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What Is the Stabilizing Interaction with Nucleophilic Solvents in the Transition State for Solvolysis of Tertiary Derivatives: Nucleophilic Solvent Participation or Nucleophilic Solvation?

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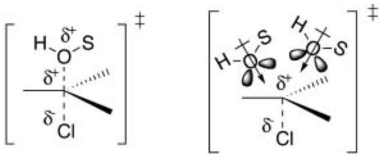
ABSTRACT



We propose that controversy concerning the mechanism for solvolysis at tertiary carbon is semantic and can be avoided by making a clear distinction between (1) *nucleophilic solvent participation*, which is stabilization of the transition state for *concerted* solvolysis by formation of a partial covalent bond to the solvent nucleophile, and (2) *nucleophilic solvation*, which is stabilization of the transition state for *stepwise* solvolysis through carbocation or ion pair intermediates by charge–dipole interactions with nucleophilic solvents.

Recent studies designed to refine our understanding of solvolysis reactions have identified numerous stabilizing interactions with solvent in the transition state.[1−6] At the same time, there has been little effort toward reconciliation of results which point to a role for nucleophilic assistance from solvent in stabilization of the transition state for solvolysis of simple tertiary derivatives with those which do not support significant transition state stabilization by formation of a covalent bond to the incoming solvent nucleophile. This creates the impression that studies of solvolysis at tertiary carbon have resulted in a morass of experimental data and which, when interpreted individually, provide support for conflicting mechanistic conclusions. For example, a recent important evaluation of the energetics of nucleophilic assistance from solvent in the solvolysis reactions of a series of tertiary chlorides with alkyl substituents of varying steric bulk was interpreted as providing evidence for stabilization of the transition state for solvolysis of *tert*-butyl chloride by “nucleophilic solvent participation” (NSP).[7] However, NSP was not rigorously defined and there was no clear physical picture of the nature of the nucleophilic assistance. Moreover, these important new experimental results were not placed within the context of convincing evidence from earlier studies that there is little or no stabilization of the transition state for solvolysis of simple tertiary derivatives by formation of a partial covalent bond to the incoming solvent nucleophile.[8,9]

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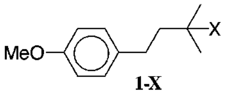
We propose that results of the wealth of investigation of solvolysis reactions at tertiary carbon can be reconciled by a simple model for the physical role of nucleophilic solvents in transition state stabilization. These studies have proceeded essentially along two different lines:

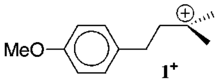
(1) The effects of a change in the bulk solvent on k_{obsd} (s^{-1}) for solvolysis of *tert*-butyl and related tertiary alkyl derivatives have been characterized.[1,10,11] The results show that k_{obsd} depends strongly on the ability of solvent to stabilize free ions. In some cases, k_{obsd} also depends on the ability of solvent to develop "backside" nucleophilic interactions with the developing cationic carbon in the transition state,[2] to provide "frontside" solvation of the incipient leaving group anion,[5] and to provide specific solvation of peripheral alkyl and aryl substituents.[3,4] The best efforts to evaluate these various factors are consistent with the conclusion that there is a small dependence of k_{obsd} for solvolysis of *tert*-butyl derivatives[12,13] and some cumyl derivatives[14] on solvent nucleophilicity.

(2) The products of the reaction of simple tertiary derivatives such as **1-X** in the presence of strongly nucleophilic reagents have been determined,[8] and estimates of the lifetime of tertiary carbocations in largely aqueous solvents have been obtained.[4,8] The results show that there is little or no stabilization of the transition state for the rate- and/or product-determining step for the reactions of **1-X** by interaction of the nucleophilic solvent component methanol or the strongly nucleophilic azide ion with the electrophilic carbon at the substrate **1-X** and/or at the ion pair intermediate $\mathbf{1^+{\cdot}X^-}$.[8]



1-X

X = Cl, $O_2CC_6F_5$, OH/H^+

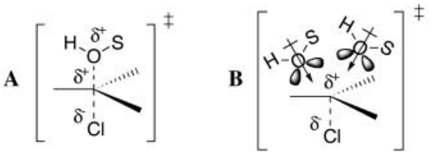


$\mathbf{1^+}$

Nucleophilic Solvation and Nucleophilic Solvent Participation. We propose that controversy concerning the mechanism for solvolysis of simple tertiary derivatives is essentially semantic and results from the failure to define and distinguish the following two physically different interactions of nucleophilic solvents with the developing cationic carbon in the transition state.

(1) Nucleophilic Solvent Participation (NSP). Traditionally this is thought of as an interaction which accelerates solvolysis by formation of a partial covalent bond between the incoming solvent nucleophile and the developing cationic carbon in the transition state for cleavage of the bond to the leaving group (Scheme 1A). It is analogous to the well-defined stabilization of the transition state for concerted A_ND_N (S_N2)[15] nucleophilic substitution. NSP has been defined as "kinetically significant involvement of the solvent as nucleophile or base by partial bonding (as distinct from general electrostatic solvation) to any atom of the substrate (e.g., α-carbon, β-hydrogen, etc.)" [13] or as "electron donation from solvent to the developing positive dipole of a reacting C−X bond".[5] We suggest that this stabilization of the transition state by formation of a partial covalent bond to the incoming solvent nucleophile, in what must necessarily be a *concerted* reaction *without* a carbocation intermediate, be referred to exclusively as *nucleophilic solvent participation* (NSP, Scheme 1A).

Scheme 1



(2) Nucleophilic Solvation (NS). Historically, the literature on nucleophilic substitution reactions of solvent at aliphatic carbon has been dominated by studies designed to distinguish between stepwise $D_N + A_N$ (S_N1)[15] and concerted A_ND_N (S_N2)[15] mechanisms.[11,12,16−18] Therefore, the abundant evidence for stabilization of the transition state for solvolysis by nucleophilic solvents has been discussed mainly in terms of NSP (see above), for which the interaction of solvent with the developing cationic center is functionally equivalent to the role of any nucleophile in a concerted S_N2 process (Scheme 1A). This partial covalent bond to the nucleophile, and the resulting stabilization of the transition state for concerted bimolecular substitution, will become weaker with increasing stabilization of the putative carbocation intermediate.[19] When the carbocation is stable enough to form as a reaction intermediate, the mechanism for solvolysis will change from a *concerted* displacement to a *stepwise* process, and this covalent interaction ceases to be important.[19,20] We attribute any nucleophilic stabilization of the late carbocation-

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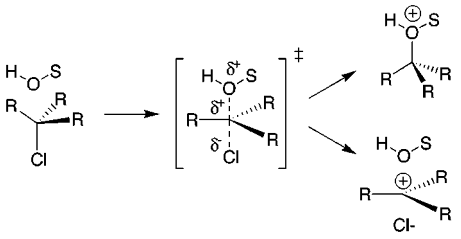
like transition state for cleavage of the bond to the leaving group in *stepwise* solvolysis reactions to charge−dipole interactions with polar solvents. These stabilizing interactions are expected to be similar in size and nature to the stabilizing solvation of cations such as the tetramethylammonium ion.[21] Such dipolar interactions with nucleophilic solvents are essentially independent of carbocation stability,[22] but they may change systematically with changes in the structure of the carbocation which result in changes in the steric accessibility of solvent to the cationic center.[7,23] We suggest that stabilizing interactions between the dipole of nucleophilic solvents and carbocations, and the corresponding interactions in the transition state for their formation in *stepwise* solvolysis reactions, be referred to exclusively as *nucleophilic solvation* (NS, Scheme 1B).

Solvolysis Reactions at Tertiary Carbon. Studies of the effects of changing solvent nucleophilicity on the observed rate constants and product distribution for solvolysis reactions at tertiary carbon are consistent with the following mechanistic picture.

(1) These reactions are limiting cases for which the transition state is stabilized only by nucleophilic solvation (Scheme 1B), because there is very little stabilization of the transition state for the rate- or the product-determining step by formation of a partial covalent bond to the incoming solvent nucleophile. This is supported by the following experimental results:

(a) There is no significant increase in k_{obsd} (s^{-1}) for reaction of the simple tertiary derivatives **1-Cl** and **1-$O_2CC_6F_5$** in largely aqueous solvents when the concentration of azide ion is increased from 0 to 0.5 M, and small values of the product rate constant ratio $k_{az}/k_s = 0.3-0.4\ M^{-1}$ for formation of **1-N_3** and **1-OSolv** were determined.[8] Therefore, there is no interaction between the substrate and the strong nucleophile azide ion that provides significant transition state stabilization for nucleophilic substitution at tertiary carbon (see above).[8,9,18] This eliminates the possibility of bimolecular nucleophilic substitution reactions of hydroxylic solvents (NSP) because these are much more weakly nucleophilic than azide ion (Scheme 2, upper pathway).[18] It is also not reasonable that there be significant transition state stabilization by formation of a partial covalent bond to the solvent nucleophile which is then *broken* on proceeding to a tertiary carbocation intermediate (Scheme 2, lower pathway). This is because the large thermodynamic driving force and the very small kinetic barrier for reaction of tertiary carbocations with nucleophilic solvents strongly favor collapse to product of any transition state in which there is a partial bond to the solvent nucleophile over cleavage of this bond to form a "solvated" carbocation.[8]

Scheme 2



(b) The small values of the product rate constant ratio $k_{MeOH}/k_{TFE} = 1.2-2.0$ for formation of **1-OMe** and **1-OCH_2CF_3** from reaction of **1-X** in largely aqueous mixed alcohol solvents[8] show that there is very little stabilization of the transition state for reaction of a reversibly formed ion pair by formation of a partial covalent bond to the incoming solvent nucleophile. There is good evidence that the *chemical* barrier to reaction of $\mathbf{1}^+$ with nucleophilic solvents is similar to the barrier for rotation of a molecule of solvent into a "reactive" position, which occurs by reorganization of the surrounding solvent cage ($k_{reorg} \approx 10^{11}\ s^{-1}$).[8] Therefore, the solvent adducts are formed by capture of the ion pair intermediate $\mathbf{1}^+ \cdot \mathbf{X}^-$ by a molecule of solvent that is present in the local solvation shell at the time of its formation from **1-X**, in a process that is nearly independent of solvent nucleophilicity.

(c) There is no strong imperative for *concerted* displacement reactions of solvent at tertiary carbon (Scheme 2, upper pathway) because solvolysis of chiral tertiary derivatives gives substitution products with both retention and inversion of configuration.[17,24] The excess of products that form with inversion is consistent with *stepwise* reactions through short-lived ion pair intermediates that are shielded by the leaving group from frontside solvent addition and which react with a molecule of solvent present in the local solvation shell at the time of ion pair formation.

(2) The sensitivity of k_{obsd} (s^{-1}) for solvolysis of tertiary derivatives to solvent nucleophilicity represents transition state stabilization by nucleophilic solvation. This is largely electrostatic in nature because there is no significant transition state stabilization by formation of a partial covalent bond to the solvent nucleophile (see above). This is supported by the following experimental results:

(a) The activation barriers for solvolysis of a series of caged and bridgehead tertiary alkyl chlorides RCl relative to that for 1-adamantyl chloride **8** ($\Delta\Delta G^\ddagger$) in the weakly nucleophilic solvent 97% HFIP/H_2O (HFIP = hexafluoro-2-propanol) and in the strongly nucleophilic solvent 80% EtOH/H_2O exhibit similar good correlations with the Gibbs free energy change for transfer of chloride ion from RCl to the 1-adamantyl carbocation in the gas phase ($\Delta G°$, eq 1).[7]

$$\text{1-Ad}^+\ (g) + \text{RCl}\ (g) \xrightleftharpoons{\Delta G^\circ} \text{1-AdCl}\ (g) + \text{R}^+\ (g) \qquad (1)$$

The positive deviation of $\Delta\Delta G^\ddagger$ for solvolysis of *tert*-butyl

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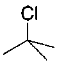
chloride **2** from the correlation in 80% EtOH/H_2O shows that this solvent provides a 7.4 kcal/mol greater stabilization of the transition state for solvolysis of **2** than of the transition state for solvolysis of caged and bridgehead chlorides. The smaller 3.1 kcal/mol positive deviation of $\Delta\Delta G^{\ddagger}$ for solvolysis of **2** from the almost identical correlation in 97% HFIP/H_2O requires a ca. 4.3 kcal/mol greater stabilization of the transition state for solvolysis of **2** by 80% EtOH/H_2O than by 97% HFIP/H_2O.[7]

(b) The 7.4 kcal/mol greater stabilization of the transition state for solvolysis of *tert*-butyl chloride **2** by 80% EtOH/H_2O than of that for solvolysis of caged and bridgehead chlorides is much smaller than the estimated 49 kcal/mol free energy of solvation the *tert*-butyl carbocation by 100% H_2O.[21] A similar solvation energy is expected for tertiary carbocations in 80% EtOH/H_2O (ca. 30 mol % of water) so that the 7.4 kcal/mol differential stabilization of the transition state for solvolysis of **2** corresponds to a relatively small fraction of the total solvation energy of the *tert*-butyl carbocation. This is consistent with steric shielding by the hydrocarbon framework of caged and bridgehead tertiary carbocations which minimizes stabilizing nucleophilic solvation by charge−dipole interactions between solvent and the cationic center. The 4.3 kcal/mol greater stabilization of the transition state for solvolysis of **2** by 80% EtOH/H_2O than by 97% HFIP/H_2O could reflect the reduced steric bulk of the former solvent which may allow for interaction of a larger number of solvent molecules with the cationic center.[25] Computational studies designed to model these effects would be useful.

(3) The stabilization of carbocations and carbocation-like transition states by nucleophilic solvation becomes smaller with increasing congestion at the substrate and steric hindrance to backside charge−dipole interactions with nucleophilic solvents (Scheme 1B). This is supported by the decreases in the positive deviation of $\Delta\Delta G^{\ddagger}$ for solvolysis of **2**−**7** from the rate-equilibrium correlation in 80% EtOH/H_2O (see above) with increasing branching and steric congestion at RCl. The magnitudes of these deviations provide estimates for the differential stabilization of the transition state for solvolysis of **2**−**7** over that for solvolysis of caged and bridgehead chlorides by nucleophilic solvation.



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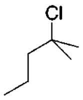

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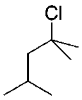

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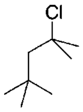

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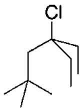

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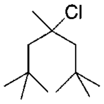

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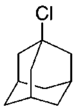

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In summary, recent data strongly support the solvolysis of tertiary derivatives by a *stepwise* mechanism with rate-determining ionization to form a carbocation intermediate. There is no significant stabilization of the transition state by formation of a partial covalent bond to the incoming solvent nucleophile (NSP) but rather the carbocation-like transition state is stabilized by interaction with the dipole of nucleophilic solvents (NS). The use of carefully defined terms that distinguish stabilization of the transition state for solvolysis at tertiary carbon by participation of the solvent as a nucleophile in a *concerted* reaction (nucleophilic solvent participation, Scheme 1A) from stabilization by charge−dipole interactions in a *stepwise* reaction (nucleophilic solvation, Scheme 1B) will minimize controversy about the interpretation of experimental results of studies of solvolysis mechanisms. Although we have chosen to use the conventional term nucleophilic solvation, we realize that its use to describe transition state stabilization for reactions in which formation of a covalent bond to the incoming solvent nucleophile in the rate-limiting step has been specifically excluded is confusing. A term such as *dipolar solvation*, or more simply, *solvation*, may be more appropriate.

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[25] Dipole moments of 2.05 D for HFIP, 2.03 D for CF_3CH_2OH, and 1.65 D for EtOH have been determined in cyclohexane at 25 °C (Kivinen, A.; Murto, J.; Lehtonen, M. *Suom. Kemistilehti B* **1968**, *41*, 359−363). However, nucleophilic solvation of carbocations by fluorinated alcohols may be less effective than by EtOH because the CF_3 groups should result in a significant change in the *orientation* of the dipole such that its negative end is positioned between the bulky CF_3 groups and the hydroxyl group. This may result in reduced accessibility of the "hindered" dipole of fluorinated alcohols to the cationic center.