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Demonstration of the Chemical Competence of an Iminodiazonium Ion To Serve as the Reactive Intermediate of a Schmidt Reaction

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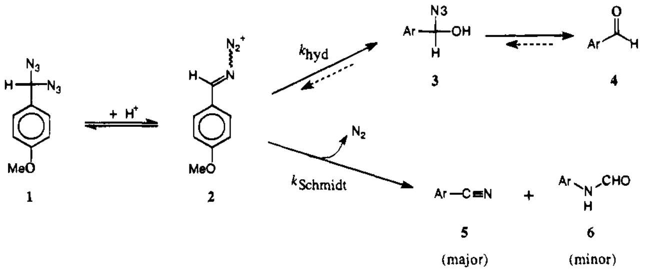
We report the generation of an iminodiazonium ion (α-azido carbocation) in acetonitrile and the first direct demonstration that such species are chemically competent to serve as the reactive intermediates of classic Schmidt rearrangement reactions.

The Schmidt reaction of aldehydes and ketones in strongly acidic media containing hydrazoic acid is a versatile approach to amides, lactams, and nitriles.[1−4] The most widely accepted mechanism involves rearrangement with loss of molecular nitrogen of putative iminodiazonium ions (e.g. **2**, Scheme 1).[2,5,6] However, the direct rearrangement of azidohydrins (e.g. **3**), which are precursors to iminodiazonium ions, has also been invoked in order to account for some experimental observations.[5,7] We have shown[8,9] that ring-substituted benzylic iminodiazonium ions, generated as intermediates in the solvolyses of the corresponding *gem*-diazides (e.g. **1**) in aqueous trifluoroethanol, give quantitative yields of the solvent adducts (chiefly benzaldehydes). Under these conditions, there are *no* products resulting from loss of molecular nitrogen, $k_{\rm hyd} \gg k_{\rm Schmidt}$, where $k_{\rm hyd}$ and $k_{\rm Schmidt}$ are first-order rate constants for capture of the iminodiazonium ion by water and Schmidt-type rearrangement, respectively (Scheme 1).[8,9] These results raised questions about the chemical reactivity of iminodiazonium ions, and they led us to address experimentally the possibility that, in essentially anhydrous organic solvents, Schmidt-type rearrangement of iminodiazonium ions would compete with their nucleophilic capture by water ($k_{\rm Schmidt} \geq k_{\rm hyd}$).[10] Such experiments might finally resolve the question of the chemical competence of iminodiazonium ions as the reactive intermediates of Schmidt reactions.

The time course for the acid-catalyzed (3 mM D_2SO_4) reaction of diazido(4-methoxyphenyl)methane (**1**, 0.1 M) in CD_3CN was followed by monitoring changes in the concentrations of the reactant and products by ^{1}H NMR spectroscopy.[11a] At early reaction times, the major product is 4-methoxybenzaldehyde (95% of **4** is formed during disappearance of the first 40% of **1**), but at later times there is a dramatic reversal, and the major product becomes 4-methoxybenzonitrile (92% of **5** is formed during disappearance of the last 60% of **1**).[11b] These data are in qualitative agreement with the mechanism shown in Scheme 1. At early reaction times, **4** results from the scavenging by **2** of residual water, $[H_2O]_{\rm res}$, in the solvent ($[H_2O]_{\rm res} <$ [**1**] and $k_{\rm hyd} > k_{\rm Schmidt}$), but at later times, in the now "dry" solvent, the predominant product becomes **5** ($k_{\rm Schmidt} > k_{\rm hyd}$).

Scheme 1



In a second type of experiment, the acid-catalyzed (3 mM H_2SO_4) reaction of **1** (0.1−0.2 mM) in "anhydrous" acetonitrile ([**1**] < $[H_2O]_{\rm res}$) gave a very high total yield of the Schmidt-type products 4-methoxybenzonitrile (**5**, 86%) and 4-methoxyformanilide (**6**, 2%), along with 12% of **4**.[12,13] The addition of 0.023 M water to this solvent leads to a 3.5-fold *decrease* in $k_{\rm obsd}$ (s^{-1}) for the disappearance of **1**[15] and a large increase in the yield of **4**, the ultimate product of hydrolysis of **1**, at the expense of the Schmidt-type products **5** and **6** (Figure 1). These results are inconsistent with a bimolecular substitution reaction of water with **1**, because a 7.5-fold *increase* in $k_{\rm obsd}$ would be required in order to account for the observed increase in the yield of **4**. They provide strong evidence that, as observed in aqueous solvents,[8,9] the reaction of **1** in acetonitrile proceeds by a $D_N + A_N$ (S_N1)[16,17] mechanism through an iminodiazonium ion intermediate (**2**, Scheme 1).

The ratio of the benzaldehyde (**4**) to the Schmidt-type products (**5** and **6**), [ArCHO]/[Schmidt], shows a very strong second-order dependence on the concentration of added water in acetonitrile, $[H_2O]_{\rm add}$, (Figure 1). Nonlinear curve-fitting of the product data to eq 1,[18] derived for the mechanism shown in Scheme 1, using a concentration of residual water in the solvent

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(1) Wolff, H. *Organic Reactions*; John Wiley and Sons: New York, 1946; Vol. 3.

(2) Smith, P. A. S. In *Molecular Rearrangements*; de Mayo, P., Ed.; John Wiley and Sons: New York, 1967; Vol. 1, pp 457−591.

(3) Beckwith, A. L. J. In *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley Interscience: London, 1970; pp 73−185.

(4) Scriven, E. F. V. *Chem. Rev.* **1988**, *88*, 297−368.

(5) For recent discussions of mechanisms for the Schmidt reaction, see: Sprecher, M.; Kost, D. *J. Am. Chem. Soc.* **1994**, *116*, 1016−1026. Bach, R. D.; Wolber, G. J. *J. Org. Chem.* **1982**, *47*, 239−245.

(6) Smith, P. A. S. *J. Am. Chem. Soc.* **1948**, *70*, 320−323.

(7) Fikes, L. E.; Shechter, H. *J. Org. Chem.* **1979**, *44*, 741−744.

(8) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1867−1869.

(9) Richard, J. P.; Jagannadham, V.; Amyes, T. L., unpublished results.

(10) The treatment of diazidodiphenylmethane (benzhydrylidene diazide) with sulfuric acid gives benzanilide in 98% yield (Götzky, S. *Chem. Ber.* **1931**, *64*, 1555) and has been suggested to involve an iminodiazonium ion intermediate.[2]

(11) (a) ^{1}H NMR spectra at 200 MHz and 25 °C were recorded on a Varian Gemini spectrometer at the University of Kentucky. (b) The relative amounts of **1**, **4**, and **5** were determined from the integrated areas of the singlets due to their methoxy groups at 3.81, 3.88, and 3.85 ppm, respectively.

(12) These experiments were conducted in HPLC grade acetonitrile (rated <0.003% water) from Fisher Scientific. Qualitatively similar results were obtained using anhydrous (rated <0.005% water) acetonitrile from Aldrich, except that the yield of **4** was significantly larger than can be accounted for by differences in the concentration of residual water in the two solvents (determined by Karl Fischer titration).[19] The reaction of water with **2** is strongly catalyzed by a second molecule of water (see text), and presumably even more so by stronger bases, so the apparent increased reactivity of water in the latter solvent is probably due to trace levels of a basic impurity.

(13) The reactions were carried out at ambient temperature in a glovebox under argon. Products were analyzed and quantified as described previously,[14] except that peak detection was by a Waters 996 diode array detector. **4**, **5**, and **6** were identified by comparison of their HPLC retention times and UV spectra with those of authentic materials and were shown to be stable to the reaction conditions for extended periods of time.

(14) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361−1372. Richard, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 1455−1465. Richard, J. P.; Amyes, T. L.; Bei, L.; Stubblefield, V. *J. Am. Chem. Soc.* **1990**, *112*, 9513−9519.

(15) Pseudo-first-order rate constants, $k_{\rm obsd}$ (s^{-1}), for the reactions of **1** (0.01−0.02 mM) in acetonitrile at 25 °C were determined spectroscopically by monitoring the appearance of **5** at 250 nm or of **4** at 272 nm. At zero added water and $[H_2SO_4]$ = 3 mM, $k_{\rm obsd}$ for reaction of **1** is 0.041 s^{-1}.

(16) IUPAC Commission on Physical Organic Chemistry. *Pure Appl. Chem.* **1989**, *61*, 23−56.

(17) Guthrie, R. D.; Jencks, W. P. *Acc. Chem. Res.* **1989**, *22*, 343−349.

(18) The numerator on the right of eq 1 replaces the term $k_{\rm hyd}$ in Scheme 1. Part of the water in acetonitrile will undergo protonation by the sulfuric acid catalyst ($[H_2SO_4]$ = 3 mM) to give H_3O^+ which cannot act as a nucleophile to trap **2**. Equation 1 makes no distinction between free water and H_3O^+ and will therefore probably fail at low $[H_2O]_{\rm add}$. This might account for some of the deviations from the fit shown in Figure 1, but our data do not allow us to address this point in detail.

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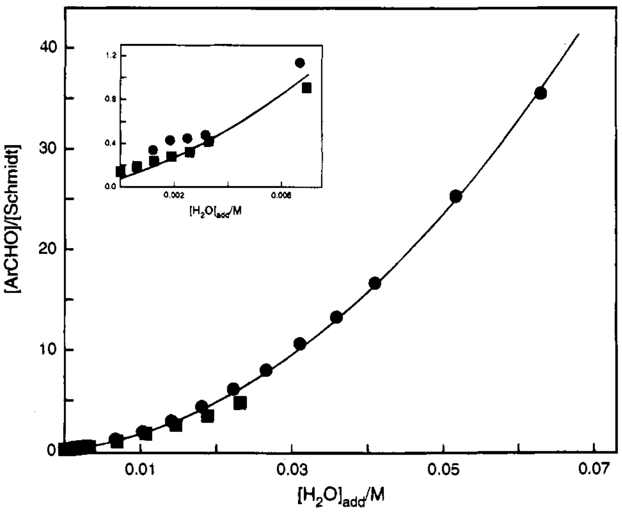


Figure 1. Dependence on the concentration of added water in acetonitrile, $[H_2O]_{add}$, of the ratio of 4-methoxybenzaldehyde (**4**) to Schmidt-type products (**5** + **6**) obtained from the acid-catalyzed (3 mM $[H_2SO_4]$) reaction of diazido(4-methoxyphenyl)methane (**1**). The circles and squares represent data from two separate experiments. The inset is an expansion of the region of $[H_2O]_{add}$ < 0.008 M. The curves show the fit of the experimental data to eq 1, derived for the mechanism shown in Scheme 1 (see text).

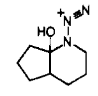
of $[H_2O]_{res}$ = 1 mM (determined by Karl Fischer titration),[19] gives $k_T/k_{Schmidt}$ = 7700 M^{-2} and $k_B/k_{Schmidt}$ = 70 M^{-1} for partitioning of the iminodiazonium ion **2** between capture by water in termolecular and bimolecular processes, respectively, and Schmidt-type rearrangement with loss of molecular nitrogen.

$$\frac{[\mathrm{ArCHO}]}{[\mathrm{Schmidt}]} = \frac{k_B([H_2O]_{res} + [H_2O]_{add}) + k_T([H_2O]_{res} + [H_2O]_{add})^2}{k_{Schmidt}} \qquad (1)$$

The ratio $k_T/k_B \approx 100\ M^{-1}$ shows that, in the relatively nonpolar solvent acetonitrile, where formation of localized charge is unfavorable, the presence of a second molecule of water in the transition state for addition of water to the highly delocalized **2** provides substantial stabilization of the developing localized positive charge at the oxygen of the attacking water molecule. This may correspond to classical general base catalysis or to stabilization by hydrogen bonding without formal proton transfer. The attack of alcohols on several acyl halides in organic solvents is also catalyzed by a second molecule of alcohol, although the catalysis is smaller than that found here for capture of the charged iminodiazonium ion.[20-23] The barriers to carbocation–anion combination reactions in the gas phase are expected to be considerably lower than those in aqueous solution, because of the larger thermodynamic driving force for neutralization of ions in the gas phase. By contrast, our results suggest that the reaction of the neutral nucleophile water with *delocalized* carbocations in aqueous solution may be faster than that in the gas phase, because localized charge on oxygen in the transition state can be stabilized by an interaction with a second molecule of water that can be described as "solvation".

There is no mechanistically reasonable path for formation of the benzonitrile **5** by direct rearrangement with loss of molecular nitrogen of the azidohydrin **3**: such a rearrangement would give only 4-methoxybenzamide (not observed) and/or 4-methoxyformanilide (**6**). The limiting yield of 100% **4** at high $[H_2O]_{add}$ shows that, under our reaction conditions (low $[H^+]$ and $[HN_3]$), there is *no* significant rearrangement of the azidohydrin **3** to give the formanilide **6**; **3** reacts solely by the irreversible loss of HN_3 to give **4**. The product ratio [**5**]/[**6**] = 40 is strictly independent of $[H_2O]_{add}$,[24] which shows that both the benzonitrile **5** and the formanilide **6** are formed from the same intermediate, the iminodiazonium ion **2**. This demonstrates that **2** is chemically competent to serve as the reactive intermediate of the Schmidt rearrangement reaction of the benzaldehyde **4**.

Schmidt-type rearrangement of azidohydrins is much more likely to take place for species such as **7**, which are putative intermediates of intramolecular Schmidt-type reactions of alkyl azides with cyclic ketones.[25] Here, the direct rearrangement of **7** is favored because there is no mechanistically reasonable pathway for formation of the observed lactam products from the highly unstable dication **8**.[25]



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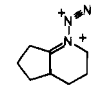

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[19] Karl Fischer titration was carried out using a Metrohm 684 KF coulometer at the University of Western Ontario, Canada.

[20] Hudson, R. F.; Saville, B. *J. Chem. Soc.* **1955**, 4121–4129. Hudson, R. F.; Loveday, G. W.; Fliszár, S.; Salvadori, G. *J. Chem. Soc. B* **1966**, 769–774.

[21] Kevill, D. N.; Foss, F. D. *J. Am. Chem. Soc.* **1969**, *91*, 5054–5059. Kevill, D. N.; Kim, C.-B. *Bull. Soc. Chim. Fr.* **1988**, 383–390.

[22] Ross, S. D. *J. Am. Chem. Soc.* **1970**, *92*, 5998–6002.

[23] Bentley, T. W.; Harris, H. C. *J. Org. Chem.* **1988**, *53*, 724–728. Bentley, T. W.; Jones, R. O. *J. Chem. Soc., Perkin Trans. 2* **1992**, 743–744.

[24] The Schmidt reaction of 4-methoxybenzaldehyde in benzene/sulfuric acid has been reported to give only 4-methoxybenzonitrile, which may undergo subsequent hydrolysis to 4-methoxybenzamide: McEwen, W. E.; Conrad, W. E.; Van der Werf, C. A. *J. Am. Chem. Soc.* **1952**, *74*, 1168–1171.

[25] Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965–8966. Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635–1637.