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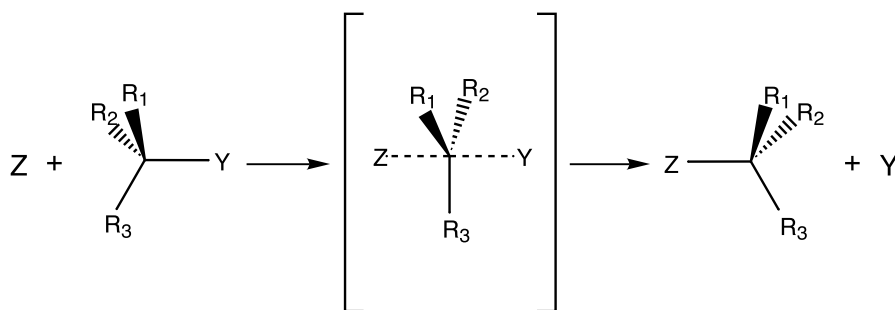
Steric Effects and Solvent Effects in Ionic Reactions

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Rates of S_N2 reactions of chloride ion with methyl- and *tert*-butyl-substituted chloroacetonitrile 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

steric hindrance. 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 ef-



Scheme 1.

fects might not account for all of the barrier in solution (8), but only internal effects, such as the change in polar effects with substitution, were proposed to explain the rest of the barrier seen in solution (7). Solvation of transition states was considered equivalent in all cases. However, although structural interference clearly affects chemical behavior (5), we believe that steric effects in ionic reactions in solution are convoluted with solvent effects

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 sol-

vent. 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 ef-

fects in a way that has not been explored.

Much of the barrier to the reaction of ions in solution is due to the desolvation of the nucleophile and the greater charge dispersal in the transition state (3, 9, 10). To isolate the role of solvation, however, it is necessary to look at thermoneutral reactions (11), such as isotopic exchange. Interpretation of an activation barrier for exothermic reactions requires a knowledge of the exothermicity and the intrinsic barrier of the reaction (12, 13), thus making gas-phase versus solution interpretations difficult, at best.

Numerous gas-phase studies have shown that alkyl bulk does affect reactivity in the absence of solvent (10, 11, 14–18). Thermoneutral reactions of alkyl halides have proven to be too slow, so only exothermic reactions have been studied. Because alkyl bulk slows S_N2 reactions, often to a point where they are too slow to be measured accurately, there is no complete series of reactions with the prototypical types of substitution described in solution where the rates of, and barriers to, reaction have been determined accurately. The most extensively studied reaction, $Cl^- + RBr$, is nearly complete, but does not include the reactions where $R = \textit{tert}$ -butyl or neopentyl.

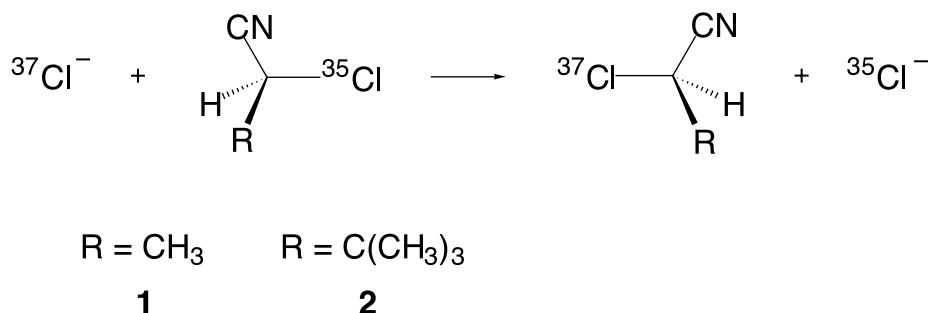
We report a gas-phase mass spectrometric study of thermoneutral S_N2 reactions of alkyl-substituted chloronitriles done to determine steric effects in different solvents in the absence of exothermicity and competing reactions. We show that differential solvation of the differently sized alkyl-substituted transition states plays 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 of transition states relative to each other contributes to the increased barriers seen in S_N2 reactions in solution for larger substrates.

Table 1. Reactions of Cl^- with alkylchloronitriles.

Chloronitrile	K_{exp} (molecules $s^{-1} \text{ cm}^{-3}$)	ΔE_{diff} (kcal mol^{-1})
2-Chloropropanenitrile, 1	1.0×10^{-11}	-1.6
2-Chloro-3,3-dimethylbutanenitrile, 2	1.6×10^{-12}	0.0

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Scheme 2.

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 S_N2 barrier height relative to the separated reactants (ΔE_{diff}) (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 ΔE_{diff}. The value of ΔE_{diff} 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 S_N2 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 S_N2 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)

Fig. 1. Effects of steric hindrance (ΔΔE_{steric}) and solvation (ΔΔE_{solvation}) on S_N2 potential energy surfaces. Solid line, R relatively unhindered. Dashed line, R relatively hindered.

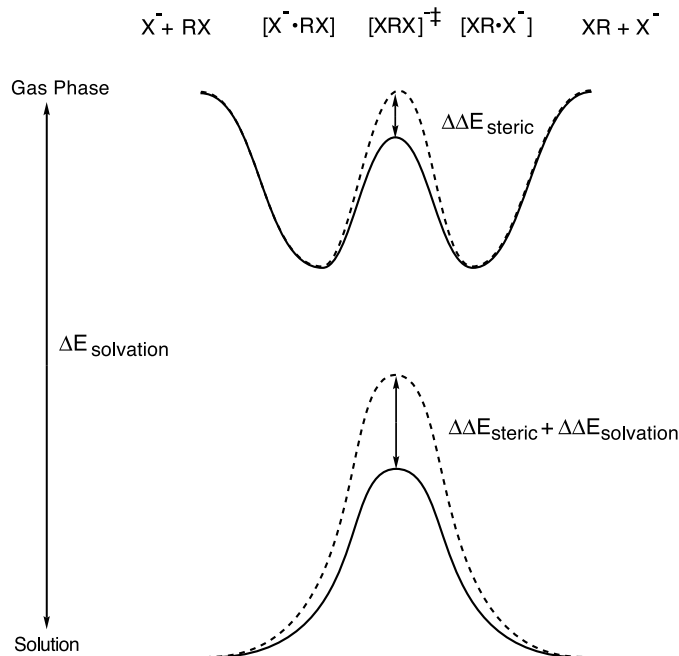
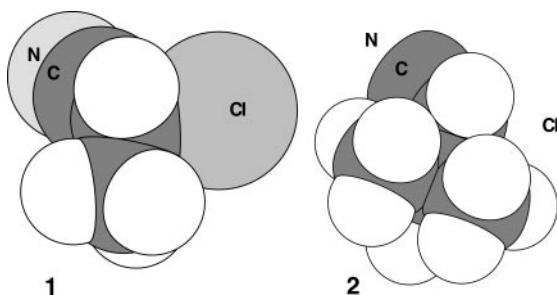


Fig. 2. Space-filling models of **1** and **2**.



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 states 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 S_N2 reaction.

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Liquid-State NMR and Scalar Couplings in Microtesla Magnetic Fields

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John Clarke^{1,3}

We obtained nuclear magnetic resonance (NMR) spectra of liquids in fields of a few microtesla, 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-phosphorus 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.

In 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.

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Fig. 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 ($\pi/2-\tau-\pi-\tau$ -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 μ T 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.

