes place mainly according to the classical S_N2 mechanism. The most relevant difference is that $\Delta G^{\ddagger}$ for the frontside attack of water to *t*-BuCl is disfavored only by ca. 2 kcal/mol with regard to the backside attack but by ca. 23 kcal/mol in the case of MeCl. The higher solvolysis rate in water of *t*-BuCl in relation to AdCl is not due to steric factors affecting the specific solvation of the corresponding transition states, but to differential bulk solvent effects, which are accounted for by the PCM model.

Introduction

Alkyl transfer reactions are important in organic synthesis[1] and in biochemical processes.[2] A general type of these reactions takes place between neutral nucleophiles (Nu:) and electrophiles (RX) according to eq 1 and

$$\text{Nu:} + \text{RX} \rightleftharpoons \text{RNu}^+ + \text{X}^- \qquad (1)$$

are usually carried out in aqueous solution.[1,2] The Menshutkin reaction in which Nu: is an amine base has received extensive theoretical attention.[1,3]

The solvolysis of alkyl halides is even more interesting because it has long been a key reference reaction in physical organic chemistry, especially as the subject for theories of solvent effects on organic reaction rates. According to the traditional unimolecular−bimolecular scheme for the nucleophilic aliphatic substitution introduced by Ingold,[4] methyl chloride (MeCl) and *tert*-butyl chloride (*t*-BuCl) are usually[4−6] considered as S_N2 and S_N1 model substrates, respectively. However, a great deal of studies over the decades have been dedicated to the

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controversy surrounding the role of nucleophilic or electrophilic solvent assistance (NSA or ESA) in the solvolysis of *t*-BuCl and 1-adamantyl chloride (AdCl) in hydroxylic solvents.

Several chemical experiments have been developed to detect the contribution of NSA in the solvolysis of alkyl derivatives by measuring the effect of added anionic nucleophiles on reaction rates and products,[7–9] as well as the stereochemical outcome of the solvolysis of tertiary derivatives, particularly chlorides (*t*-RCl).[10,11] Because of the contradictory results obtained, it has been concluded that neither stereochemical data nor chemical experiments allow a final conclusion about the extension of NSA in the solvolysis of *t*-BuCl.[7–11]

The classical methodology for the study of solvent effects on reaction rates of solvolysis is based on multiparameter linear free-energy relationships (LFER). LFER procedures attempt to correlate the values of ln k or $\Delta G^{\ddagger}$ for a given reaction in a set of solvents with some physical parameters characteristic of the solvent,[12–25] such as, polarity (Y or the Kirkwood−Onsager function of the dielectric constant ϵ), polarizability (function of the refraction index, n), dipolarity (π^*, related with the polarizability and polarity), electrophilicity (AN, E, or α), nucleophilicity (N, B, or β), the solvatochromic Dimroth−Reichard parameter (E_T), or the solvent self-association expressed by the Hildebrand parameter (δ^2).[24] This parameter is needed to accommodate the so-called cavity effect.[23] Contradictory results about NSA of water in the solvolysis of *t*-BuCl have been obtained using different LFER equations.[12–28,30] Thus, Bentley, Schleyer,[17] and Kevill[19] have reached the conclusion that appreciable backside solvation (NSA) is possible for a developing *tert*-butyl cation, *t*-Bu(+). On the contrary, solvent electrophilicity has been suggested to explain the moderate differences in response to the solvent variation observed for the rate of solvolysis of AdCl and *t*-BuCl because AdCl should be more sensible to changes in the electrophilicity of the solvent than *t*-BuCl.[21] In the Koppel−Palm treatment,[22] it has been concluded that contribution of the B (nucleophilicity) parameter is unimportant and that contribution of the E term (electrophilicity) is the most important. This result suggests that hydrogen bonding makes the withdrawal of a chloride anion easier.[13]

Kamlet−Taft[23] treatment of solvent effects on the solvolysis of *tert*-butyl halides reaches the conclusion that, although the intrinsic volumes of the *t*-BuCl ground state and transition state (TS) should be very similar and, by themselves, will lead to a negligible cavity term, the electrostriction effect may lead to reaction rates being dependent on the solvent cohesive energy density (CED), as defined by the Hildebrand parameter. Moreover, the nucleophilic assistance term for the solvolysis of *t*-BuCl is statistically significant at the 99.5% confidence level. Nevertheless, the nucleophilic assistance term should be the smallest of the contributing terms.

The Gajewski treatment is based on the KOMPH2 multiparameter equation.[27] Besides the neglect of significant NSA in the S_N1 reaction of every *t*-RCl in any solvent, the more relevant mechanistic implication of Gayjewski's treatment is the need for ESA to stabilize the departing anion.[28] Particularly, it has been assumed to be more important with AdCl than with *t*-BuCl because of steric effects. As experimental proof for the greater sensitivity of 1-adamantyl derivatives to electrophilic catalysis, which was previously attributed to steric effects, Kramer's results[29] on the increased hydride donor rates from the bridgehead carbon of adamantane relative to that from isobutane have been adduced. It is noteworthy that this interpretation is against that proposed by Kramer because the lower reactivity of isobutane was attributed to unfavorable activation entropy of the hydride exchange with *t*-Bu(+).[29]

By correlation analysis of solvolysis rates, mainly obtained by the verdazyl method, using the Koppel−Palm and Kamlet−Taft equations, Dvorko et al.[30] reached the conclusion that the solvolysis rate of tertiary substrates, including *t*-BuCl and AdCl, decreases with increasing solvent nucleophilicity. This conclusion is in contradiction with classical as well as recent results using the Kamlet−

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Taft equation[25] because the coefficient for β in the t-BuCl correlation is positive. In our opinion, the main defect of the LFER methods consists of the strong collinearity between the parameters measuring the electrophilicity and nucleophilicity of hydroxylic solvents.[13,25−27] Moreover, small changes in the input data of the ROH data set can lead to extraordinarily large changes in the coefficients of the "independent" variables, together with relative minor changes in the accuracy of the fit.[25] It is also noteworthy that, following essentially statistical four-parameter approaches,[20] conclusions considered as chemically absurd were deduced.[13]

The nature of the ionization step in S_N1 reactions has been explained[31,32] using a valence-bond formalism. Water was not considered as solvent because it should be difficult to incorporate the so-called anomalous entropy effect into the dielectric continuum description. The entropy effect lies in a very significant entropy decrease when t-BuCl is solvated in water, associated with an increase in the ordering of water molecules surrounding the solute.[33] This increases the free energy associated with the initial state (IS) of hydrolysis, rendering activation free-energy values significantly lower than those in other solvents.[33]

Hydration of ion pairs and molecules is an essential process for the determination of specific solvent effects in aqueous solution.[34−37] Most of the quantitative study of the solute−solvent interaction at the molecular level in S_N2 reactions has been focused on identity processes, in which Nu: $= X^-$ (see eq 1), as well as on the Menshutkin reaction using statistical mechanical Monte Carlo (MC) and molecular dynamics (MD) techniques. The hydration and energetics for the separation of t-Bu(+) and chloride ions in water have been studied by Jorgensen et al.[38] with MC simulations using statistical perturbation theory and integral equation calculations with extended RISM methodology[39] as well as thermodynamic parameters.[12,40,41] Potential of mean force (PMF) calculations for the dissociation of t-BuCl in water have been carried out by Merz and Hartsough[42] using a QM/MM coupled potential. Unfortunately, the results are dependent on the selected potential for long-range electrostatic interactions. Common features of the aforementioned statistical methods are the computational cost and the lack of individualization of water molecules. As a consequence, the hydrolysis could be followed only until the formation of ion pairs. Thus, the chloride/water substitution step was not described.

Ab initio and density functional theory (DFT) computations have been performed to study the effect of microsolvation.[35,36,44−49] The number of solvating molecules causes only small changes in the TS geometry for MeCl, whereas the TS for t-BuCl becomes significantly looser.[46] The calculation of the activation enthalpy ($\Delta H^\ddagger$) for the hydrolysis of MeCl using 13 water molecules at the HF/6-31+G(d) level (26.23 kcal/mol) reproduced the experimental value quite well (26.6 kcal/mol; see Table 2).[48,49] The reaction between t-BuCl and water clusters, $(H_2O)_n$ with $n = 6$ and 14, has been studied by Yamabe and Tsuchida using the B3LYP/6-31G(d) method to clarify several points of the ion-pair mechanism.[50] However, an activation energy ($\Delta E^\ddagger$) of 14.30 kcal/mol (with the participation of nine water molecules) has been computed, which is in poor agreement with the experimental $\Delta G^\ddagger$ value (19.5 kcal/mol; see Table 2). It is noteworthy that the notion of molecularity is lost using microsolvation methods. Thus, there are no significant differences between the mechanisms of solvolysis of MeCl and t-BuCl, besides the possibility of HCl elimination in the case of t-BuCl.

The dissociative proton attachment (DPA) developed by Abboud et al.[51b,52] is an accurate (by ca. 2 kcal/mol) experimental method for the determination of the gas-phase stability of carbocations. The determined ΔG value for Ad(+) and t-Bu(+) cations (9.4 kcal/mol) correlates with their stability in relation to the respective hydrocarbons (10.3 kcal/mol) computed at the MP2/6-311G(d,p) level using isodesmic reaction 2. The relative rate constants (log k) for solvolysis of alkyl chlorides, RCl, in 80% aqueous EtOH correlate satisfactorily (0.986) with the relative stabilities (ΔG) of the carbocations determined in the gas phase. However, t-Bu(+) is the only significant (99%) deviating point in this correlation. It was concluded

$$t\text{-BuH(g)} + \text{Ad(+)(g)} \rightleftharpoons t\text{-Bu(+)(g)} + \text{AdH(g)} \quad (2)$$

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that *t*-Bu(+) is more stable by 7.9 kcal/mol at 70 °C in 80% EtOH than Ad(+). The discrepancy with the gas-phase results was ascribed to NSA in the solvolysis of *t*-BuCl in 80% EtOH.

An inversion of the relative stability of the *t*-Bu(+) and Ad(+) cations on going from the gas phase to HSO_3F/SbF_5 solution (10.8 vs −3.7 kcal/mol) has also been experimentally found by Beauchamp et al.[51a] using ion cyclotron resonance (ICR) techniques and heats of ionization in solution.

The purpose of the present study is to find an inexpensive computational methodology able to afford both accurate computation of hydrolysis rates and a microscopic insight into the nature of solvent participation in the hydrolysis of *t*-BuCl, MeCl, and AdCl. A condition needed to obtain reliable calculations of solvent effects is the choice of a reliable method to model the reaction in the gas phase. Therefore, we first describe our computations on the energetics of the isodesmic reaction represented by eq 2 and, afterward, on the potential energy surface (PES) for the S_N2 reaction of the monohydrates of the corresponding chlorides.

Computational Methods

All computations have been performed using the GAUSSIAN 03 (revision A1) package of programs[53a] and the C3D graphical interface[53b] using the density functional theory (DFT) based on Becke's three-parameter hybrid exchange functional involving the gradient-corrected correlation functional of Lee, Yang, and Parr, with the polarized split-valence 6-31G* basis set (B3LYP/6-31G* method).[54,55] The 6-31G(d) basis set is fairly flexible, and the method seems to be good enough for computation of reactions involving carbocations.[56−58]

The inclusion of diffuse functions is thought to be important for the proper description of lone pairs and anions.[54a] We have then used the 6-31+G(d) basis set to compute the activation energy ($\Delta E^{\ddagger}$) for the reaction between *t*-BuCl and one water molecule. However, this value is very similar to the computed value without diffuse functions (see Table 2). Thus, the computationally inexpensive DFT theoretical level with the 6-31G(d) basis set is used throughout this study for the computation of single-point total energies (*E*) in the gas phase, without any corrections.[56,57] Although thermal enthalpy and entropy can be calculated within the rigid-rotor harmonic-frequency approximation,[53,54a] the presence of low-lying frequencies in the monohydrates makes this approach less accurate.[44] Hence, we have decided not to carry out the computations of free energies of activation in the gas phase (vide infra).

The population analyses of the TSs have been carried out with the Mulliken method. Unfortunately, the more accurate atoms in molecules (AIM) and natural bond orbital (NBO) procedures[53] aborted attempting to compute the bond orders of the TS in the case of *t*-BuCl.

Self-consistent reaction field (SCRF) models have been used successfully in reproducing experimental solvent effects for a variety of processes in aprotic solvents.[59] Particularly, the PCM[60] model of the SCRF theory is a convenient approach to the computation of solvent effects because it allows the self-consistent computation of free energies of solvation, including polarized solute/solvent (PSS) interactions and nonelectrostatic terms in the Hamiltonian. The total nonelectrostatic (TNE) terms correspond to the cavitation, dispersive, and repulsive interactions. The calculations have been performed at 298.0 K using a scaling factor for all atoms of 1.21 and a value of 70 tesserae per sphere. It is accepted that the use of the solvent's bulk ϵ in SCRF calculations is justified if the solvent is free to adopt random orientations in relation to the solute. Hence, in view of the strong hydrogen bonding found in an aqueous medium, the SCRF model does not seem to be appropriate.[1] Probably because of these reasons, the SCRF theory has been scarcely applied to the study of the reactivity in water solution.[60,61] However, it should be noted that the PCM model can afford $\Delta G^{\ddagger}$ values comparable to those obtained using computationally expensive QM/MM methods in the case of the Menshutkin reaction in water solution.[1,62] Moreover, computations with the B3LYP/6-31G(d) method at the DFT theoretical level in combination with the SCRF PCM model on bridgehead carbocations have been used by us for the quantitative explanation of the methyl effect on the solvolysis rates of bridgehead derivatives.[57]

Results and Discussion

Isodesmic Reaction 2. We have computed the total energy differences, ΔE(g), without any corrections and the free-energy differences, ΔG(g), including thermal, zero-point vibrational energy (ZPVE), and symmetry-number entropy corrections for the hydride-transfer isodesmic reaction (eq 2) in the gas phase, using several ab initio and DFT methods. The results are shown in Table 1. ΔE(g) and ΔG(g) values computed with the ab initio Möller−Plesset[54] MP2/6-311G(d,p) method are very similar to those obtained with the two density functional theory (DFT)[55] methods. Moreover, the computed ΔG(g) values are in very good agreement with the experimental results (9.4 kcal/mol), determined with the DPA method.[51b] On the contrary, the Hartree−Fock (HF) theoretical level (neglecting the electronic correlation energy) affords too low ΔE(g) values. In fact, the inclusion of polarization functions and electron correlation has proved to be essential for the reliable calculation of carbocation energies.[56−58]

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TABLE 1. Computed ΔE(g) and ΔG(g)[a] for the Isodesmic Reaction (Eq 2)

method	ΔE(g)	ΔG(g)	ΔG(w)
HF/6-31G(d)	6.62[b]		
HF/6-31+G(d)	6.21		
PCM/HF/6-31G(d) (water)			−2.85 (−1.7)[b,c]
MP2(full)/6-311G(d,p)	14.70		
MP2/6-311G(d,p)	12.47[b]	10.3[b]	
MP2(full)/6-31+G(d,p)	15.03		
B3LYP/6-31G(d)	12.29	10.70	
PCM/B3LYP/6-31G(d) (water)			−5.33 (−4.18)[d]
B3LYP/6-31+G(d)	12.23		

[a] In kcal/mol, at 1 atm and 298 K. [b] According to ref 52. [c] According to ref 52, without symmetry-number entropy correction. [d] Without symmetry-number entropy correction.

The PCM model has been applied to the computation of ΔG in water solution, ΔG(w) (Table 1), of the isodesmic reaction, but at the low HF theoretical level using the HF/6-31G(d) method.[52] The computed ΔG values in water (Table 1) (−1.7[52] and −2.85 kcal/mol with symmetry-number entropy correction[63]) reveal inversion of the relative stability of *t*-Bu(+) and Ad(+) cations on going from the gas phase to water solution, which is in agreement with the ΔG value (−2.39 kcal/mol), calculated from the experimental observation that the hydrolysis at 298 K of *t*-BuCl ($k = 1.72 \times 10^{-2}$ s^{-1}, calculated from the data described in ref 43) is 57.3 times faster than the hydrolysis of AdCl ($k = 3.0 \times 10^{-4}$ s^{-1})[6] at the same temperature (see eq 3)

$$k(t\text{-BuCl})/k(\text{AdCl})\ (\text{water, 298 K}) = 57.3 \qquad (3)$$

This surprisingly good agreement could be interpreted in the sense that the basis for the stability inversion is due only to unspecific solvent interactions of the species involved in the isodesmic reaction, the only type of solvent interactions considered in the SCRF theory. Hence, it could be concluded that the hydrolysis of both chlorides takes place without any specific solvent assistance. However, it is also possible that the specific NSA in the case of *t*-BuCl is compensated by the specific ESA in the case of AdCl. To obtain a more accurate value of ΔG for eq 2, we have used the B3LYP/6-31G(d) method. The computed value in water is now −4.18 kcal/mol (Table 1) (−5.33 kcal/mol with symmetry-number entropy correction) and, hence, is more negative than the experimental result. Seemingly, the ESA in the case of AdCl is ca. 2 kcal/mol higher than the NSA in the case of the solvolysis of *t*-BuCl. This result is in agreement with the postulated higher solvent assistance in the case of AdCl in comparison to *t*-BuCl.[29]

In a previous work, we have successfully used isodesmic reactions for the computation of relative solvolysis rates in the case of bridgehead derivatives using PCM/DFT methods.[57] However, it is noteworthy that from the analysis of an isodesmic reaction[54] only relative stabilities of free (unsolvated) carbocations but no absolute values for the solvent assistance can be obtained. Consequently, methodologies based on isodesmic equations cannot be employed for the calculation of solvolysis rates (cf. ref 54b) in the case of substrates exposed to different types of solvent participation. It is then necessary to develop new inexpensive computational methods able to give a quantitative answer to the question of the solvent assistance as well as a molecular insight into the mechanism of the hydrolysis of alkyl chlorides.

Potential Energy Surface (PES) for the S$_N$2 Reaction of the Monohydrates of MeCl, *t*-BuCl, and AdCl in the Gas Phase. In our opinion, the study of the potential energy surface (PES) for the substitution reaction of the monohydrates of alkyl chlorides could be a convenient way to achieve both accurate computation of hydrolysis rates and microscopic insight into the nature of solvent participation. Strikingly, there are no computations on the PES for S$_N$2 reactions of monohydrates of alkyl derivatives, despite its analogy with the Menshutkin reaction.[1,3,62] This situation has prompted us to carry out the computation of the reaction between a water molecule and MeCl, *t*-BuCl, and AdCl in the gas phase.

The relative total energy values, ΔE(g), of the critical points of the PESs computed by us in the gas phase for the substitution reaction of the monohydrates of MeCl, *t*-BuCl, and AdCl are given in Table 2, and relevant data of the corresponding geometries are given in Table 3.

Attempts to optimize the initial state (IS) for the backside water attack in the case of MeCl lead to the more stable IS for the frontside attack, corresponding to a complex with antiparallel disposition of the molecular dipoles, which is electrostatically more stable than the parallel orientation (cf. ref 1). Therefore, the backside IS for MeCl could only be optimized with a frozen A(O,C,Cl) angle of 180°. The backside IS in the case of *t*-BuCl was, however, easily optimized without any restrictions. Two ISs were found in the case of AdCl, according to the geometry of approximation of the water molecule. The staggered disposition, IS(S), is 5.8 kcal/mol more stable than the eclipsed disposition, IS(E) (see Supporting Information and Table 2). The final states (FS) of the reactions were obtained by optimizing the complexes formed from the optimized hydrated carbocationic species R(+)·OH$_2$ and a backsided chloride anion, at frozen C−O distances.

The PES for the backside attack to the MeCl molecule has been explored by running relaxed potential energy scans of the R(C,O) distance in the presence of a backsided chloride ion. The ΔE values of the optimized structures have been represented against the difference between the R(C,Cl) and R(C,O) distances (ΔR), which was chosen as the reaction coordinate. The result (see Supporting Information) was similar to the double-well energy profile found for the corresponding Menshutkin reaction.[1,3,62] However, in our case, the position of the TS ($\Delta E^{\ddagger} = 50.84$ kcal/mol at $\Delta R = 0.767$ Å) could only be determined from the data points by the second-derivative method, whereas in the case of the related Menshutkin reaction between NH$_3$ and MeCl, the TS ($\Delta E^{\ddagger} = 31.97$ kcal/mol) was easily recognizable by a zero-slope region at $\Delta R = 0.705$ Å.[1] The higher $\Delta E^{\ddagger}$ and ΔR values resulting for the reaction between water and MeCl in relation to the Menshutkin reaction are consistent with the higher nucleophilicity of ammonia in relation to water. The fact that the geometry of the TS for the hydrolysis is similar to the final state (FS) of the S$_N$2

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TABLE 2. Relative Energies of Relevant Stationary States[a] on the PES of the Monohydrates of MeCl, *t*-BuCl, and AdCl in the Gas Phase and in Water and Experimental Free Energies of Solvolysis in Water[b]

substrate	stationary state (for a determined attack type)	ΔE(g)	$\Delta G^‡$(w)[c]	$\Delta G^‡$(w) (exptl)
		Backside Attack		
MeCl	IS	0.0	0.0	
	TS	50.84	28.14[d]	27.9 (26.6[e])[48]
		Frontside Attack		
	IS	0.0	0.0	
	TS	56.74	51.40	
	FS	1.33		
	ΔE^f	−2.56		
	ΔG^f		−1.13	
		Backside Attack		
t-BuCl	IS	0.0	0.0	
	TS	48.51 (47.76)[g]	23.54 (22.96)[g] 22.04[d] (21.46)[d,g]	19.5 (23.2[e])[43]
		Frontside Attack		
	IS	0.0	0.0	
	TS	33.03	25.27	
	FS	−2.35		
	ΔE^f	−2.17		
	ΔG^f		−1.06	
		Frontside Attack		
AdCl	IS(S)	0.0	0.0	
	IS(E)	5.80		
	TS	42.24	21.65	21.89 (22.2[e])[6]
	FS	−2.40		

[a] In kcal/mol. IS = initial state. TS = transition state. FS = final state. [b] In kcal/mol, at 298 K and 1 atm. [c] Computed with the PCM model. [d] Corrected by the entropy of symmetry. [e] $\Delta H^‡$ values. [f] E(or G)(IS) (frontside attack) − E(or G)(IS) (backside attack). [g] Values computed with the B3LYP/6-31+G(d) method.

TABLE 3. Selected Geometrical Data[a] of Critical Points in the Hydrolysis of MeCl, *t*-BuCl, and AdCl, Computed with the B3LYP/6-31G(d) Method in the Gas Phase (g) and in Water Solution (w)

substrate	critical points	R(C,Cl)	R(C,O)	ΔR	A(H,C,Cl) or A(C,C,Cl)	A(O,C,Cl)
			Backside Attack			
MeCl	IS	1.809	3.109	−1.300	108.5	180.0
	TS(g)	2.424	1.657	0.767	81.5	180.0
	TS(w)	2.457	1.779	0.678	82.0	180.0
	FS	2.651	1.525	1.126	79.7	180.0
			Frontside Attack			
	IS	1.814	3.283	−1.469	106.9	78.0
	TS	2.597	2.172	0.425	72.0	75.0
	FS	3.277	1.522	1.755	35.0	79.0
			Backside Attack			
t-BuCl	IS	1.869	3.860	−1.991	107.3	180.0
	TS(g)[b]	3.419	1.682	1.737	75.0	180.0
	TS(w)	3.390	1.742	1.648	77.0	180.0
			Frontside Attack			
	IS	1.884	3.707	−1.823	106.2	68.0
	TS	3.740	2.312	1.428	121.0	58.0
	FS	3.899	1.682	2.217	155.0	45.0
AdCl	IS(S)	1.869	3.724	−1.855	108.5	65.0
	IS(E)	1.864	4.174	−2.310	109.6	55.0
	TS	3.164	2.564	0.600	27.0	54.0
	FS	3.953	1.449	2.504	109.9	45.0

[a] R in Å and A in deg. [b] Assumed to be FS.

reaction (ΔR = 1.126 Å, Table 3) is also in agreement with the Hammond postulate.[2,34]

The PES function for the hydrolysis of *t*-BuCl in the gas phase could not be followed by the scanning method because of the appearance of HCl elimination in the proximity of both IS and FS. Therefore, backside water attack in the gas phase should yield isobutylene only. That is, clearly, not the case for the solvolysis in water, because only ca. 3% of isobutylene is formed.[8] The predominant elimination in the gas phase can be attributed to the electrostatic interaction between the incipient chloride anion and a syn disposed hydrogen atom of a methyl group (see Figure 1). Thus, the elimination is preceded by a shift of the incipient chloride anion toward the hydrogen atom. In water solution, however, electrostatic interactions do not play any decisive role (because of the high dielectric constant of water) and, hence, the substitution reaction can be completed. Be-

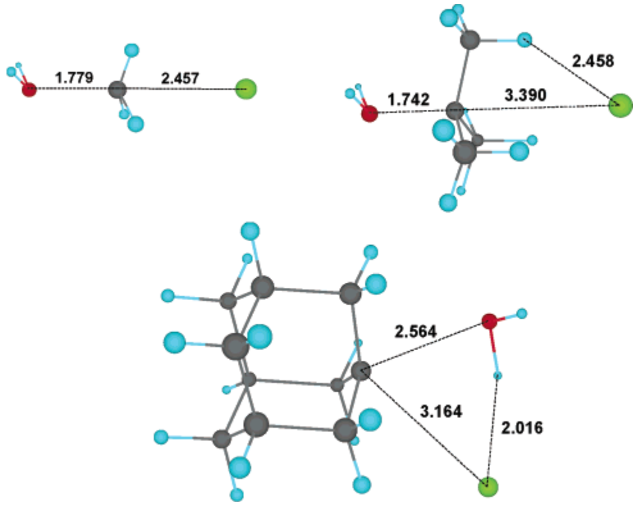

FIGURE 1. Computed geometries (selected distances in Å) for the backside transition states in the hydrolysis of MeCl and *t*-BuCl and for the frontside transition state in the hydrolysis of AdCl.

cause not enough data points for numerical differentiation were available, the TS ($\Delta E^{\ddagger} = 47.76$ kcal/mol, $\Delta R = 1.737$ Å) for the substitution reaction in the gas phase has been assumed to be the FS. It is noteworthy that *R*(C,Cl) distances of the TS structures increase on going from MeCl to *t*-BuCl (Table 3 and Figure 1), according to the corresponding distances computed by us with the B3LYP/6-31G(d) method for the isolated *t*-BuCl (1.862 Å) and MeCl (1.804 Å) molecules as well as the *R*(C,Cl) distances of the ISs for the backside attack (Table 3). Thus, the TSs become looser by methyl substitution, which is in agreement with the results for identity S_N2 reactions with chloride as the nucleophile.[64−67] However, the $\Delta E^{\ddagger}$ value for MeCl is computed to be higher (by ca. 2 kcal/mol) than that for the solvolysis of *t*-BuCl. Strikingly, this reactivity order is not in agreement with the steric hindrance for the approximation of the chloride ion to bulky R groups, as in the case of identity S_N2 reactions,[45] but rather with the stability of cations in the gas phase as well as with the formation of stabilizing O···H−C hydrogen bonds with the methyl hydrogens[2] in the case of *t*-BuCl (see distances in Figure 1).

The TS for the frontside attack of water to MeCl, *t*-BuCl, and AdCl could not be located by scanning the *R*(C,Cl) distance of the IS complex with a frontsided water molecule because this procedure gives rise to elimination, in the case of *t*-BuCl, or to the shift of the water molecule toward the C−H bonds, in the case of the other two substrates. Hence, we have used the QST2 option for the determination of the TS, which is based on the geometries of the reactants (IS) and products (FS) connected by the searched TS,[53] followed by optimization of the halfway structure between the reactants and products, combining the IRC and the TS optimization facilities[53] to find the minimum energy structure with an imaginary frequency. Thus, we have applied the general protocol, despite uncertainty about frequency computations in complexes.[44,66] In the TSs for the frontside substitution, the developing chloride anion and the water molecule show a staggered disposition with regard to the C−C (or H) bonds at the cationic center. Thus, the TS structures computed by us are similar to the TS with C_s symmetry proposed for the identity frontside S_N2 reaction between MeCl and Cl^-, which takes place with retention of configuration in the gas phase,[67,68] as well as to the TS with retention of configuration for the reaction of *t*-BuCl with a water cluster.[50] Hence, the reaction path giving rise to the frontside TSs can be considered to be initiated by a bending deformation of the C−Cl bond assisted by the solvent.

The backside attack is favored in relation to the frontside attack in the case of the hydrolysis of MeCl by ca. 6 kcal/mol, whereas in the case of the identity S_N2 reaction of MeCl in the gas phase, the backside attack is favored by ca. 57 kcal/mol.[67,68] Moreover, the frontside attack in the case of *t*-BuCl is favored by ca. 15 kcal/mol in relation to the backside attack. The reason for these very relevant discrepancies is the result of the favorable disposition of the water molecule to bridge the hydrogen atoms and the incipient chloride anion in the case of the frontside attack to *t*-BuCl and MeCl molecules (see distances in Figure 1), as well as the repulsion between the chloride anions in the case of the identity reaction.

Computations in Water Solution. The study of the effect of unspecific water-induced rate effects on the PES for the solvolysis of our three monohydrates has been carried out using the PCM model of the SCRF theory with the B3LYP/6-31G(d) method.

The stationary points on the PES for the solvolysis of the backsided monohydrates of MeCl and *t*-BuCl are given in Tables 2 and 3. The TSs have been approximately located from the corresponding PES in water (see Supporting Information). In the case of *t*-BuCl, the use of the second-derivative method in the PES function in water was needed. The right TS structures (Figure 1; see also Table 3) have been determined by using the ICR facility[53] in combination with the PCM model. The frequency analysis afforded one imaginary frequency in both cases. The computed $\Delta G^{\ddagger}$ values for MeCl and *t*-BuCl, after entropy of symmetry correction, are in very good agreement with the experimental results (Table 2).

The geometries of the TSs for both *t*-Bu(+) and Me(+) are nearly-planar C_{3v} structures (Figure 1 and Table 3), with *A*(C,C,Cl) or *A*(H,C,Cl) angles of ca. 80°, which is in agreement with the TS structures obtained using solvation clusters.[34,36] In the case of *t*-Bu(+), the three C−H bonds are directed toward the incipient chloride anion.

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TABLE 4. Selected Bond Orders and Mulliken Charges[a] Computed for the Backside Transition State for the Hydrolysis of MeCl and *t*-BuCl

substrate	bond	bond order	atom	charge
MeCl	C−O	−0.174	C	+0.370[b]
	C−Cl	0.181	O	+0.224[b]
			Cl	−0.594
t-BuCl	C−O	0.076	C-1	+0.212
	C−Cl	−0.005	O	+0.258[b]
			Cl	−0.759

[a] In au (atomic units). [b] With hydrogen summed into heavy atoms.

A relevant geometrical discrepancy with published results is that the computed R(C,Cl) distance (3.39 Å) at the TS in water is higher than previous estimations[44−46] (2.5−3.0 Å) but shorter than the computed value with PMF simulations using incremented Born energies (5.2 Å).[42]

It is noteworthy that the reaction coordinates (ΔR) are (slightly) shorter than those computed in the gas phase (Table 3). This result is in agreement with the general case of a system consisting of a neutral nucleophile and an anionic leaving group, where charge separation takes place during the reaction, because the solvation effect of water should give rise to a reduction of the reaction barrier and a decrease in the endergonic character of the reaction in relation to the gas-phase reaction and, hence, to a TS shift toward the IS according to the Hammond postulate.[34] However, the shift is not as marked as the one computed with the QM/MM theory (0.45 Å) in the case of the related Menshutkin reaction of MeCl. The analysis of the PES in water solution also reveals that the intimate ion pair (IIP)[7,44] is located at $\Delta R = 0.980$ Å and is separated by a barrier of only 0.3 kcal/mol in relation to the TS.

In the case of *t*-BuCl, the computed $\Delta G^\ddagger$ value is higher than the experimental result but very similar to the experimental $\Delta H^\ddagger$ value (Table 2). This result is very interesting because it could reveal that the PCM model is not able to reproduce the anomalous high-activation entropy for the solvolysis of *t*-BuCl.[33] There are, however, doubts about this question because an improved $\Delta G^\ddagger$ value is obtained, introducing the entropy of symmetry correction and using the 6-31+G(d) method (21.46 kcal/mol, Table 2). It is noteworthy that, unlike the MeCl hydrolysis, there is only a negligible shortening (by 0.1 Å) of the reaction coordinate ΔR on going from the gas phase to water solution.

The population analysis of the TSs in water has been carried out using the Mulliken method. The results are summarized in Table 4. The computed bond orders show that the C···Cl interaction is bonding in the case of MeCl but antibonding for *t*-BuCl, whereas the opposite situation takes place in the C···O interaction. The opposite sign of the two bond orders for the same substrate shows that the cationoid carbon atom is not covalently pentacoordinated.[68] The calculated atomic charges reveal a charge localization by 59% and 76% at the incipient chloride anion in the TSs of MeCl and *t*-BuCl, respectively. The last value is in agreement with the 80% charge separation estimated for the hydrolysis of *t*-BuCl.[12,40]

TABLE 5. Computed Solvent Assistance, ΔE(SA) for the Gas Phase and ΔG(SA) for Water Solution, for the Hydrolysis of MeCl, *t*-BuCl, and AdCl[a]

	MeCl·H_2O	*t*-BuCl·H_2O	AdCl·H_2O
ΔE(SA)(IS)	−2.16	−3.36 (−5.70)[b]	−5.61
ΔE(SA)(TS)	4.41	−8.29[c] (−18.31)[b]	−15.03
ΔE(SA)(FS)	−4.37	−8.29	−91.14
ΔG(SA)(IS)	−0.40	−0.32 (−4.70)[b]	−2.91
ΔG(SA)(TS)	−36.76	−37.50 (−15.26)[b]	−20.68
ΔG(SA)(FS)	−33.04	−26.06	−74.69
$\Delta E^\ddagger$(SA)	6.16	−4.87 (−12.61)[b]	−9.62
$\Delta G^\ddagger$(SA)	−36.36	−37.18 (−11.06)[b]	−17.77

[a] In kcal/mol at 298 K. [b] Frontside attack. [c] The TS was assumed to be the FS.

The $\Delta G^\ddagger$ values (Table 2) for the water frontside attack to the three studied chlorides have been calculated from the G values computed with the PCM method, using the geometries of the corresponding ISs and TSs in the gas phase (see Figure 1) without any corrections resulting from the Hammond postulate. In the case of MeCl, the backside attack is much more favored in relation to the frontside attack, in agreement with the admitted S_N2 character for this reaction. However, in the case of *t*-BuCl hydrolysis, the backside attack is favored by ca. 2.0 kcal/mol. This result offers a (qualitative) explanation for the formation of products with retained configuration in the case of the solvolysis of *t*-RX derivatives.[11] The reason for the higher stability of the frontsided TS in the case of *t*-BuCl seems to be the attractive interaction between the water molecule and the methylic hydrogens.

The excellent accordance between the $\Delta G^\ddagger$ values computed by us for the hydrolysis reactions of MeCl, *t*-BuCl, and AdCl and the experimental values (Table 2) clearly shows that our protocol for the calculation of the free energy of activation of the hydrolysis of alkyl chlorides is the most simple and accurate procedure for the quantum-mechanical computation of solvolysis rates.

Computing the Solvent Assistance to the Hydrolysis of AdCl, MeCl, and *t*-BuCl. The solvent stabilization (or assistance), ΔE(SA), by water of a reaction intermediate is given by the corresponding energy of hydration according to eq 4, in which the E(RCl)

$$\Delta E(\mathrm{SA}) = E(\mathrm{RCl{\cdot}H_2O}) - [E(\mathrm{H_2O}) + E(\mathrm{RCl})] \quad (4)$$

term represents the single-point energy of the unrelaxed RCl species obtained by deleting the water molecule in the corresponding water complex and $E(H_2O)$ is the energy of the unrelaxed water molecule. The contribution of the basis set superposition error (BSSE) to the hydration energies is negligible (ca. 0.1 kcal/mol), according to our computations based on the counterpoise method (CP).[53,69]

As shown in Table 5, ΔE(SA) is a substrate-dependent function of the reaction coordinate ΔR. The ΔE(SA) values for the backside complexes can be identified as the NSA for the reaction in the gas phase, whereas the ΔE(SA) values for the frontside reactions are a measurement of the so-called ESA. The effects of unspecific interactions in water as the solvent, as expressed by the ΔG(SA) values computed with the PCM model, are also a function of the reaction coordinate, and therefore, very different values were computed for the FSs, TSs, and ISs

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TABLE 6. Summary of the Variational PCM Results[a] for the FS and IS Complexes

	FS complexes				
	MeCl(FS)	MeCl[b]	*t*-BuCl(FS)	*t*-BuCl[b]	H_2O (mean values)
PSS[c]	−37.08	−4.07	−32.48	−12.38	−3.54
TNE[d]	4.43	5.76	8.48	9.02	2.24

	IS complexes			
	MeCl(IS)	MeCl[e]	*t*-BuCl(IS)	*t*-BuCl[e]
PSS[c]	−4.15	−1.33	−4.96	−1.51
TNE[d]	5.53	4.41	9.43	7.80

[a] In kcal/mol. [b] Computed for the unrelaxed RCl species and obtained by deleting the water molecule from the FS complex. [c] Polarized solute/solvent interactions. [d] Total nonelectrostatic terms. [e] Computed for the fully optimized structures.

(Table 5). The specific water effects on the hydrolysis rates in the gas phase are given by the $\Delta E^{\ddagger}$(SA) values, the differences between the ΔE(SA) values of the TSs and the values of the corresponding ISs. On the other hand, the corresponding $\Delta G^{\ddagger}$(SA) values are a measure of the evolution of unspecific water interactions of the water complexes on going from the ISs to the TSs.

The arrangement of the $\Delta E^{\ddagger}$(SA) values in the gas phase for the backside attack to *t*-BuCl and MeCl could seem surprisingly in agreement with the conventional representation of the S_N2 reactions[4] because $\Delta E^{\ddagger}$(SA) is higher for *t*-BuCl. The relative ΔE(SA) values for the solvolysis of MeCl and *t*-BuCl can be rationalized, however, in terms of the stability of the corresponding complexes, considering that the water molecule is involved in hydrogen bonds (as a donor) and electrostatic interactions with the methylic hydrogen atoms of *t*-BuCl. Moreover, the C···O interaction is bonding in the TS of the hydrolysis of *t*-BuCl but antibonding in the case of MeCl (Table 4).

According to the solvation model offered by the PCM model, a striking inversion of the SA in water solution is computed because of the effect of unspecific solute−solvent interactions (examples of variational PCM results for the backsided attack are given in Table 6). The formation of the $RCl{\cdot}H_2O$ complexes, and hence the SA, is favored by the PSS electrostatic interactions but disfavored by the TNE interactions in relation to the corresponding nonhydrated species. In the case of the ISs, the solvent effect is relatively small but negative. This complex-stabilizing interaction of water is a peculiarity of the hydrolysis reaction because, in the case both of the related Menshutkin reaction and identity S_N2 substitutions, the separated reactants are stabilized in polar solvents to make the dipole complex (the IS) disappear.[1,45] In contrast, the complex-stabilizing interaction is very high for the corresponding TSs and FSs, particularly for the hydrolysis of MeCl, in which the strong PSS interactions are dominant. As a consequence, the global NSA for the hydrolysis of MeCl becomes very similar to the NSA for *t*-BuCl, and therefore, it can be concluded that the reaction of both water complexes in water solution takes place with S_N2 character because of unspecific solvent interactions.

Another interesting consequence of the unspecific water interactions is that the ESA for the frontsided attack to *t*-BuCl is lower than that for AdCl in water solution but higher in the gas phase (see Table 5). Hence, the relative ESA in both cases is not determined by steric effects, unlike usual interpretations,[25,27] but by unspecific solvent effects.

This result is in total contradiction with the conclusion of Gayewski's work against NSA in the *t*-BuCl TS and for higher hydrogen bond donation (ESA) in the TS of the AdCl hydrolysis.[27]

Summary and Conclusions

The predictive success of the LFER methods is undeniable, but the mechanistic implications are questionable, mainly because of the collinearity among the parameters defining the solvent. Moreover, such parameters are based on bulky and, sometimes, ad hoc selected solvent properties.

On the other hand, the use of isodesmic reactions has been proposed as a method for the detection of NSA.[54b] However, our results show that isodesmic reactions are inadequate for the accurate study of reactions involving solvated cations of different types.

We have also demonstrated that the PES in water solution for the substitution reaction of the monohydrates of MeCl, *t*-BuCl, and AdCl computed with the computationally inexpensive PCM/B3LYP/6-31G(d) method allows the determination of the corresponding free energies of activation in fair accordance with the experimental values. Thus, there is a marked parallelism between hydrolysis and the Menshutkin reaction in water of alkyl halides with regard not only to the mechanism but also to the success of the PCM model.

Neither the valence bond (VB) method of Hynes[32] nor the statistical methods used for the study of the dissociation of *t*-BuCl can account for the products formed from the intermediate *t*-Bu(+). However, our treatment of the hydrolysis of *t*-BuCl affords a computational explanation for the formation of products with retention of configuration in the solvolysis of tertiary alkyl (*t*-R) derivatives. Moreover, the elimination reaction can be followed by scanning the reaction coordinate ΔR in the gas phase. This reaction is initiated by the electrostatic attraction between the incipient chloride anion and the methylic hydrogen atoms of the intermediate cation.

The most relevant mechanistic conclusion is that the hydrolysis of MeCl and *t*-BuCl takes place clearly under NSA because of unspecific interactions with the solvent. The similarity between the hydrolysis mechanisms of MeCl and *t*-BuCl is also demonstrated by computationally expensive microsolvation methods.

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Supporting Information Available: Optimized geometries (Cartesian coordinates) of the studied water complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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