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Can Transacylation Reactions Occur via S_N2 Pathways in the Gas Phase? Insights via Ion–Molecule Reactions of *N*-Acylpyridinium Ions and *ab Initio* Calculations

Richard A. J. O'Hair* and N. K. Androutsopoulos

School of Chemistry, The University of Melbourne, Parkville, Victoria 3010, Australia

r.ohair@chemistry.unimelb.edu.au

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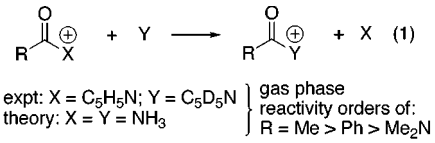
ABSTRACT



The *gas-phase* identity exchange reactions of *N*-acylpyridinium ions with pyridine have been examined experimentally in an ion trap mass spectrometer through the use of isotope labeling experiments. The nature of the acyl group plays a crucial role, with the bimolecular rates following the order acetyl > benzoyl > *N*,*N*-dimethylaminocarbamyl. The experimental results correlate with *ab initio* calculations on the simple model system $RC(O)NH_3^+ + NH_3$, which also demonstrates that these are "S_N2 like" processes.

Transacylation reactions play important roles in solution-phase organic and bioorganic chemistry and can proceed intramolecularly or intermolecularly.[1] There has been continuing interest in the mechanisms of these reactions which can range from dissociative (i.e., "S_N1 like") to "associative" mechanisms. The gas phase is an ideal environment to study intrinsic reactivity in the absence of solvent and counterion effects, and several studies have examined bimolecular reactions between nucleophiles and acylating agents.[2] Of these, the reactions between anionic nucleophiles and neutral acylating agents[3] have received more attention than those between neutral nucleophiles and cationic acylating reagents.[4]

For the former class of reactions, it is difficult to experimentally distinguish between mechanisms where the tetrahedral species is an intermediate versus those in which it is a transition state (i.e., "S_N2 like"). Indeed, recent *ab initio* calculations on reactions between halide ions and acyl halides (RC(O)X) indicate that the potential energy profiles can vary from double wells (where the tetrahedral species is a transition state which is separated by pre and post complexes) to triple wells (where the tetrahedral species is an intermediate) depending upon the nature of the nucleophile, nucleofuge, and acyl group.[5]

Determining the mechanisms of reactions between neutral nucleophiles and protonated acylating reagents involves a different challenge, namely "pinning down" the site of protonation and how this effects the mode of reactivity.[4] In the gas phase, where solvent molecules cannot mediate

(1) For reviews and detailed discussions of the mechanisms of acylation reactions in solution, see: (a) Satchell, D. P. N.; Satchell, R. S. In *Supplement B: The Chemistry of Acid Derivatives*; Patai, S., Ed.; Wiley: New York, 1992; Volume 2, Chapter 13. (b) Page, M.; Williams, A. *Organic and Bioorganic Mechanisms*; Longman: Harlow, 1997; pp 145−152.

(2) For a review, see: Riveros, J. M.; Jose, S. M.; Takashima, K. *Adv. Phys. Org. Chem.* **1985**, *21*, 197.

(3) (a) Zhong, M.; Brauman, J. I.. *J. Am. Chem. Soc.* **1999**, *121*, 2508. (b) Asubiojo, O. I.; Brauman, J. I. *J. Am. Chem. Soc.* **1979**, *101*, 3175. (c) Van Doren, J. M.; DePuy, C. H.; Bierbaum, V. M. *J. Phys. Chem.* **1989**, *93*, 2508. (d) Fink, B. T.; Hadad, C. M. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2397.

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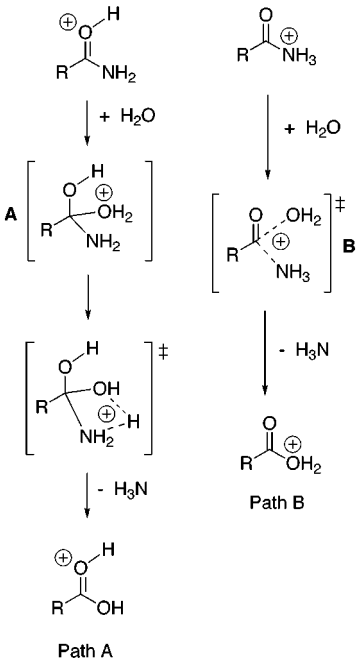
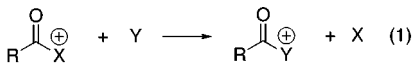
proton transfer reactions, the thermodynamically favored site of protonation (e.g., O-protonated amide) may not be kinetically favored in terms of transacylation, since a high-energy 1,3 proton transfer is required in order for the tetrahedral intermediate **A** to decompose to products (Path A, Scheme 1). Indeed, *ab initio* calculations reveal this to

Scheme 1



be the case for the hydrolysis of protonated formamide, in which transacylation via a double well "S_N2" pathway (transition state **B** in Path B, Scheme 1) is preferred.[6] One way of overcoming the site of protonation issue which has been exploited in solution is through the use of fixed charged derivatives such as *N*-acylpyridinium salts.[7] We were thus intrigued by a recent report in which the transacylation reaction of **C** did not occur (Scheme 2) in the *gas phase*.[8] If

Scheme 2



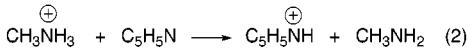
C: R = 4-$CF_3C_6H_5$; X = 4-$Me_2NC_5H_4N$; Y = triethylenediamine and hexamethylenetetramine

such reactions do proceed via "S_N2 like" pathways, then a likely explanation is that the energy of the transition state is above that of separated reactants. Provided the nucleophile and nucleofuge are the same (i.e., an identity exchange reaction), then the intrinsic barrier will be unperturbed by differences in their nucleophilicity.[9] While gas-phase kinetic studies have been carried out for identity exchange transcylation reactions between $^{37}Cl^-$ and acyl chlorides,[3a−c] none have been reported for positively charged systems. This has prompted us to report our results on the reactions shown in eq 1 both experimentally (X = C_5H_5N or C_5D_5N; Y = C_5D_5N or C_5H_5N) and theoretically (X = Y = NH_3) for the acyl systems R = Me, Ph, and Me_2N.

Electrospray ionization using dry acetonitrile as the solvent affords the desired *N*-acylpyridinium ions, which are readily mass selected in the ion trap mass spectrometer.[10] An important observation is that these ions are extremely stable in the gas phase and can be trapped in the mass spectrometer for up to 10 s without any losses due to decompositions (e.g., via "S_N1 like" pathways). In fact, cleavage of the acyl−pyridinium bond to give acyl cations (in the cases of the *N*-benzoyl and *N*,*N*-dimethylaminocarbamyl systems) or protonated pyridine (for the acetyl case) can only be induced via collisional activation.

Introduction of a reactive neutral into the mass spectrometer allows the gas-phase bimolecular reactivity of mass-selected *N*-acylpyridinium ions to be probed. We have examined six different identity exchange systems of reaction 1: (a) $[MeC(O)NC_5H_5]^+ + NC_5D_5$; (b) $[MeC(O)NC_5D_5]^+ + NC_5H_5$; (c) $[PhC(O)NC_5H_5]^+ + NC_5D_5$; (d) $[PhC(O)NC_5D_5]^+ + NC_5H_5$; (e) $[Me_2NC(O)NC_5H_5]^+ + NC_5D_5$; (f) $[Me_2NC(O)NC_5D_5]^+ + NC_5H_5$. Reaction 1 was observed for systems a−d *as the sole reaction channel*.[11] Systems e and f yield no new products, suggesting that these acylpyridinium ions are unreactive toward pyridine under our experimental conditions.

To quantify the order of reactivity, we have examined the rates of systems b and d. The pyridine concentration in the ion trap was maintained at a constant pressure, and both rates were measured followed by a rate measurement of a known proton-transfer reaction involving pyridine (eq 2).[12] Since



the rate constant for reaction 2 is known, the rates of 1b and 1d were converted to rate constants, thereby allowing their efficiencies to be compared. Each of the experimental rate measurements, the derived rate constants and reaction efficiencies are given in Table 1. The reaction efficiency (RE) shows dependence on the nature of the acyl group (RC(O)),

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(8) Katrizky, A. R.; Burton, R. D.; Shipkova, P. A.; Qi, M.; Watson, C. H.; Eyler, J. R. *J. Chem. Soc., Perkin Trans. 2* **1998**, 835.
(9) DePuy, C. H.; Gronert, S.; Mullin, A.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1990**, *112*, 8560.
(10) The *N*-acylpyridinium salts were prepared by a literature procedure (King, J. A., Jr.; Bryant, G. L., Jr. *J. Org. Chem.* **1992**, *57*, 5136) and were used immediately without further purification. Ion−molecule reactions were carried out using a LCQ mass spectrometer which was modified to allow the introduction of neutral reagents through the end cap of the quadrupole ion trap. The neutrals were introduced through a leak valve.
(11) We find no evidence for the bimolecular elimination of ketene from the acetyl systems a and b.
(12) Aue, D. H.; Bowers, M. T. In *Gas-Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic Press: New York, 1979; Volume 2, Chapter 9, p 11.

Table 1. Rates and Rate Constants for Various Gas-Phase Reactions

reaction	rate (s^{-1}), $\times 10^{-3}$	$k \times 10^{-11}$ (cm^3 $molecule^{-1}$ s^{-1})	reaction efficiency[c]
1b	0.77	14.6[a]	0.07
1d	0.15	2.9[a]	0.02
2	2.79	53[b]	0.20

[a] The rate constant was calculated by multiplying the ratio of the rates of eqs 1 and 2 by the published rate constant (ref 12) for eq 2. [b] Taken from ref 12. [c] Reaction efficiencies are calculated by dividing the observed rate constant by the theoretical rate constant (ref 13).

with the most efficient reaction being observed for the acetyl group (R = Me, RE = 0.07), followed by the benzoyl group (R = Ph, RE = 0.02). Given these results, and that the dimethylaminocarbamyl group is unreactive, this suggests the intrinsic reactivity order for the acyl groups of MeC(O) > PhC(O) > $Me_2NC(O)$.

To confirm this reactivity order and to verify that these reactions proceed via "S_N2 like" transition states, we have carried out *ab initio* calculations on the simpler systems where the nucleophile and nucleofuge are both NH_3.[14] As the benzoyl system is computationally demanding, we have used the CBS-4M method[15] throughout to determine the barrier heights relative to separated reactants.[16] The optimized geometries of the transition states are shown in Figure 1. As might be expected for an identity exchange reaction, the nucleophile and nucleofuge show identical bond lengths. While this suggests a similarity to an S_N2 reaction, the nucleophile−acyl carbon−nucleofuge are not collinear but have bond angles closer to the expected tetrahedral geometry. Both the structures of these transition states and their imaginary frequencies are similar to those reported for anionic acylation reactions.[3a,5] The most important results are the transition state energies relative to separated reactants,

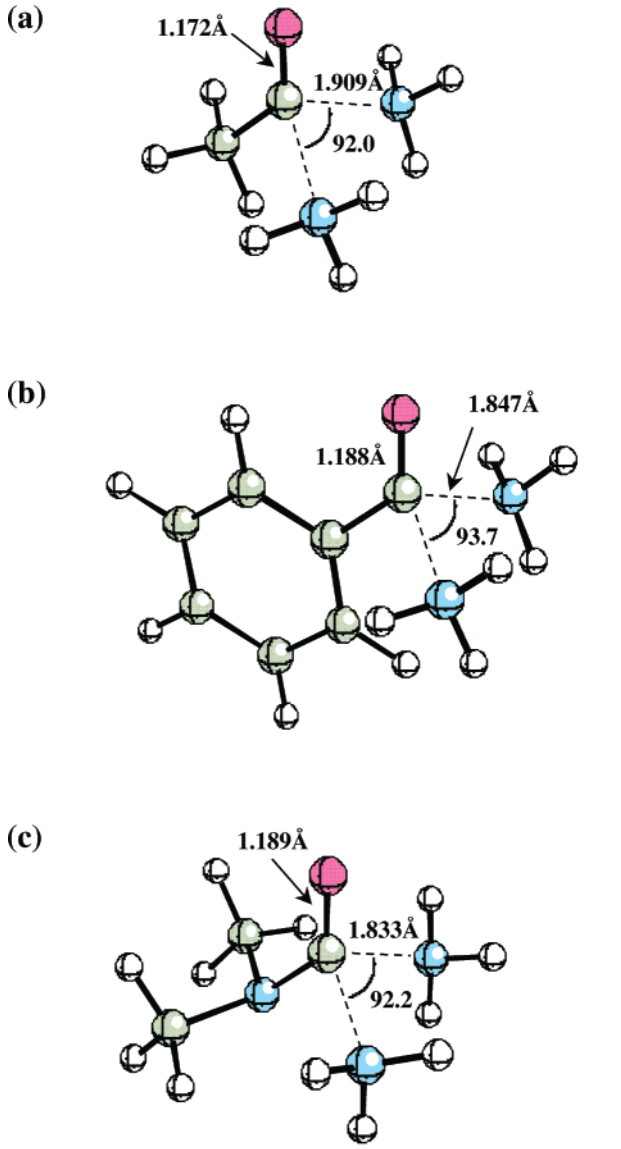

Figure 1. Transition states for transacylation reactions: (a) acetyl system has an imaginary frequency of −324.7 cm^{-1} and lies −3.3 kcal mol^{-1} below reactants; (b) benzoyl system has an imaginary frequency of −307.6 cm^{-1} and lies −1.1 kcal mol^{-1} below reactants; (c) *N*,*N*-dimethyaminocarbamyl system has an imaginary frequency of −283.7 cm^{-1} and lies +12.4 kcal mol^{-1} above reactants

which were calculated at 298 K (Figure 1). Only the acetyl and benzoyl systems lie *below* reactants, while the *N*,*N*-dimethyaminocarbamyl transition state lies over 10 kcal mol^{-1} *above* the reactants.

Thus, the *ab initio* results are in total accord with the experimental observations, supporting the following intrinsic reactivity order for acyl groups: MeC(O) > PhC(O) > Me_2-NC(O). Interestingly, the same reactivity order of MeC(O) > PhC(O) has been reported for related gas-phase identity exchange reactions between chloride ions and acyl chlorides[3b] and for condensed-phase reactions between amines and acyl chlorides.[17a] In contrast, the hydrolysis of acyl chlorides

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(16) The "double well" potential energy profiles for these systems require the formation of pre and post complexes (i.e., ion−molecule complexes) of the type $[RC(O)NH_3^+\cdots NH_3]$. IRC runs on each of the transition states indicates that they are likely to connect to such species. Unfortunately, optimizations of these complexes have proved to be impossible using the modest HF/3-21G* basis set. For example, the $[CH_3C(O)NH_3^+\cdots NH_3]$ complex fails to converge after 700 steps. At higher levels of theory, such complexes have, however, been found to connect to the S_N2 like transition state for the $HC(O)NH_3^+ + NH_3$ system (O'Hair, R. A. J. Manuscript in preparation). Finally, we find no evidence for the existence of stable tetrahedral intermediates.

follows the order MeC(O) > $Me_2NC(O)$ > PhC(O),[17b] but the behavior of $Me_2NC(O)Cl$ has been ascribed to an S_N1 like mechanisms. Further gas-phase studies of identity exchange reactions could unravel the contributions of electronic and steric effects of the RC(O) group.

We are continuing our studies on the transacylation reactions of peptides[18,19] and will report our results on the reactions between neutral nucleophiles and protonated peptides[20] in due course.

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