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Reactions of carbocations with water and azide ion: calculation of rate constants from equilibrium constants and distortion energies using No Barrier Theory[†]

J. Peter Guthrie* and Vladimir Pitchko

Department of Chemistry, University of Western Ontario, London, Ontario, Canada N6A 5B7

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ABSTRACT: Rate constants for the reaction of water or azide ion with various substituted benzylic carbocations can be calculated from the equilibrium constants for cation formation and distortion energies by means of the No Barrier Theory. Rate constants for the water reactions span 10 orders of magnitude. Most but not all of the azide reactions are diffusion controlled. The rate constants, and in particular those less than diffusion controlled, were successfully calculated. The set of equilibrium constants available from the literature was supplemented using alkyl chloride hydrolysis equilibrium constants and relative cation formation equilibrium constants derived from DFT/continuum calculations. The model used for these reactions allows for the entropic cost of bringing solutes together, the desolvational cost of losing hydrogen bonding solvation by water and the cost of moving the aryl ring through the solvent as the central atom changes from sp^2 to sp^3 hybridization and from planar to pyramidal geometry. Copyright © 2004 John Wiley & Sons, Ltd.
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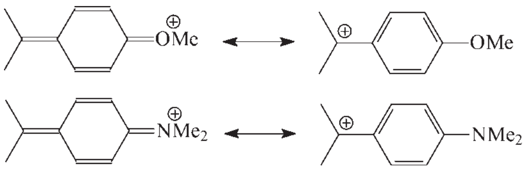
KEYWORDS: carbocations; water; azide ion; equilibrium constants; distortion energies; No Barrier Theory

INTRODUCTION

The S_N1 mechanism has been extensively studied for many years,[1–4] but only recently has it been possible to determine rate constants for the second stage of the reaction of reactive carbocations, where a solvent molecule or other nucleophile traps the carbocation to give a stable product.[5,6] For at least some systems there are now rate and equilibrium constants. The available data, and values estimated in this work, are given in Table 1. This provides a starting point for examining the application of No Barrier Theory[7–10] to the S_N1 mechanism. This theory allows calculation of rate constants using the equilibrium constants as the experimental input data. Equilibrium constants for the formation of carbocations from the usual starting materials are available for only a very small number of compounds at this time.

No Barrier Theory has been applied to the reactions of water with carbonyl compounds[7] and protonated carbonyl compounds,[7] which can be regarded as carbocations with very good electron-releasing substituents.

Since the approach worked in these cases, it seems reasonable to hope that it will work in analogous cases with extended conjugation:



or even for carbocations with only aryl or alkyl substituents.

We now report that No Barrier Theory successfully calculates the rate constants for trapping of carbocations over a range of 10 powers of 10 in rate constant.

THEORY

General

No Barrier Theory (NBT)[7–10] states that if it were possible to have only one thing happen in a chemical reaction, then there would be no kinetic barrier to the reaction, but only the thermodynamic cost if the reaction proceeded uphill in energy, and no barrier at all if the reaction were downhill in energy. This is, of course, contrary to experience with almost all real reactions. The key is the clause 'if only one thing happens'; most

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**Correspondence to:* J. P. Guthrie, Department of Chemistry, University of Western Ontario, London, Ontario, Canada N6A 5B7.
E-mail: peter.guthrie@uwo.ca
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Table 1. Rate and equilibrium constant data for reactions of nucleophiles with carbocations[a]

	Water		Azide	
Compound	pK_R[b]	Log k_w[c]	Log K_{az}[d]	Log k_{az}[e]
$C_6H_5CH_2^+$	≤ -20.7[f]	≥ 11.7[f]		
$CH_3OC_6H_4CH_2^+$	−10.1[g]	8.60[h]	19.13[h]	9.7[h]
$C_6H_5CH(CH_3)^+$	−16.2[f]	11.2[f]		
$CH_3OC_6H_4CH(CH_3)^+$	−9.4[i] −8.5[g]	7.9[i]	16.59[h]	9.41[j,k]
$(CH_3)_2NC_6H_4CH(CH_3)^+$	0.5[l]	1.90[m]	8.15[n]	7.20[m]
$C_6H_5C(CH_3)_2^+$	−13.1[f]	10.4[f]		
$CH_3OC_6H_4C(CH_3)_2^+$	−6.6[o]	7.3[o]	14.17[h]	9.11[j,k]
$C_6H_5CH(CF_3)^+$	−28.5[p]	11.0[q]		
$CH_3OC_6H_4CH(CF_3)^+$	−20.8[g]	8.0[h]	23.47[h]	9.43[j,k]
$(CH_3)_2NC_6H_4CH(CF_3)^+$	−9.3[p]	3.2[r]		
$C_6H_5C(CH_3)(CF_3)^+$	−23.7[p]	10.4[s]		
$CH_3OC_6H_4C(CH_3)(CF_3)^+$	−13.8[p]	6.51[t]	21.44[h]	9.7[h]
$C_6H_5C(CF_3)_2^+$	−35.7[p]	10.4[s]		
$CH_3OC_6H_4C(CF_3)_2^+$	−26.0[g]	6.48[u]	26.70[h]	9.7[h]

[a] At 25 °C, in aqueous solution, unless noted otherwise.

[b] −Log K for $ArC^+RR' + H_2O \rightleftharpoons ArC(OH)RR' + H^+$; p$K_R$ values are corrected from 1:1 TFE–water to pure water as suggested in Ref. 23.

[c] k is for the pseudo-first-order reaction, $ArC^+RR' + H_2O$; log k values are calculated, using $[H_2O] = 55.5$ M, from second-order rate constants determined in 1:1 TFE–water.

[d] Log K for $ArC^+RR' + N_3^- \rightleftharpoons ArC(N_3)RR'$.

[e] k is for the second-order reaction.

[f] Ref. 23.

[g] Estimated from the equilibrium constant for ionization of the corresponding chloride, as described in the text; see Table 2.

[h] Ref. 32.

[i] Ref. 33.

[j] In 1:1 trifluoroethanol–water.

[k] Ref. 24.

[l] Ref. 5.

[m] Ref. 34.

[n] Estimated as described in the text.

[o] Ref. 35.

[p] Estimated from the correlation of solution and gas phase relative cation formation free energies, as described in the text.

[q] Estimated by extrapolation of logarithms of rate constants for reaction of $pXC_6H_4CH(CF3)^+$ [36] vs σ;[37,38] see Table S2.

[r] Ref. 36.

[s] Assumed to be the same as for $C_6H_5C(CH_3)_2^+$ based on the observed similar values of rate constants for $4\text{-}CH_3OC_6H_4C(CH_3)_2^+$ and $4\text{-}CH_3OC_6H_4C(CF_3)_2^+$.[24]

[t] Assumed to be the same as the average of the rate constans for $4\text{-}CH_3OC_6H_4C(CH_3)_2^+$ and $4\text{-}CH_3OC_6H_4C(CF_3)_2^+$.[24]

[u] Ref. 24.

real chemical reactions require at least two things to happen: a bond making/breaking process and a geometry change. Two (or more) simple reaction dimensions, for each of which the energy is a quadratic function of the reaction coordinate, combine to give a kinetic barrier for the overall process in which all reaction coordinates proceed to completion.

No Barrier Theory is based on the following postulates:

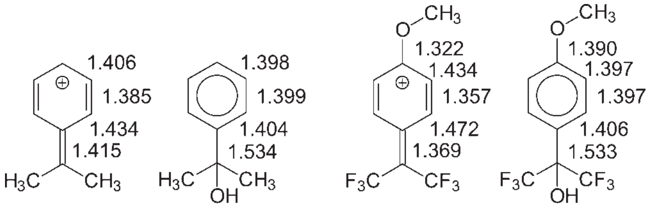
1. Reactants (here we are using 'reactants' to mean the molecular system involved in the chemical reaction at any point on the reaction hypersurface) are in equilibrium with starting material or product at each point along each reaction coordinate.
2. For any process where only one elementary reaction coordinate changes, the energy will be a quadratic function of the corresponding reaction coordinate.
3. Heterolytic bond cleavage constitutes an elementary reaction coordinate.
4. For an anion to react at carbon, it must first undergo partial desolvation so that its reactive lone pair can be in van der Waals contact with the carbon.
5. Proton transfer between two atoms constitutes an elementary reaction coordinate.

For convenience in carrying out the calculations, all reaction coordinates are defined so that they run from 0 to 1 as the reaction proceeds.

The application of the theory is visualized in terms of an N-dimensional reaction diagram with two (square), three (cube), four (hypercube), etc., reaction dimensions, each of which is a 'simple' process with an associated quadratic potential energy term. The energies of any corners corresponding to actual chemical species in potential energy wells (as opposed to unstable species at an energy cusp) are taken from experiment, either directly or by linear free energy relations. The energies of corners corresponding to a distortion are calculated by MO theory.

Addition of water to carbocations

Examination of the structures of the cations and the product alcohols showed that in addition to the expected change in geometry from sp^2 to sp^3 at the reaction center, there are considerable changes in bond lengths throughout the aromatic ring, and to the methoxy or dimethylamino substituent if present. The extent of change in bond length depended on the nature of the alkyl and aryl groups, as shown:



These changes, implying pronounced loss of aromatic character accompanying a transfer of charge from the hexafluoroisopropyl group to the methoxy oxygen, suggested that the bond lengths might be an important reaction dimension, and so it proved.

It seemed plausible to consider a proton transfer dimension because the product of simple addition of water, the protonated carbinol, is sure to be more acidic than protonated water. Protonated methanol itself is more acidic than protonated water [$pK_{BH^+} = -2.05$ (Ref. 11) vs -1.74] and any protonated aryl dialkyl carbinol is going to be more acidic than protonated methanol, because the aryl group is more electron withdrawing than methyl. However, there is no assurance that the proton transfer will in fact occur before or during the transition state—it may well occur after the transition state, even though the protonated alcohol is unlikely to have a significant lifetime.

The first model which was used to calculate free energies of activation for the water reaction is

and will be referred to as Model 1. This leads to a four-dimensional hypercubic reaction diagram, for which the four reaction dimensions are C—O bond formation, geometry change at carbon, bond length change in the conjugated system and proton transfer from oxygen to oxygen. It is necessary to calculate the free energy of each corner relative to the starting point. In these calculations, allowance must be made for the entropic cost of bringing reactants together, any hydrogen bonding or electrostatic interactions and any imposed desolvation. This general model will be more elaborate than is really needed for most of the reactions, but should be able to accommodate the range of compounds considered here. Examination of the results for all the compounds suggests that in most if not all cases it would be permissible to ignore the proton transfer dimension and calculate the rate for the reaction leading to protonated alcohol, even though this is expected to have no lifetime, and not to be the actual product. Distortion energies for protonated alcohol species will be calculated using geometries based on the neutral final product and the initial carbocation. The extent of proton transfer at the transition state was invariably very small, generally < 0.1, although in one case, 4-dimethylaminotrifluorophenethyl, the extent of proton transfer was between 0.1 and 0.2. The calculated extents of proton transfer are given in Table 2. Even in this case, when calculations were carried out with the 3D model, for reaction leading to a protonated carbinol, essentially the same free energy of activation was obtained. We consider that it is advantageous to use a very general model for the initial calculations, and then examine the results to see if simplification is permissible, rather than make the simplifications first and then add features as needed to obtain agreement. Since in this case it proved unnecessary to treat proton transfer as a separate reaction coordinate, we will drop it from consideration and use a three-dimensional diagram, which will be called Model 2. The corresponding cubic reaction diagram is shown in Fig. 1.

Table 2. Extent of proton transfer for the 4D model (Model 1), for reaction of water with the carbocation

Cation	Extent of proton transfer at the transition state
$C_6H_5CH_2^+$	0.05
$CH_3OC_6H_4CH_2^+$	0.03
$C_6H_5CH(CH_3)^+$	0.02
$CH_3OC_6H_4CH(CH_3)^+$	0.01
$(CH_3)_2NC_6H_4CH(CH_3)^+$	0.05
$C_6H_5C(CH_3)_2^+$	0.04
$CH_3OC_6H_4C(CH_3)_2^+$	0.01
$C_6H_5CH(CF_3)^+$	0.02
$CH_3OC_6H_4CH(CF_3)^+$	0.02
$(CH_3)_2NC_6H_4CH(CF_3)^+$	0.16
$C_6H_5C(CH_3)(CF_3)^+$	0.04
$CH_3OC_6H_4C(CH_3)(CF_3)^+$	0.16
$C_6H_5C(CF_3)_2^+$	0.01
$CH_3OC_6H_4C(CF_3)_2^+$	0.02

In the cations, significant positive charge would be dispersed on to *p*-dimethylamino or *p*-methoxy substituents. Hence these substituents are not expected to be hydrogen bonded to water in the cation, which in turn implies that in the newly formed carbinol they will be partially desolvated, with no hydrogen bond to the N or O. The cost of this desolvation can be estimated from the difference in free energies of solvation between *N*,*N*-dimethylaniline and isopropyl benzene, 3.16 kcal mol^{-1} (1 kcal = 4.184 kJ), and between anisole and ethylbenzene, 1.66 kcal mol^{-1} (free energies of transfer, gas phase, 1 atm, to aqueous solution, 1 M, are available in the literature: *N*,*N*-dimethylaniline, -1.56 kcal mol^{-1};[12] isopropylbenzene, $+1.60$ kcal mol^{-1};[13] anisole, -0.56 kcal mol^{-1};[13] ethylbenzene, $+1.10$ kcal mol^{-1} [13]). This desolvation energy is added to each form of the carbinol.

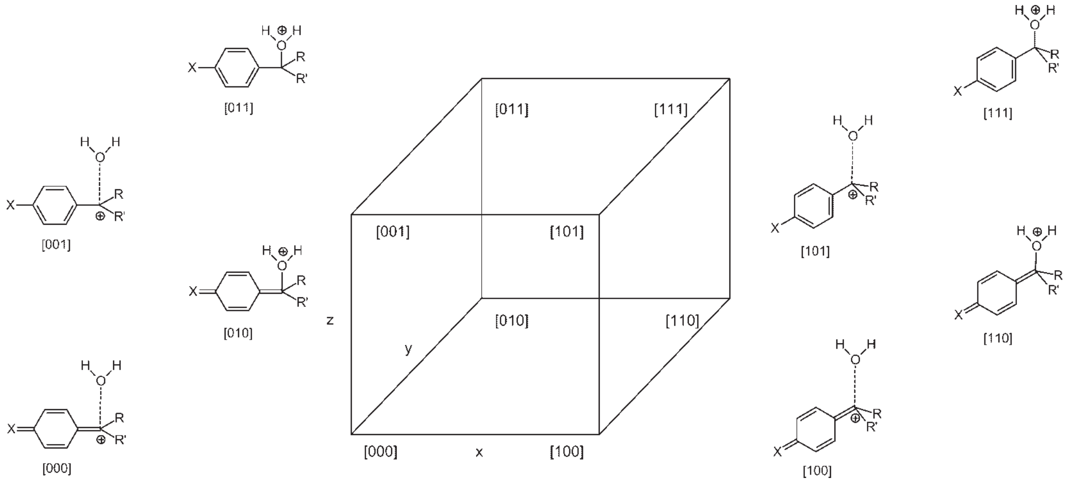


Figure 1. Cubic reaction diagram for the reaction of water with a carbocation

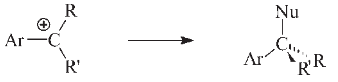
Often the equilibrium conformation of the product alcohol will not have the C—O bond making a dihedral angle of 90° to the plane of the benzene ring, which is the stereoelectronically required geometry for the product of addition to the planar cation. For simplicity (because the energies involved are in fact reasonably small), we have assumed that reaction occurs from the planar cation with a twist angle of zero to the protonated alcohol with the C—O bond making a dihedral angle of 90° to the plane of the benzene ring. The small energy cost of moving to these conformations of product is added to the model as distortion energies of the final states.

An additional feature of the reaction became apparent, particularly for reactions of the 4-dimethylaminophenyl-substituted cations, which were invariably slower than was implied by the free energies of activation calculated as described above. What needs to be added to the model is allowance for the difficulty of moving a large substituent, such as a substituted phenyl ring, through the solvent, sweeping out a considerable volume. In the procedure used for calculating rates this motion is treated as a kind of vibration, occurring on the 10^{-14} s time-scale. Movement of solvent molecules, essential if the aryl group is to move freely, occurs on the 10^{-11} s time scale. Thus, as far as vibrational motion is concerned, the solvent is a very resistive medium with the full effects of the high internal pressure. In the case of water this is 1690 atm[14] (there is some confusion in the literature between cohesive energy density and internal pressure; for non-polar liquids they are very similar, but for water they are not;[14] one sometimes sees statements that the internal pressure of water is 20 000 atm,[15] which in fact is the value for the cohesive energy density). In order to make an approximate estimate of the volume change imposed by this motion, we used the coordinates of the atoms of the aryl group projected on to the plane of the ring, with each atom extended by its van der Waals radius. A polygon was constructed by joining lines tangent to adjacent atoms, with the start and finish at the actual carbon atom to which the aryl group is bonded. This polygon was used for integration of the volume swept out by the aryl group for motion from planar to tetrahedral geometry. The equation used to calculate the volume changes is derived in Appendix 1 (Appendices and supplementary tables are available as supplementary material in Wiley Interscience). The coordinates used to define the polygons for dimethylaminophenyl, *p*-methoxyphenyl and phenyl are given in Table S1 as are the results of integration for each segment of volume. The volume changes so calculated and the implied $P\Delta V$ work are given in Table 3.

This was used in the calculation of free energy of activation. The $P\Delta V$ work was added to the energies of each corner species which had gone from planar to tetrahedral. The energies involved are small but not insignificant with one aryl group. For the triarylmethyl cations which we are currently examining, this effect will be more important. This revised model is referred to as Model 3.

Although the idea that there is a rate-retarding energy cost of moving parts of a molecule through the solvent[16] is not new, we believe that using $P\Delta V$ work to estimate the magnitude of this cost for molecular motions affecting a kinetic process is new. An equivalent way of

Table 3. $P\Delta V$ work for conversion of a planar cation to a tetrahedral product[a]



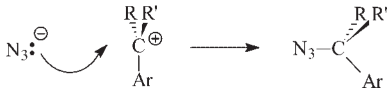
Aryl group	ΔV (Å^3 per molecule)[b]	$P\Delta V$ (kcal mol^{-1})[c]
$pMe_2NC_6H_4$	49.16	1.21
$pMeOC_6H_4$	37.03	0.91
C_6H_5	14.05	0.35

[a] For aqueous solution, 25 °C.
[b] Calculated using the geometric data in Table S8, as described in Appendix 3.
[c] Calculated using the internal pressure of water, 1690 atm, or 41 kcal l^{-1}.[14]

looking at the process of moving a bulky group through the solvent is that a cavity in the solvent large enough to permit free motion must be created. Berg and Jencks[17] estimated the work of creating such a cavity as $P\Delta V$.

Addition of azide to carbocations

The model used to describe these reactions and permit calculation of the rate constants is



for which a cubic reaction diagram is required, the three reaction dimensions being C—N bond formation, geometry change at carbon and bond length change in the conjugated system. The reaction cube is the same as that for hydration (Fig. 1), except that azide replaces water. This model is referred to as Model 4, and includes consideration of the desolvation, in the products, of the methyl or dimethylamino substituents, and the energy costs of attaining the reactive conformations of starting materials or products, as discussed for addition of water. Inclusion of a correction for the $P\Delta V$ work of moving the aryl group through the solvent leads to Model 5.

RESULTS

Work from various laboratories has led to a body of rate and equilibrium constant data for reactions of carbocations with nucleophiles. We have supplemented the experimental pK_R data with the help of DFT calculations of energies and entropies and continuum solvation energies.

Some further pK_R values are available starting with equilibrium constants for alkyl chloride ionization reported by Richard *et al.*,[18] who studied a number of compounds of the type ArCRR′Cl giving ArCRR′(+); their values are given in Table 4. We have calculated free energies for the reaction

$$\text{ArCRR}'\text{Cl} + \text{H}_2\text{O} \rightleftharpoons \text{ArCRR}'\text{OH} + \text{H}^+ + \text{Cl}^-$$

by computational methods. Free energies for gaseous ArCRR′Cl, ArCRR′OH, H_2O and HCl were calculated using Gaussian 98[19] (B3LYP/GTLarge//B3LYP/6–31 + G** energies corrected to free energies at 298 K using statistical mechanics with frequencies calculated at B3LYP/6–31 + G**). Solvation energies for ArCRR′Cl and ArCRR′OH were calculated using the IPCM method; experimental values for the solvation energies of H_2O and HCl were used. (These are really the free energy differences between gaseous and liquid water, and gaseous molecular HCl and fully ionized aqueous HCl; values from the NBS review were used[20].) In this way we determined the equilibrium constants for hydrolysis of the chlorides, as given in Table 4, based on computational free energies in Table 5. By combining equilibrium constants we could calculate the pK_R for ArCRR′OH; these values are also given in Table 4.

Table 4. pK_R values from equilibrium constants for ionization of chlorides[a]

Compound	Log K_{eq}^{ion}	Log K_{eq}^{hydrol}	pK_R for ArCRR′OH
$AnCH_2Cl$	−9.47	0.63	−10.1
$AnCH(CH_3)Cl$	−6.30	2.24	−8.5
$AnCH(CF_3)Cl$	−13.52	7.41	−20.8
$AnCH(CF_3)Br$	−12.51		
$AnC(CF_3)_2Br$	−14.74		
$AnC(CF_3)_2Cl$	−15.7[b]	10.26	−26.0

[a] All in aqueous solution at 25 °C; the equilibrium constants for ionization of alkyl halides were determined in 50:50 (v/v) trifluoroethanol–water, and are assumed to be the same in pure water.

[b] Estimated, using the ratio of equilibrium constants for $AnCH(CF_3)X$.

The one case where a pK_R is also available directly is 4-methoxyphenethyl alcohol, for which $pK_R = -9.4$ has been reported (see Table 1). The agreement, within less than an order of magnitude, is as good as can be expected.

The same computational methods were used to estimate equilibrium constants for carbocation formation from alcohols, ArCRR′OH. At this level the absolute values were not correct, although they seemed to be linearly related to the experimental values where these were known. By using both the published pK_R values and the values estimated as described above, from equilibrium constants for ionization of alkyl chlorides, we now have nine experimental (or partly experimental) pK_R values which can be compared with the purely computational values. To achieve maximum cancellation of errors we calculated free energies for the hypothetical exchange reactions

$$\text{cumyl cation} + \text{ArCRR}'\text{OH} \rightleftharpoons \text{cumylOH} + \text{ArCRR}'\text{cation}$$

Least-squares regression led to

$$\Delta\Delta G^\circ = (-1.03 \pm 0.65) + (0.896 \pm 0.055)\Delta\Delta G_{\text{computational}},\ r^2 = 0.97$$

This correlation permitted estimation of further $\Delta\Delta G^\circ$ values and hence pK_R values. The pK_R values so estimated are given in Table 1. The computational results used in this correlation are given in Tables 5 and 6. A very similar correlation coefficient was obtained using gas phase $\Delta\Delta G_{\text{computational}}$ values, so no large error was introduced by using solvation energies. The quality of the correlation

Table 5. Computational free energies and free energies of transfer[a]

Compound	G^{b}(hartree)	ΔG_{t}^{c}(kcal mol^{-1}
4-Dimethylamino-1-phenylethyl cation	−443.969583	−38.05
4-Dimethylamino-2,2,2-trifluoro-1-phenylethyl cation	−741.810740	−42.53
4-Methoxybenzyl cation	−385.220437	−41.55
4-Methoxy-1-phenylethyl cation	−424.537598	−41.80
4-Methoxycumyl cation	−463.848324	−38.33
4-Methoxy-2,2,2-trifluoro-1-phenylethyl cation	−722.372446	−42.91
4-Methoxytrifluorocumyl cation	−761.684337	−41.36
4-Methoxyhexafluorocumyl cation	−1059.508283	−43.91
Benzyl cation	−270.657267	−45.85
Phenethyl cation	−309.979082	−43.68
Cumyl cation	−349.292325	−41.24
2,2,2-Trifluoro-1-phenylethyl cation	−607.806290	−46.09
Trifluorocumyl cation	−647.123186	−43.18
Hexafluorocumyl cation	−944.941932	−45.10
4-Dimethylamino-1-phenylethyl alcohol	−520.047769	−1.59
4-Dimethylamino-2,2,2-trifluorophenethyl alcohol	−817.913590	−5.41
4-Methoxybenzyl alcohol	−461.334400	−3.40
4-Methoxy-1-phenethyl alcohol	−500.639735	−1.76
4-Methoxycumyl alcohol	−539.941114	−5.42
4-Methoxy-2,2,2-trifluoro-1-phenethyl alcohol	−798.503442	−6.73
4-Methoxytrifluorocumyl alcohol	−837.804888	−6.47
4-Methoxyhexafluorocumyl alcohol	−1135.657576	−2.39
Benzyl alcohol	−346.797703	−1.30
Phenethyl alcohol	−386.103962	−2.21
Cumyl alcohol	−425.404495	−2.89
2,2,2-Trifluoro-1-phenethyl alcohol	−683.966378	−2.35
Trifluorocumyl alcohol	−723.268297	−1.51
Hexafluorocumyl alcohol	−1021.119224	−1.47
4-Methoxybenzyl chloride	−845.733698	−3.66
4-Methoxy-1-phenylethyl chloride	−885.035579	−1.99
4-Methoxycumyl chloride	−924.332924	−0.81
4-Methoxy-2,2,2-trifluorophenethyl chloride	−1182.895753	−2.12
4-Methoxytrifluorocumyl chloride	−1222.193619	−2.93
4-Methoxyhexafluorocumyl chloride	−1520.040474	0.21
Benzyl chloride	−731.197191	−2.88
Phenethyl chloride	−770.499431	−2.24
Cumyl chloride	−809.797137	−1.32
Trifluorophenethyl chloride	−1068.358777	−1.68
Trifluorocumyl chloride	−1107.656436	0.54
Hexafluorocumyl chloride	−1405.503210	0.94
Water	−76.4593860	−2.05
Hydrogen chloride	−460.8502240	−8.48

[a] Standard states are gas phase at 1 atm, and aqueous solution at 1 M, with an infinitely dilute reference state.

[b] Free energy in the gas state, based on single-point energies at B3LYP/GTLarge//B3LYP/6–31+G** and entropies based on frequencies at B3LYP/6–31+G**.

[c] Free energy of transfer from the gas at 1 atm to aqueous solution at 1 M.

between calculated and experimental relative free energies of cation formation is shown in Fig. 2.

Addition of water to carbocations

In order to apply No Barrier Theory to these reactions, we required the equilibrium constant for the actual rate-determining step, which might be either the reaction of water with the carbocation to give the protonated alcohol, or reaction of two water molecules, one acting as a general base, to give the alcohol and hydronium ion. In order to calculate the equilibrium constant for the first possibility from the available equilibrium constant, pK_R, we need to estimate the pK_{BH^+} for protonation of the product alcohol:

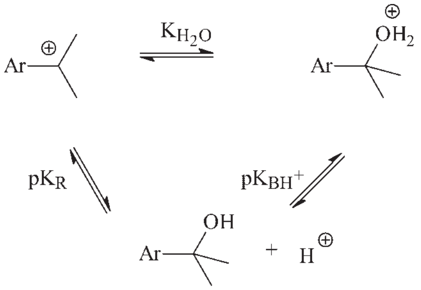


Table 6. Experimental and computational relative free energies of carbocation formation

Cation	$\delta\Delta G_R$ (aq)[a] (kcal mol^{-1})	$\delta\Delta G$ (gas)[b] (kcal mol^{-1})	$\delta\Delta G$ (aq)[c] (kcal mol^{-1})
4-Dimethylamino-1-phenethyl	−18.58	−21.33	−19.44
4-Dimethylamino-2,2,2-trifluoro-1-phenylethyl		−5.85	−4.62
4-Methoxybenzyl	−4.10	1.13	1.33
4-Methoxy-1-phenethyl	−6.23	−6.30	−7.99
4-Methoxycumyl	−8.88	−12.16	−8.48
4-Methoxy-2,2,2-trifluoro-1-phenylethyl	10.55	11.81	13.98
4-Methoxytrifluorocumyl		5.26	2.25
4-Methoxyhexafluorocumyl	17.62	23.30	20.13
Benzyl	10.38	17.74	11.54
1-Phenylethyl	4.23	7.98	4.86
Cumyl	0.00	0.00	0.00
2,2,2-Trifluoro-1-phenylethyl		30.07	24.68
Trifluorocumyl		20.67	17.35
Hexafluorocumyl		40.86	35.58

[a] In aqueous solution at 25 °C, calculated from the pK_R values in Table 1.

[b] Calculated using computational free energies in the gas phase, at 1 atm and 25 °C, from Table 5.

[c] Calculated using computational free energies in aqueous solution, at 1 atm and 25 °C, calculated using DFT free energies and continuum solvation energies from Table 5.

This we do by a linear free energy relationship previously used for tetrahedral intermediates:[21]

$$pK_a = -2.12 - 0.89\Sigma\sigma^*$$

For cationic acids we use $\sigma^*_H = 0.0$.[22]

Rate constants for water attack on carbocations, k_w, were taken from the literature wherever they have been reported; see Table 1. Rate constants in 1:1 trifluoroethanol–water were corrected to pure water by calculating the second-order rate constant for the water reaction and multiplying it by 55.5 M. For $PhCH(CF_3)^+$ the rate constant was estimated from an extrapolation of a plot of log k vs σ^+ for *para* substituents; see Appendix 2 and Table S2. For $PhC(CH_3)(CF_3)^+$ and $PhC(CF_3)_2^+$ it was assumed that the rate constant was the same as for $PhC(CH_3)_2^+$[23] based on the near identity of these rate constants for the corresponding 4-methoxy cations.[24] In any case, the rate constant for $PhC(CH_3)_2^+$ is close to the upper limit for trapping by water, and the fluorinated derivatives will be even less stable.

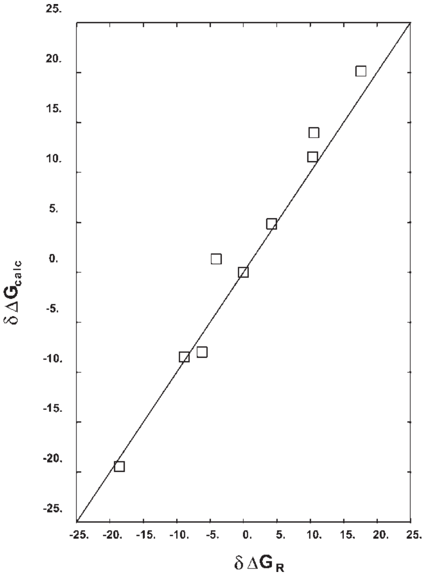
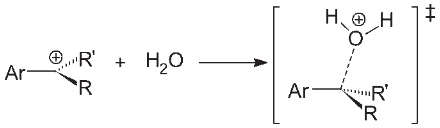


Figure 2. Correlation between calculated and experimental relative free energies for carbocation formation, with cumyl cation as the standard

Clearly, the rate constants for water attack taken as the product of the second-order rate constant for water attack in 1:1 (v/v) trifluoroethanol–water times the concentration of water in pure water will not be exactly the value for this rate constant if it were measured in pure water, but the following argument suggests that it should be close. Amyes *et al.*[23] found a shift of −0.8 pK_a unit from 1:1 (v/v) trifluoroethanol–water to pure water for the process

$$ArC(R)(R')^+ + H_2O \rightleftharpoons ArC(OH)(R)(R') + H^+$$

and for highly delocalized cations such as those considered here it seems reasonable that this shift should be largely determined by the difference in solvation energies for H^+. Trifluoroethanol is expected to be much less effective at solvating H^+ because it is less basic. The transition state for addition of water to one of these cations is closely analogous to hydronium ion, although with less positive charge on the oxygen.



Hence one might expect the shift in rate constant, $\delta\log k \leq 0.5 \times 0.67 \times (-0.8) = 0.27$, where the extent of C—O bond formation is taken as 0.5, since the value found by No Barrier Theory calculations was less than that for all but *p*-dimethylaminophenethyl cation, the number of oxonium protons needing solvation is two-thirds that in H_3O^+, and the effect of full development of H^+ is taken as -0.8. This suggests that the error from using a rate constant based on measurements in 1:1 (v/v) trifluoroethanol–water will be less than the inherent error of the No Barrier Theory free energies of activation, generally $\sim 2\,\mathrm{kcal\,mol^{-1}}$.

The results of calculations of the free energies of activation for reactions of water with carbocations are given in Table 7. For Model 1, the 4D model including proton transfer to a second water, the results are satisfactory, and very similar results are obtained with Model 2, the 3D model with only one water molecule involved. There is a systematic tendency for compounds with larger substituents on the benzene ring to have calculated $\Delta G^{\ddagger}$ values which are too low. For Model 2, the average signed error [the average of the difference between observed and calculated values (signed error) should be zero for a good fit, but will have a non-zero value if there is a systematic deviation] for benzylic cations with no ring substituent was 0.10. For *p*-methoxy-substituted benzylic cations the average signed error was -0.49, meaning that the calculated free energies of activation were too low, and for *p*-dimethylamino-substituted benzylic cations the average signed error was -1.72. For all reactions the average signed error was -0.41. Inclusion of a correction for the $P\Delta V$ work of moving the substituted benzene ring through the solvent, Model 3, leads to a slightly better overall fit. The calculation of $P\Delta V$ values is detailed in Appendix 1 and Table S1. The new values are as follows: unsubstituted, average signed error $= 0.18$; *p*-methoxy, average signed error $= -0.07$; *p*-dimethylamino, average signed error $= -0.86$, which is distinctly better for *p*-dimethylamino-substituted compounds and better for *p*-methoxy substituted compounds although slightly poorer for the phenyl compounds. For all reactions the average signed error was -0.07. The distortion energies used to calculate free energies of activation are given in Appendix 5, and Tables S5. The results of all of these calculations are summarized in Table 7 and illustrated in Fig. 3.

Table 7. Observed and calculated free energies of activation for the reaction of water with carbocations[a]

Cation	$\Delta G^{*}_{\mathrm{obs}}$[b] (kcal mol^{-1})	$\Delta G^{*}_{\mathrm{calc}}$[c] (kcal mol^{-1})	Error[d] (kcal mol^{-1})
$C_6H_5CH_2^+$	1.47	1.23	−0.24
		1.22	−0.24
		1.26	−0.21
$CH_3OC_6H_4CH_2^+$	5.70	6.45	0.74
		6.47	0.77
		6.89	1.19
$C_6H_5CH(CH_3)^+$	2.15	3.17	1.02
		3.18	1.03
		3.28	1.13
$CH_3OC_6H_4CH(CH_3)^+$	6.66	7.08	0.43
		7.08	0.42
		7.54	0.88
$(CH_3)_2NC_6H_4CH(CH_3)^+$	14.85	14.67	−0.18
		14.69	−0.17
		15.61	0.75
$C_6H_5C(CH_3)_2^+$	3.24	3.97	0.72
		3.99	0.74
		4.11	0.87
$CH_3OC_6H_4C(CH_3)_2^+$	7.48	9.91	2.43
		9.91	2.44
		10.45	2.97
$C_6H_5CH(CF_3)^+$	2.42	1.77	−0.65
		1.78	−0.64
		1.84	−0.59
$CH_3OC_6H_4CH(CF_3)^+$	6.52	4.09	−2.43
		4.09	−2.43
		4.41	−2.11
$(CH_3)_2NC_6H_4CH(CF_3)^+$	13.08	9.77	−3.31
		9.81	−3.27
		10.61	−2.47
$C_6H_5C(CH_3)(CF_3)^+$	3.24	4.14	0.90
		4.17	0.93
		4.28	1.04
$CH_3OC_6H_5C(CH_3)(CF_3)^+$	8.56	8.51	−0.04
		8.53	−0.03
		9.03	0.47
$C_6H_5C(CF_3)_2^+$	3.25	2.02	−1.22
		2.03	−1.21
		2.09	−1.15
$CH_3OC_6H_5C(CF_3)_2^+$	8.60	4.46	−4.14
		4.46	−4.14
		4.80	−3.80

[a] In aqueous solution at 25 °C. Of the entries under $\Delta G^{*}_{\mathrm{calc}}$ and error, the first is for Model 1, the four-dimensional model including a proton transfer to a second water molecule, with no consideration of $P\Delta V$ work, the second is for Model 2, the three-dimensional model with only one water molecule considered with no consideration of $P\Delta V$ work, and the third is for Model 3, the three-dimensional model with only one water molecule considered, but now including the effect of $P\Delta V$ work.

[b] Calculated from rate constants in Table 1.

[c] Calculated as described in the text, by the application of No Barrier Theory.

[d] $\Delta G^{*}_{\mathrm{calc}} - \Delta G^{*}_{\mathrm{obs}}$.

Equilibrium constants for addition of azide to carbocations

Most, but not all, of the cations considered in this work react at diffusion-controlled rates with azide ion, which allows azide trapping to be used as a clock reaction. It is of interest to see if NBT can correctly predict which reactions are, and which are not, diffusion controlled. One of the problems with the use of clock reactions is to determine the limits of reactivity below which the assumption of diffusion-controlled trapping ceases to hold. NBT offers a way to investigate this question without requiring fast kinetic experiments, although the latter provide the definitive proof.

Equilibrium constants for azide trapping are available for a number of 4-methoxybenzylic cations, but not for 4-dimethylaminophenylethyl cation, for which the rate constant for azide trapping has been reported. In order to estimate this missing value we calculated $\log K^{\mathrm{roh}}_{\mathrm{rn3}}$,[25] the equilibrium constant for conversion of the alcohol to the azide by the hypothetical process

$$\mathrm{ArC(R_1)(R_2)OH + HN_3 \rightleftharpoons ArC(R_1)(R_2)N_3(+H_2O)}$$

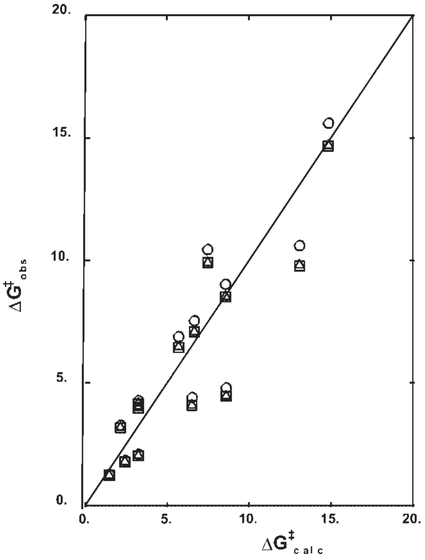


Figure 3. Calculated and observed free energies of activation for the reaction of water with carbocations. (□) 4D model with no $P\Delta V$ correction, Model 1; (Δ) 3D model with no $P\Delta V$ correction, Model 2; (○) 3D model with the $P\Delta V$ correction included, Model 3

and then plotted this quantity against $\Sigma\sigma^*$ for the three substituents on the central carbon of the alcohol/azide. The calculations are described in Appendix 6 and the data used are given in Table S11. This plot can be described by a linear correlation

$$\log K_{\mathrm{rn3}}^{\mathrm{roh}} = (3.66 \pm 0.17) - (0.803 \pm 0.060)\Sigma\sigma^*$$

which may now be used to interpolate a value for 4-dimethylaminophenylethyl cation. This in turn requires a value of σ^* for 4-dimethylaminophenyl, and Perrin *et al.*[26] did not give one. One can fit literature data for dissociation of ammonium ions, $XCH_2NH_3^+$ (see Appendix 3 and Table S3), to σ_X^*, so obtaining $pK_a = (10.234 \pm 0.175) - (1.615 \pm 0.105)\sigma_X^*$, and from the pK_a value for p-$Me_2NC_6H_4CH_2NH_3^+$,[27] obtain a σ^* value for p-$Me_2NC_6H_4$. The value so obtained was 0.35. This value and corresponding values for phenyl and p-$MeOC_6H_4$ should be better suited to predicting pK_a values for $ArCRR'XH^+$ than the usual values based on ionization of carboxylic acids or base-catalyzed ester hydrolysis. In fact, the results of the NBT calculations are very insensitive to the value of σ^* used for the aryl groups.

Addition of azide to carbocations

Equilibrium constants have been reported for all the azide–carbocation reactions in Table 1 except that for 1-(4-dimethylaminophenyl)ethyl cation. For this reaction, we estimated an equilibrium constant as described above. Rate constants for the recombination reaction have been reported.

From the values of the equilibrium constants for the reactions of azide with carbocations and the appropriate distortion energies, the free energies of activation can be calculated. In calculating the corner energies, one must allow for a desolvation cost when azide loses a hydrogen bond from water to nitrogen in order to bring that nitrogen into contact with the carbocationic center. The difference in pK_a values for hydrazoic acid between water[28] and DMSO[29] is 3.2, which implies that loss of all hydrogen bonding solvation would cost 4.40 kcal mol^{-1}. Azide ion is presumably able to form four hydrogen bonds to water, which would make the strength of one hydrogen bond 1.1 kcal mol^{-1}. Since it seems clear that at least one hydrogen bond must be lost for azide to make non-covalent contact with the carbocation center, we take this value as the desolvation cost for attaining the reactive encounter complex. Thus the model for azide ion combining with a carbocation involves an entropic cost, a desolvation and an electrostatic interaction.

$$ArCRR'^{\oplus} + N_3^{\ominus} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArCRR'^{\oplus}, N_3^{\ominus} \xrightarrow{k_2} ArC(N_3)RR'$$

The corner energies used to calculate free energies of activation are given in Appendix 6 and Table S6; the calculated free energies of activation for reaction within the encounter complex are given in Table 8. There is an extra complication for these reactions which are often nearly diffusion controlled. What is calculated directly is $\Delta G_2^{\ddagger}{}_{\mathrm{calc}}$, whereas what is observed, $\Delta G^{\ddagger}{}_{\mathrm{obs}}$, corresponds to $k_{\mathrm{obs}} = k_1k_2/(k_{-1} + k_2)$, where k_1 is the rate constant for diffusion-controlled encounter, taken as $5 \times 10^9\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$. Using our estimated free energy for encounter complex formation, 1.67 kcal mol^{-1}, we calculated a value for k_{-1}, and thus calculated $\Delta G^{\ddagger}{}_{\mathrm{calc}}$ from k_1, k_{-1} and $\Delta G_2^{\ddagger}{}_{\mathrm{calc}}$. Alternatively, we could deduce a value for '$\Delta G_2^{\ddagger}{}_{\mathrm{obs}}$' from k_{obs} k_1 and k_{-1} and compare it with $\Delta G_2^{\ddagger}{}_{\mathrm{calc}}$. The latter is in some senses the most direct comparison, but, for reactions which are nearly diffusion controlled, the value of '$\Delta G_2^{\ddagger}{}_{\mathrm{obs}}$ is very sensitive to the exact value of k_{obs} and the assumed values of k_1 and k_{-1}. The comparison of $\Delta G^{\ddagger}{}_{\mathrm{calc}}$ with $\Delta G^{\ddagger}{}_{\mathrm{obs}}$ is in some senses less direct, but is a comparison with the actual observable.

DISCUSSION

The principal conclusion from this work is that No Barrier Theory provides a satisfactory method for calculating rate constants for reactions of nucleophiles with benzylic cations, provided that the equilibrium constant is known.

The principal limitation to the further application of this method to S_N1 reactions is the shortage of equilibrium data. In principle, it would be possible to invert the calculations, and extract equilibrium constants from rate

Table 8. Observed and calculated free energies of activation for the reaction of azide ion with carbocations[a]

Cation	$\Delta G^{\ddagger}_{\mathrm{obs}}$ [b] (kcal mol^{-1})	$\Delta G^{\ddagger}_{\mathrm{calc}}$ [c] (kcal mol^{-1})	Error[d] (kcal mol^{-1})	'$\Delta G_2{}^{\ddagger}{}_{\mathrm{obs}}$' [e] (kcal mol^{-1})	$\Delta G_2{}^{\ddagger}{}_{\mathrm{calc}}$ [d] (kcal mol^{-1})	Error[f] (kcal mol^{-1})
$CH_3OC_6H_4CH_2^+$	4.20	4.59	0.39	≤1.17	2.48	≥1.31
		4.67	0.47		2.65	≥1.48
$CH_3OC_6H_4CH(CH_3)^+$	4.59	5.91	1.32	2.50	4.21	1.71
		6.15	1.56		4.46	1.96
$(CH_3)_2NC_6H_4CH(CH_3)^+$	7.61	9.83	2.22	5.95	8.16	2.21
		10.40	2.79		8.73	2.78
$CH_3OC_6H_4C(CH_3)_2^+$	5.00	7.22	2.22	3.16	5.55	2.39
		7.56	2.56		5.89	2.73
$CH_3OC_6H_4CH(CF_3)^+$	4.57	5.39	0.82	2.44	3.63	1.19
		5.60	1.03		3.87	1.43
$CH_3OC_6H_4C(CH_3)(CF_3)^+$	4.20	6.11	1.91	≤1.17	4.42	≥3.25
		6.38	2.18		4.70	≥3.53
$CH_3OC_6H_4C(CF_3)_2^+$	4.20	6.48	2.28	≤1.17	4.80	≥3.63
		6.79	2.59		5.12	≥3.95

[a] In aqueous solution at 25 °C.
[b] Calculated from rate constants in Table 1.
[c] Free energy of activation for the second-order reaction of azide with the carbocation; the first number is for Model 4 and the second for Model 5.
[d] $\Delta G^{\ddagger}_{\mathrm{calc}} - \Delta G^{\ddagger}_{\mathrm{obs}}$.
[e] Free energy of activation for reaction of azide with the carbocation within the encounter complex, calculated from $\Delta G^{\ddagger}_{\mathrm{obs}}$ as described in the text.
[f] $\Delta G_2^{\mathrm{calc}} - \Delta G_2^{\mathrm{obs}}$.

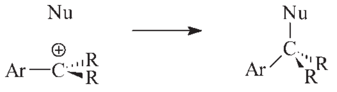
constants for systems already known to involve well-defined carbocation intermediates.

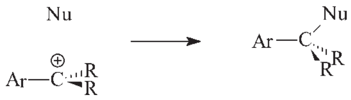
Application of No Barrier Theory forces one to have a very specific and detailed model for a reaction. In terms of Marcus theory, the model must account for both the work term and the intrinsic barrier. If the elements which enter into the work term (hydrogen bond energies, desolvation costs, electrostatic interactions, entropic cost of bringing reactants or products together) are incorrect, then the calculated free energy of activation will be in error and could be either too high or too low. The intrinsic barrier is in effect calculated by the actual No Barrier Theory model in terms of the simple reaction dimensions into which the actual reaction is analyzed. If this describes the correct mechanism for the reaction then it should lead to the correct (within about 2 kcal mol^{-1}) value of the free energy of activation. If it describes an incorrect mechanism, then the calculated free energy of activation will be too high. Only if the analysis is incorrect, and one of the assumed 'simple' reaction dimensions is actually more than one simple dimension merged, or if a necessary dimension has been left out, will the No Barrier Theory calculation lead to a low value of the free energy of activation. Normally it is necessary to try several models.

For the addition of water to carbocations, the initial state is the solvated carbocation and the final state is the neutral alcohol with a hydronium ion still in an encounter complex. Preliminary calculations (Models 1 and 2) showed that the proton transfer had proceeded to a negligible extent at the transition state and that a three-dimensional model could be used. For Models 1 and 2, the r.m.s. error was 1.79 kcal mol^{-1}. The principles of No Barrier Theory require that the geometries used to calculate distortion energies be based on the last species with a finite lifetime before the transition state and the first species with a finite lifetime after it. Hence the distortion energies for the cationic corner species which are distorted protonated alcohols should have geometries based on the neutral alcohol. This turns out to matter because the distortion energies calculated using the protonated alcohol as reference state are too small for some reactants, whereas distortion energies calculated for neutral corner species with neutral alcohol as reference state, and then used unchanged for the cationic corners, are too large for some reactions. Distortions calculated for cationic corner species with neutral reference state were successful for all cases, with the exception of 2-(*p*-methoxyphenyl)-1,1,1,3,3,3-hexafluoro-2-propyl cation, where there is probably a special problem which we do not know how to treat; see below.

The reaction of water with 2-(*p*-methoxyphenyl)-1,1,1,3,3,3-hexafluoro-2-propyl cation gives the worst deviations. For this compound there is a particular problem for two of the distortions (010 and 110) for which the OH_2^+ is bonded to a planar center. For these structures hydrogen bonding to one H is seriously hindered by the two flanking CF_3 groups, which are just enough larger than CH_3 groups in *p*-methoxycumyl cation, which is well handled by these calculations, to make this a plausible explanation. Estimating the cost of this impaired solvation is more difficult, and we have not devised a satisfactory approach.

There are in principle two ways in which a planar carbocation could react with a nucleophile to give a tetrahedral product. The three substituents on the carbocation center could move through the solvent while the nucleophile stays essentially fixed, or the nucleophile and two of the substituents on the carbocation center could move, while the third (the largest) remains essentially unmoved.





For both, the R groups move through the solvent, but the R groups in the examples considered in this paper are small and their motion should not make significant contributions to the activation energy. The nucleophile (H_2O or N_3^-) looks small and thus might be expected to move more easily through the solvent than the aryl group. However, the nucleophile is firmly embedded in the solvent by hydrogen bonding and dipolar interactions, and moving it would entail moving the entire primary solvation shell or else losing the hydrogen bonding solvation, either of which would impose a much higher energy cost than moving the aryl group through the solvent. For a water in contact with a carbocation center to lose its hydrogen bonds to the surrounding solvent would cost at least 4 kcal mol^{-1}, and this would grow larger as the C—O bond formed and the water became an oxonium ion with even stronger hydrogen bonds. This is far more than the cost of moving a substituted phenyl through the solvent. For the reactions studied in this work, the evidence for an effect on rates of the difficulty of moving a substituent through the solvent is not compelling; although there is a distinct improvement of the largest substituent, *p*-dimethylaminophenyl, the overall improvement is small. For the substituents for which data are available, size and charge-delocalizing ability increase in parallel, so one cannot rule out an imperfection in the computational allowance for conjugation effects.

It is now possible to calculate rate constants for reactions of cations with nucleophiles with no kinetic information, if the equilibrium constant is available.

CALCULATIONS

Molecular orbital calculations were carried out using the Gaussian 98[19] suite of programs. Density functional calculations used the B3LYP functional.[30,31] Free energies in the gas phase were calculated using energies at the B3LYP/GTLarge//B3LYP/6–31+G** level, and statistical mechanics corrections based on frequencies calculated at the B3LYP/6–31+G** level. Solvation energies were based on the IPCM continuum model, as implemented in Gaussian 98. Distortion energies were calculated at the B3LYP/3–21+G* level.

The procedure for calculating distortion energies for protonated alcohol corners was as follows. The geometry at all centers except the OH_2^+ was locked at that of the neutral product, while the geometry of this center was subjected to partial optimization, with the coordinates of the two hydrogens allowed to relax to optimum values to avoid a spurious distortion cost. The reference state, assumed to correspond to the estimated pK_{BH^+} value, was the optimized protonated alcohol with only the C—OH_2^+ bond length locked at the value of the neutral alcohol. This was to avoid cleavage of this bond, which would happen in some cases. All distortions were calculated relative to the equilibrium (C—OH_2^+ bond length locked) protonated alcohol.

Transition states were located using the algorithm previously described.[7]

Supplementary material

The following are available in Wiley Interscience. Appendix 1. Calculation of the volumes swept out by the motion of an aryl group as the atom is bonded to changes from sp^2 to sp^3 hybridization. Table S1. Coordinates used to define the polygons for $P\Delta V$ calculations. Appendix 2. Estimation of rate constants for the reaction of water with $C_6H_5CH(CF_3)^+$. Table S2. Rate constants for the reaction of water with $4\text{-}XC_6H_4CH(CF_3)^+$. Appendix 3. Linear free energy relations for pK_as of aliphatic amines, used to estimate σ^* for a substituted phenyl group. Table S3. Determination of the dependence of pK_a on σ^* for substituted methylammonium ions. Appendix 4. Estimation of the equilibrium constant for carbocation formation from an azide. Table S4. Estimation of the equilibrium constant for carbocation formation from an azide. Appendix 5. Data used to calculate rate constants for the reaction of water with carbocations. Table S5. Data used to calculate rate constants for the reaction of water with carbocations. Appendix 6. Data used to calculate rate constants for the reaction of azide with carbocations. Table S6. Data used to calculate rate constants for the reaction of azide ion with carbocations.

Acknowledgments

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