Steric Effects and Solvent Effects in Ionic Reactions

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Rates of $S_N2$ reactions of chloride ion with methyl- and tert-butyl–substituted chloroacetanilide were measured by using Fourier transform–ion cyclotron resonance spectrometry to follow the isotopic exchange reaction. Barrier heights for these reactions indicate that steric effects in the gas phase are diminished relative to apparent steric effects in solution. We attribute the increased barrier in solution to a solvation effect. Monte Carlo simulations done using statistical perturbation theory confirm that steric hindrance to solvation contributes to $S_N2$ barriers in solution.

In the $S_N2$ nucleophilic displacement reaction, a nucleophile, $Z$ (often negatively charged), reacts with a saturated carbon and displaces a leaving group, $Y$ (Scheme 1). Increasing the size of the substituents, $R$, decreases the rate of the reaction by creating nonbonded interactions (steric effects) that raise the energy of the transition state.

The idea of a steric effect was first proposed by Hofmann (1, 2) 130 years ago, but a quantitative understanding of this effect in the $S_N2$ reaction remains elusive (3, 4). In solution, there is a dramatic reduction in rates and an increase in activation barriers associated with increasing alkyl substitution at the central carbon atom, regardless of the solvent. Early theoretical attempts using classical models to quantitatively understand the effect of structure on the energetics were mixed (3, 5, 6). Ingold’s discussion of steric effects is the benchmark for other studies (3, 7). This early work indicated that steric effects might not account for all of the barrier in solution (8), but only internal effects, such as the change in polar effects with substituents mixed (3, 5, 6). In solution, there is a significant role in the increased barrier to reaction as the alkyl bulk is increased in solution (Fig. 1). Our Monte Carlo simulations with statistical perturbation theory on related thermoneutral reactions of alkyl chlorides confirm the hypothesis that differential solvation effects in different solvents in the transition state plays a significant role in the increased barriers to reaction associated with increasing alkyl substitution in solution.

<table>
<thead>
<tr>
<th>Chloronitrile</th>
<th>$K_{\text{exp}}$ (molecules s$^{-1}$ cm$^{-3}$)</th>
<th>$\Delta E_{\text{diff}}$ (kcal mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Chloropropanenitrile, 1</td>
<td>1.0 $\times$ 10$^{-11}$</td>
<td>-1.6</td>
</tr>
<tr>
<td>2-Chloro-3,3-dimethylbutanenitrile, 2</td>
<td>1.6 $\times$ 10$^{-12}$</td>
<td>0.0</td>
</tr>
</tbody>
</table>

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We chose alkylchloronitriles for our experiments because the identity displacement reactions are fast enough to study conveniently (15, 17, 19) [Scheme 2, R = CH₃ and C(CH₃)₃]. All of these reactions have the same nucleophile and leaving group (X = Z), and thus, identically, zero thermodynamic driving force. No assumptions need be made about comparing intrinsic barriers. We consider the nitrile (CN) substituent to be structurally neutral, but the acceleration it confers allows us to add alkyl substituents that slow the reaction and still keep it in a measurable range so we can study the steric effects. We examined reactions with the same degree of substitution and believe that the effect of the CN substituent is the same for both compounds.

We compared reactions of Cl⁻ with 2-chloropropanenitrile, 1, and 2-chloro-3,3-dimethylbutanenitrile, 2, for which an understanding of intrinsic structural effects without complication of additional effects is possible.

The reaction of Cl⁻ with chloroacetonitrile exhibits statistical behavior, in contrast to the behavior of the analogous methyl halide system (20), allowing for modeling with RRKM (Rice-Ramsperger-Kassel-Marcus) statistical rate theory (19, 21, 22). We believe that all of the reactions in this series behave statistically. This assumption is critical, because interpretation of the kinetics and derivation of the barrier heights would otherwise require a much more elaborate procedure, if it were possible at all.

Our experiments were carried out using an IonSpec OMEGA Fourier transform–ion cyclotron resonance spectrometer (23, 24). After ion thermalization, all of the ions except the less abundant 37Cl⁻ isotope were ejected from the cell, and 37Cl⁻ was allowed to react with the neutral chloronitrile over a period of up to 4500 ms. The 37Cl⁻ isotope signal decreased with time while 35Cl⁻ increased. Rate constants were determined from the approach to isotopic equilibrium, 35Cl⁻:37Cl⁻ = 3:1. Chloride ion complexation energies were determined using the method of Larson and McMahon (25–27).

Both identity exchange reactions were slow but measurable and reproducible. RRKM statistical rate theory was used to determine the Sₐ2 barrier height relative to the separated reactants (ΔEₐₚ) (28). Essentially, the rate depends on the branching of a metastable complex of Cl⁻ with the alkyl halide (X⁻RX) (Fig. 1). The branching ratio was calculated using the unimolecular reaction rate (RRKM) theory as a function of ΔEₐₚ. The value of ΔEₐₚ was chosen to agree with the experimental result (19, 29). The methodology used here has been extensively tested.

Kinetic and energetic results are reported in Table 1. The difference in barrier heights between the two systems is a measure of the steric effect. There is no question that the tert-butyl compound, 2, is sterically hindered (Fig. 2). Clearly, however, the difference of 1.6 kcal/mol is much smaller than that seen in solution in an analogous comparison of the Sₐ2 barriers for the reaction of Cl⁻ with ethyl chloride and neopentyl chloride, which is about 5 to 7 kcal/mol (3, 9). We propose that differential solvation of variously sized transition states accounts for the increased steric effect in solution.

Jorgensen pioneered the use of Monte Carlo simulations on gas-phase reaction coordinates to understand the effect of solvent on intrinsic reactivity, and in particular on the phase dependence of the Sₐ2 reaction of Cl⁻ with CH₃Cl (30–32). We built on this work by studying the effect of solvation on the identity exchange reactions of chloride ion with both methyl chloride and neopentyl chloride. We repeated the Cl⁻/CH₃Cl calculations to ensure that our simulations were performed properly, as well as to conserve as many variables as possible between the simulations of the two systems. Using Jorgensen’s BOSS program with a TIP4P model for H₂O, and following the reaction coordinate from separated reactants to the transition state, we found a greater increase in the (positive)
free energy of desolvation for the larger neopentyl system relative to the methyl chloride system (33). Initial work indicates that the difference in free energy of solvation between the methyl chloride and neopentyl chloride reactions in water is about 4 kcal/mol, suggesting that the observed barrier in solution would be that much greater than the intrinsic barrier.

In summary, differential solvation of the transition state accounts for a significant part of the barrier differences in solution and explains the difference seen between gas-phase and solution-phase experimental results for the S₂⁻ reaction.

References and Notes
8. The calculated steric energy remained high in the case of neopentyl chloride. Ingold acknowledged that the classical treatment could not consider all important interactions in a timely manner.
19. That difference is small in the comparison between separated reactants and transition states actually contains the differential effect of polarizability between separated reactants and transition states in addition to the energy of the steric effect. Another choice for the measure of the steric effect (Δr∥), the S₂⁻ barrier height as measured from the bottom of the well, controls for differences in polarizability. That difference is small in the comparison between the complexes of chloride ion with 1 and 2.

High-field, liquid-state nuclear magnetic resonance (NMR) spectroscopy, chemical shifts and electron-mediated scalar spin-spin (J) couplings yield diagnostic information about chemical bonding and molecular structure (J). The information content of the spectrum is often limited by spectral resolution, which is determined by the width of the NMR lines. To attain the resolution necessary to distinguish different resonance lines, very high field homogeneity (a few parts per billion) is required. In modern commercial NMR spectrometers, homogeneity is achieved by supplementing the large magnet with sophisticated and meticulously tuned shim coils.

Figure 1. (A) NMR spectrum of 5 ml of mineral oil acquired in a static field of 1.8 mT using a conventional Hahn spin echo sequence (π/2–τ–π–τ–acq) involving resonant radio frequency pulses. The spectrum is the average of 10,000 transients. The proton line is roughly 1 kHz wide, because the homogeneity of the static field is about 10,000 ppm over the volume of the sample. (B) NMR spectrum of 5 ml of mineral oil measured in a field of 1.8 μT using the sequence of Fig. 2B. The sample was polarized in a field of around 2 mT; the measurement field was applied with the same magnet used in (A). The spectrum is the average of only 100 transients. The inset displays the spectrum on an expanded frequency scale. The linewidth is of the order of 1 Hz.

References and Notes
4. 1 was obtained from Aldrich, and 2 was synthesized according to literature procedures (34, 35). Both compounds were purified by low-pressure distillation and preparative gas chromatography before use to ensure that the slow reactions would not be affected by impurities. Chloride ion was generated by electron impact ionization on the chloronitrile under study.
16. The calculated steric energy remained high in the case of neopentyl chloride. Ingold acknowledged that the classical treatment could not consider all important interactions in a timely manner.
27. That difference is small in the comparison between separated reactants and transition states actually contains the differential effect of polarizability between separated reactants and transition states in addition to the energy of the steric effect. Another choice for the measure of the steric effect (Δr∥), the S₂⁻ barrier height as measured from the bottom of the well, controls for differences in polarizability. That difference is small in the comparison between the complexes of chloride ion with 1 and 2.

We obtained nuclear magnetic resonance (NMR) spectra of liquids in fields of a few microteslas, using prepolarization in fields of a few millitesla and detection with a dc superconducting quantum interference device (SQUID). Because the sensitivity of the SQUID is frequency independent, we enhanced both signal-to-noise ratio and spectral resolution by detecting the NMR signal in extremely low magnetic fields, where the NMR lines become very narrow even for grossly inhomogeneous measurement fields. In the absence of chemical shifts, proton-phosphorous scalar (J) couplings have been detected, indicating the presence of specific covalent bonds. This observation opens the possibility for “pure J spectroscopy” as a diagnostic tool for the detection of molecules in low magnetic fields.

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