Competing Pathways in Gas-Phase Reactions of Ambient Nucleophiles

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Determination of the contributions of competing pathways in ion–molecule reactions is a fundamental problem. Ion–molecule reactions involving ambient nucleophiles represent a particularly interesting class of multichannel reactions. The factors that influence the inherent competition associated with reactions of ambient nucleophiles in solution have been studied extensively, since the neutral products can be easily distinguished.[1] In the gas phase, however, determination of the relative contributions of such competing pathways is extremely difficult, because only ionic species are dectected (Scheme I).

Here, we report a quantitative measurement of the relative contributions of competing pathways for the gas-phase ion–molecule reactions of two ambient nucleophiles, the acetone enolate anion ($CH_3COCH_2^-$) and the cyanomethide anion (CH_2CN^-), using only product ion detection. For the addition–elimination (AE) reactions of $CH_3COCH_2^-$ and CH_2CN^- with trifluoroacetyl chloride (CF_3COCl), shown in Schemes II and III, respectively, we can distinguish between the two initial reaction pathways, which normally produce the same product ion, because the ion–molecule complex formed just *after* carbon attack undergoes proton transfer before dissociating. Conversely, the ion–molecule complex resulting from either oxygen attack in the case of the enolate reaction or nitrogen attack in the case of the cyanomethide reaction simply dissociates to Cl^-. In the AE reaction shown in Scheme II, we find that $C_5H_4F_3O_2^-$, which can only come from the carbon attack, is the major product ion (60%). Similarly, for the AE reaction shown in Scheme III, we find that the proton-transfer product $C_4HF_3NO^-$ is the major product ion formed (90%), indicating that reaction via carbon is also the dominant pathway.

The novelty and breadth of approaches that have been used to understand the behavior of ambient nucleophiles in the gas phase is a testimony to the difficulty of the problem. Ellison and co-workers[2] have employed neutral product detection to measure the competition between carbon and oxygen channels involving an enolate in an S_N2 reaction. Bartmess and co-workers[3] have studied the Claisen condensation reaction of enolates with esters in an ICR spectrometer. They were able to identify the Claisen-like product formed from secondary proton-transfer chemistry analogous to that presented here in cases that were thermodynamically allowed but were unable to quantify the relative competition of the initial competing pathways. Trenerry and Bowie[4] have investigated the ambient reactivity of the thioacetate anion in an ICR using a secondary McLafferty-type rearrangement; they find that attack by oxygen dominates. Gross and co-workers[5] have used collision-induced dissociation of aldol condensation products to probe bimolecular reactions of enolates with acetaldehyde. Finally, to determine quantitatively the relative contribution of the competing pathways, a wide variety of ambient nucleophiles, including enolate anions, have been

Scheme I

Scheme II

Scheme III

studied in a series of elegant experiments utilizing "chemical probes".[6] For example, Brickhouse and Squires have used perfluorinated propene[7] and 6,6-dimethylfulvene,[8] while Nibbering and co-workers[9,10] have employed perfluorinated aromatics. Theoretical studies on model systems have also been conducted.[11]

In previous studies involving chemical probes,[3,7,10] the competition between carbon and oxygen attack has been shown to vary significantly with not only enolate structure but also with the neutral substrate. In fact, the behavior of acetone enolate itself has been shown to vary widely depending on the system. For the reaction of acetone enolate with hexafluoropropene[7] and perfluorobenzene,[10] the observed C:O ratio was found to be 1:7, and 4:1, respectively. With such variation, it becomes clear that further studies involving other substrates are necessary to better understand this problem. Our experiments, which utilize carbonyl chemistry as the reaction probe, are of particular interest and relevance, because carbonyl reactions are often important in many synthetic and biological problems. Finally, unlike some previous experiments involving reactions with acetone enolate, in the system presented here, both carbon and oxygen attack channels are thermodynamically accessible (Scheme II).

Our experiments were performed using a Fourier-transform IonSpec OMEGA ion cyclotron resonance (FT-ICR) spectrometer equipped with impulse excitation.[12–14] In separate experiments, acetone enolate and the cyanomethide anion were formed by deprotonation of acetone and acetonitrile using F^-, which was generated via electron impact on NF_3. After complete reaction of F^-, all ions other than the ion of interest (either $CH_3COCH_2^-$, $m/z = 57$, or CH_2CN^-, $m/z = 40$) were ejected. The ambient nucleophile was then allowed to react with trifluoroacetyl chloride, and the product ions were detected. In both reactions only two

(1) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; The Benjamin/Cummings Publishing Co.: Menlo Park, 1972.
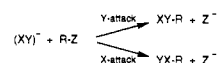
(2) Jones, M. E.; Kass, S. R.; Filley, J.; Barkley, R. M.; Ellison, G. B. *J. Am. Chem. Soc.* **1985**, *107*, 109.

(3) Bartmess, J. E.; Hays, R. L.; Caldwell, G. *J. Am. Chem. Soc.* **1981**, *103*, 1388.
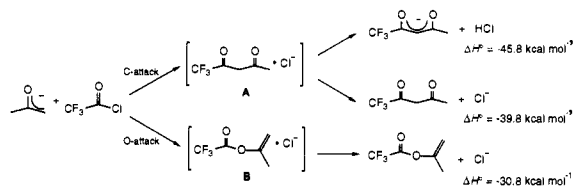
(4) Trenerry, V. C.; Bowie, J. H. *Org. Mass. Spectrom.* **1980**, *17*, 367.

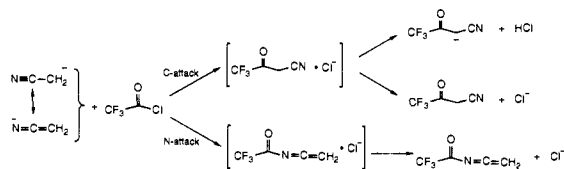(5) Hayes, R. N.; Grese, R. P.; Gross, M. L. *J. Am. Chem. Soc.* **1989**, *111*, 8336.

(6) The term "chemical probe" has been used by Brickhouse and Squires (ref 7) to indicate a reagent which, upon reaction with an ambident nucleophile (such as acetone enolate), yields distinguishable ionic products that can be used to determine the relative contributions of the competing reaction channels.

(7) Brickhouse, M. D.; Squires, R. R. *J. Phys. Org. Chem.* **1989**, *2*, 389.

(8) Brickhouse, M. D.; Squires, R. R. *J. Am. Chem. Soc.* **1988**, *110*, 2706.

(9) Ingemann, S.; Nibbering, N. M. M.; Sullivan, S. A.; DePuy, C. H. *J. Am. Chem. Soc.* **1982**, *104*, 6520.

(10) Freriks, I. L.; De Koning, L. J.; Nibbering, N. M. M. *J. Am. Chem. Soc.* **1991**, *113*, 9119.

(11) Houk, K. N.; Paddon-Row, M. N. *J. Am. Chem. Soc.* **1986**, *108*, 2659.

(12) McIver, R. T. J.; Baykut, G.; Hunter, R. L. *Int. J. Mass. Spectrom. Ion Phys.* **1989**, *89*, 343.
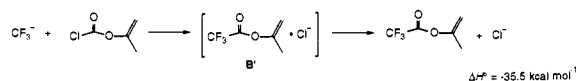
(13) McIver, R. T. J.; Hunter, R. L.; Baykut, G. *Anal. Chem.* **1989**, *61*, 489.

(14) McIver, R. T. J.; Hunter, R. L.; Baykut, G. *Rev. Sci. Instrum.* **1989**, *60*, 400.

Table I. Reactions of Ambient Nucleophiles with CF_3COCl

nucleophile	product ion ratio [R⁻]/[Cl⁻]	% C	% O, N
$CH_3COCH_2^-$	1.5:1	60	40
CH_2CN^-	9:1	90	10

Scheme IV

$\Delta H^\circ = -35.5 \text{ kcal mol}^{-1}$

product ions were observed. Typical operating pressures for the neutral reagents were in the range $(1–9) \times 10^{-7}$ Torr. All compounds were obtained from commercial sources (Aldrich, except NF_3, from Matheson) and used without further purification.

Our previous studies[15,16] on the S_N2 reaction of CN^- + $ClCH_2CN$, in which a highly energized substitution product complex $[(NC)_2CH_2 \cdot Cl^-]$ can undergo subsequent proton transfer before dissociation, provides the background for the interpretation of our experiments. In this system, the proton-transfer channel, relative to simple loss of Cl^-, is near thermoneutral at room temperature. However, when the complex is formed with excess internal energy (via the substitution reaction), the proton-transfer channel dominates; the observed product ratio, $(NC)_2CH^-:Cl^-$, is 15:1. A large favorable entropy change associated with the proton-transfer channel, due to the additional rotational degrees of freedom in HCl which are not present in the Cl^- loss channel, drives the reaction. Therefore, at the high internal energy at which the postsubstitution complex is formed, dissociation strongly favors the proton-transfer channel. Multiple dissociation channels following a primary reaction are not always available in anionic displacement reactions; in this case the addition of a cyanide group dramatically enhances the gas-phase acidity of the postsubstitution complex neutral (relative to the conjugate acid of the leaving group). Both acetone enolate and the cyanomethide anions behave similarly to CN^- in this respect (one reaction channel produces a product complex with enhanced acidity), and this forms the basis of our structural probe to study ambient nucleophiles.

Table I shows the product ion ratio for the AE reaction of acetone enolate with trifluoroacetyl chloride. The two ionic masses were observed in a ratio $C_5H_4F_3O_2^-:Cl^- = 1.5:1$. Although all of these products could originate from attack by either carbon or oxygen, it is unlikely that the vinyl ester in the product complex formed by oxygen attack (B, Scheme II) is sufficiently acidic to undergo proton transfer before dissociating to give $C_5H_4F_3O_2^-$ + HCl, even at the high internal energies at which the product complex is formed (≈ 30 kcal mol^{-1}). To rule out the possibility that the *energized* complex B was capable of proton transfer before dissociating, it was generated by an independent route (Scheme IV). The reaction of CF_3^- (generated via electron impact on hexafluoroacetone) with isopropenyl chloroformate forms a complex (B′) with approximately the same amount of excess internal energy as that for the reaction in Scheme II.[17] Under these conditions, only Cl^- (and no $C_5H_4F_3O_2^-$) was observed. This indicates that reaction of acetone enolate via attack by oxygen, which produces the product complex B (Scheme II), should produce only Cl^-.
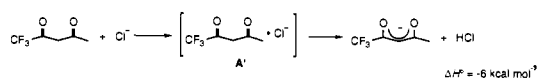
To quantify the results, we must also rule out the possibility that the ion–molecule complex resulting from carbon attack (A, Scheme II) simply dissociates to give Cl^-. This is also unlikely

Scheme V

$\Delta H^\circ = -6 \text{ kcal mol}^{-1}$

given the relative thermochemistry involved; $CF_3COCH_2COCH_3$ is 6 kcal mol^{-1} more acidic than HCl. Therefore, even if the complex $[CF_3COCH_2COCH_3 \cdot Cl^-]$ were formed with modest energy above threshold, the proton-transfer products should dominate. To confirm this, the corresponding bimolecular proton-transfer reaction rate (Scheme V) was measured directly at 350 K. The reaction was observed to proceed at the collision rate. Moreover, given that complex A, resulting from carbon attack, is formed with approximately 40 kcal mol^{-1} of excess internal energy, formation of $CF_3COCHCOCH_3^-$+ HCl from proton transfer should be even more strongly favored. This is consistent with our previous study of the S_N2 complex described above, which preferentially (15:1) undergoes proton transfer before dissociation. Based on these arguments, we believe that, within the margin of error in our experiments, the ion–molecule complex A dissociates exclusively via proton transfer to give $C_5H_4F_3O_2^-$ + HCl.

The relative abundance of the products can now be used to determine the relative contributions of the carbon and oxygen attack pathways for the reaction of acetone enolate with trifluoroacetyl chloride . Reaction via carbon attack, which is the exclusive source of the product ion $C_5H_4 F_3O_2^-$, accounts for 60% of the observed reactivity. Reaction via oxygen attack, which is the exclusive source of Cl^-, accounts for 40% of the observed reactivity.

We have also explored the generality of our method by investigating the competitive reaction channels of another ambient nucleophile, the cyanomethide anion, CH_2CN^-. The rich gas-phase chemistry of the cyanomethide anion has been explored by Bierbaum, DePuy, and co-workers in some detail.[18] In addition, Ellison and co-workers[19] have published the photoelectron spectrum of CH_2CN^-, which, in concert with theoretical *ab initio* results, was used to assign a planar structure in which the charge is localized on the nitrogen end of the molecule. Scheme III shows the AE reaction of CH_2CN^- with trifluoroacetyl chloride, which may proceed either by carbon or nitrogen attack. By analogy with our studies involving the acetone enolate anion, we can distinguish between the two pathways using only product ion detection. Reaction via carbon produces the complex C (Scheme III), which may dissociate to lose Cl^- or undergo subsequent proton transfer before dissociation to form $C_4HF_3NO^-$ + HCl. Reaction via nitrogen generates the complex D (Scheme III), which can dissociate to produce Cl^- only. Table I shows the product ion ratio of the reaction of CH_2CN^- with trifluoroacetyl chloride. The observation that $CF_3COCHCN^-$ is the major product (90%), indicates that CH_2CN^- reacts almost entirely by carbon attack.

In summary, we have described a simple method that has been used to determine the relative contributions of competing pathways in the gas-phase AE reactions of two ambient nucleophiles, acetone enolate and the cyanomethide anion, with a carbonyl substrate. Studies that explore the generality of our findings are in progress and will be the topic of a forthcoming publication.

(15) Wladkowski, B. D.; Wilbur, J. L.; Brauman, J. I. *J. Am. Chem. Soc.* **1992**, *114*, 9706.

(16) Wilbur, J. L.; Wladkowski, B. D.; Brauman, J. I. *J. Am. Chem. Soc.*, in press.

(17) $\Delta H^\circ = -35.5$ kcal mol^{-1} for the reaction in Scheme IV (estimated using Benson group additivities and the known thermochemistry of the reaction of acetyl chloride with CF_3^-).

(18) Filley, J.; DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1987**, *109*, 5992.

(19) Moran, S.; Ellis, H. B.; DeFrees, D. J.; McLean, A. D.; Ellison, G. B. *J. Am. Chem. Soc.* **1987**, *109*, 5996.