Intramolecular Microsolvation of Thermoneutral Gas-Phase S_N2 Reactions

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Solvation plays a major role in determining rates as well as equilibria in solution ionic reactions. Differential solvation of reactants and transition state can, in principle, lead to either acceleration or deceleration of solution reactions relative to the gas phase. In the case of S_N2 reactions, gas-phase reactions are much faster than those in solution because solvation of reactants is substantially greater than that of the transition state[1−9] (Figure 1). Upon addition of even one solvent molecule to the ionic reactant, the transition state energy is frequently too high for the reaction to be observed in a single-collision event, so we searched for a system in which the transition state could be stabilized relative to reactants. We report here a gas-phase system designed so that the transition state is specifically solvated whereas the ionic reactant is not, resulting in an increase in the rate of the reaction relative to its unsolvated analog.

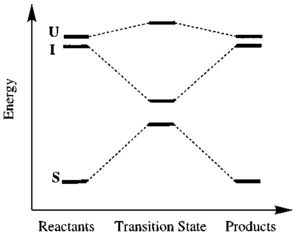

Figure 1. Relative potential energies of the reactants, transition states, and products of unsolvated (U), solvated (S), and intramolecularly solvated (I) S_N2 chloride exchange reactions. Greater solvation of reactants typically leads to a net increase in the activation energy. In our system, intramolecular solvation stabilizes the S_N2 transition state without significantly altering the energy of the reactants. The figure is not meant to convey any quantitative details about the energetics or to imply symmetry in the reaction coordinate. Intermediates and multiple transition states are omitted, and dashed lines are included for clarity.

In our system, the neutral reaction center (a primary alkyl chloride) is tethered to a solvating moiety by an alkyl chain (Figure 2). At large ion−neutral separation, solvation of the nucleophile (here, chloride ion) is negligible and the reactant energy is essentially unperturbed from the unsolvated case. At the transition state, ion−solvent interaction increases and lowers the activation energy.[10] Such an interaction is analogous to solvation insofar as it is noncovalent and predominantly through-space rather than inductive.

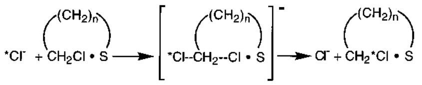

Figure 2. A pictorial representation of intramolecular solvation. In the reactants and products there is negligible interaction between the primary chloride and solvating group S, but a strongly stabilizing interaction develops at the transition state. Note that a symmetric reaction with an unsymmetric transition state must have additional reaction paths and transition states (for example, those involving solvent transfer) which are omitted from this figure.

Simple S_N2 reactions of Cl^- with unsubstituted RCl are very slow,[11,12] and the rate constant for *n*-pentyl chloride ($<10^{-12}$ $cm^3\ s^{-1}$) is too small to measure accurately in our system. We accelerate the reaction by introducing a solvating group onto the alkyl chlorides as shown in Figure 2. A nitrile was chosen as the solvating species because of its ability to stabilize negative charge, as evidenced by the chloride ion affinities of acetonitrile[13−15] and chloroacetonitrile,[16] through either a hydrogen bond or a backside ion−dipole complex.[15,16] Additionally, α-nitriles enhance S_N2 reactivity both in the gas phase[16,17] and in solution.[18]

The extent of transition state solvation can be quantified by the rate constant for chloride exchange. Experiments were carried out in a Fourier transform IonSpec FTMS-2000 ion cyclotron resonance spectrometer. Chloride ion was formed by electron impact on CCl_4, and the less abundant $^{37}Cl^-$ isotope was isolated and allowed to react with chloroalkylnitrile. The rate of appearance of $^{35}Cl^-$ was corrected for its natural isotopic abundance and converted to a rate constant for S_N2 exchange.[19]

For the substrate 1-chloro-3-cyanopropane, in which the length of the alkyl tether between the chlorine atom and nitrile group provides the opportunity for the solvating species to interact with the transition state via readily accessible ring formation, we obtain an S_N2 rate constant of 2.5×10^{-10} cm^3 s^{-1}, or a reaction efficiency of 9% relative to the calculated collision rate[20−22] (Table 1). This rate is several orders of magnitude greater than that of pentyl chloride and is indicative of differential solvation in the manner described above. Effects of induction[23−25] felt through several bonds have been documented,[26] however, and inductive stabilization of the transition state by the nitrile cannot be ruled out *a priori* in this case.

For the reactant series $Cl(CH_2)_nCN$, inductive interactions would decrease as *n* increases. As seen in Table 1, however,

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Table 1. Rate Constants, Efficiencies, and Complex Stabilities for the S_N2 Reactions $^{*}Cl^{-} + Cl(CH_2)_nCN \rightarrow Cl^{-} + {}^{*}Cl(CH_2)_nCN$[a]

substrate	k (10^{-10} cm^3 s^{-1})	ϕ^c	$\Delta G^\circ_{350}(R + Cl^- \rightarrow R{\cdot}Cl^-)^d$
$ClCH_2CN$	3.2^b	0.11	−13.1
$Cl(CH_2)_2CN$	0.7	0.03	−14.4
$Cl(CH_2)_3CN$	2.5	0.09	−13.8
$Cl(CH_2)_4CN$	1.2	0.04	−13.5
$Cl(CH_2)_5CN$	0.5	0.02	−13.8
$Cl(CH_2)_4CH_3$	<0.01	<0.001	−8.0
CH_3CN			$-8.3,^e$ -8.1^f

[a] Rate constants are averaged over a range of pressures (6×10^{-8} to 1×10^{-6} Torr) on different days. Estimated errors are ±30% in the absolute rate constants and ±10% in the relative rate constants. [b] References 16 and 17. [c] Reaction efficiency ϕ is the ratio of the observed reaction rate constant to the collision rate constant calculated according to refs 20−22. [d] Energies in kcal/mol. Errors in the absolute values are estimated to be ±0.4 kcal/mol, and errors in the relative values for the chloroalkylnitriles ±0.1 kcal/mol. [e] Reference 14, value extrapolated to 350 K. [f] Reference 15, value extrapolated to 350 K.

the rate is faster for $n = 3$ and $n = 4$ than for $n = 2$. While some through-bond stabilization cannot be ruled out, this behavior is consistent with a predominantly through-space mechanism of stabilization, in which the alkyl chain folds so that the terminal nitrile interacts favorably with the reaction center.

Further evidence against inductive effects is obtained from previous condensed-phase studies. While we have found no reports of the reactions in this paper being studied in solution, Hine and co-workers have studied the effects of β and γ halogen substituents on S_N2 reactivity.[27] In their experiments, through-space interactions of the substituents are significantly dampened by the presence of bulk solvent, while through-bond effects are much less sensitive to the presence of the solvent; β-substitution slows down the rate of halogen exchange, but γ-substitution has little effect on the reaction rate, indicating that electron-withdrawing inductive effects in S_N2 transition states are likely to be destabilizing and significant only at short separations.

The same interaction that stabilizes the transition state of the substitution reaction also should contribute to the stability of the ion−molecule complex. The free energies of chloride binding for the series of chloroalkylnitriles are reported in Table 1. Equilibrium constants were determined against reference compounds with known chloride binding affinities and also measured between chloroalkylnitriles to check for self-consistency. As seen in Table 1, all of the chloroalkylnitriles demonstrate enhanced chloride binding relative to simple alkyl chlorides and nitriles; the stabilization is thermodynamically significant in the ion−molecule complex as well as in the transition state.

Mautner has summarized previous work from several laboratories that demonstrates how molecular folding can permit intramolecular hydrogen bonds in a variety of ionic species,[28] and Catalán has suggested that such effects contribute to the stability of primary alkoxy anions.[29] More recently, Zhang *et al*. have examined the enthalpies and entropies of association of α,ω-diols with chloride anion and concluded that the diols behave as bidentate ligands for the anion.[30]

While both the transition states and ion−molecule complexes in our reaction system are stabilized, the enhanced chloride binding does not correlate exactly with enhanced reactivity. This result contrasts previous work by Wladkowski *et al.*,[31] who demonstrated that for chloride exchange reactions with substituted benzyl chlorides, reactivity correlates with the electrostatics of chloride ion complexation via a constant “intrinsic” activation barrier to nucleophilic displacement. Thus, for benzyl chlorides, the complex and the transition state are stabilized equally. In the present work the relative stabilization of the complex and transition state depends on the length of the alkyl chain, indicating a geometric constraint to chloride “solvation” at the transition state.

A likely source of stabilizing interaction in the chloroalkylnitriles is a hydrogen bond between the chloride ion and a proton α to the nitrile group; the ability of such a hydrogen bond to stabilize the anion at the transition state may be a determining factor of S_N2 reactivity (in this case, the unsymmetrical transition state for the substitution process must be accompanied by additional transition states and reaction pathways, for example, those involving solvent transfer, in order to preserve the overall symmetry of the reaction). Such a mechanism is consistent with the observed reactivity; the S_N2 reaction is fastest for those substrates that would form five- and six-membered rings in the transition state, just as intramolecular ring closures are fastest for these intermediate ring sizes. The trend in reactivity is also consistent with a stabilizing interaction due to the dipole of the C−CN bond, and further experimental and theoretical investigation is necessary to quantify the relative influence of these factors.

That the reactivity does not correlate exactly with chloride affinity shows that the stabilizing effect is partly specific for the transition state relative to the complex and indicates a geometry change between the two structures. The ion−molecule complex is less geometrically constrained because the chloride ion is not directly bonded to the reactive carbon center. For example, while the strain of forming a four-membered ring might prevent 1-chloro-2-cyanoethane from effectively stabilizing the transition state, the anion can be stabilized in the complex simultaneously by both the nitrile and the dipole of the C−Cl bond.

In conclusion, we have demonstrated that distant substituents on an alkyl chain can stabilize the transition state of S_N2 reactions. Despite limited contributions via induction, the effect on the reaction rate is dramatic; the rate constant for γ-substitution is very close to that for α-substitution. Previous theoretical work[16] has concluded that resonance is not a contributing factor in accelerating the chloride exchange reaction of chloroacetonitrile. Our results confirm that a cyano substituent can provide that degree of transition-state stabilization without a significant contribution from resonance.

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