MINDO/3 value. The cyclobutene cation radical electrocyclic reaction thus ideally illustrates the point that cation-radical pericyclic reactions are only modestly faster than the neutral variety where highly synchronous paths are involved.

Summary

Hole formation (ionization) is predicted to accelerate a variety of pericyclic reactions, especially those in which highly nonsynchronous transition states are readily accessible. The cation-radical Diels-Alder reaction path is characterized as concerted and highly nonsynchronous. The reaction path for the [2 + 1] cycloaddition emerges as a two-step sequence. An intermediate long-bond cyclobutane cation radical is formed via a nonsynchronous process, but the one-electron bonding in this usual intermediate is capable of maintaining stereochemical relationships. Reaction paths for the cation-radical Cope reaction and for the retroelectrocyclic cleavage of the cyclobutene cation radical are also discussed.

Hydrolysis of Imidazole-Containing Amide Acetals

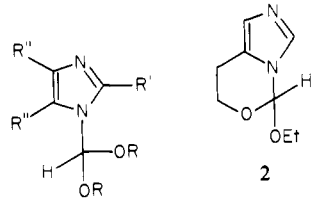
R. S. Brown* and J. G. Ulan[1]

Contribution from the Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2. *Received August 30, 1982*

Abstract: *N*-(Dialkoxymethyl)imidazoles (amide acetals **1a-c**) are shown to hydrolyze by a common mechanism between pH 1 and pH 11 that involves preequilibrium protonation of the imidazole distal N, followed by rate-limiting C-N cleavage. The Brønsted plot of the log C-N cleavage rate vs. pK_a of the parent imidazole has a slope of -1.0 and suggests a transition state in which (+) is nearly completely transferred to the departing dialkoxymethyl group. Throughout the pH range studied, C-N cleavage is the dominant process. The bicyclic amide acetal **2** formed from 4(5)-(hydroxyethyl)imidazole and triethyl orthoformate behaves similarly to the acyclic cases at pHs >5 except that the observed rate of C-N cleavage for the former is depressed by (1-2) × 10^2-fold. This apparent reduction of C-N cleavage rate is analyzed in terms of reversibility of the ring opening. Such reversal is demonstrated by the ability of good nucleophiles such as N_3^- or H_2NOH to trap the open ion, preventing reversal and hence increasing the apparent rate of loss of **2**. From pH 0 to pH 5, an additional sigmoidal event in the pH/log k_{obsd} profile for **2** is observed, which is analyzed as a protonation of the imidazole of the open ion. Such a protonation prevents the reversible reclosure and concomitantly increases the k_{obsd}. Bicyclic **2** can be taken as a model for the tetrahedral intermediate formed during intramolecular alcoholysis of an *N*-acylimidazole or intramolecular attack of an imidazole on an ester.

Some time ago we reported[2] what proved to be an easily introduced and removed protecting group for the imidazole N. An *N*-dialkoxymethyl group can be easily introduced by heating the parent imidazole and trimethyl or triethyl orthoformate in the presence of a catalytic amount of H^+ and removing the corresponding alcohol as it is formed. Isolated yields of protected products are generally high (>80%),[3a] and a variety of electrophiles can be introduced at C-2 of the imidazole following lithiation of it at -40 °C by using *n*-BuLi.[3b,c]

An additional virtue of this protecting group is its ease of removal that can be effected by stirring with aqueous or methanolic acid or, if the final product is H^+ labile, under essentially neutral conditions with aqueous acetone. Mechanistically, an understanding of the deprotection process is desirable not only for determining the optimum conditions for effecting it but also because the amide acetal unit in **1** closely resembles the tetrahedral intermediate resulting from imidazole attack on an ester or alcoholysis of an *N*-acylimidazole. Similarly, that same unit in **2** could be taken as a model for the intermediate formed during intramolecular imidazole attack on an ester or alcohol attack on an *N*-acylimidazole, the latter two processes being of direct relevance to a number of biological processes involving the serine proteases.[4]



1a, R' = R'' = H
b, R' = CH_3, R'' = H
c, R' = R'' = CH_3

2

Although some excellent and informative studies of the decomposition of amide acetals have been reported,[5] none of those has incorporated an imidazole as the N-bearing substituent. This simple structural change will be seen to significantly perturb the pH/rate constant profiles relative to those observed for secondary amine[5a] or anilide[5b] amide acetals. In the following we report a kinetic study of the hydrolyses of **1a-c** and **2** in aqueous media.

Experimental Section

Routine NMR, IR, and mass spectra were determined by using Bruker WP-80, Nicolet FTIR, and AEI-MS50 spectrometers. Compounds **1a-c** were prepared as previously reported.[2,3c] Bicyclic **2** was prepared in 26% overall yield from 1,4-dihydroxy-2-butanone[6a] (converted to 4(5)-(hydroxyethyl)imidazole by the method of Schunack.[6b] This product was extracted from an aqueous solution of the crude reaction mixture[6b] with several portions of *n*-butyl alcohol,[6c] which were

(1) Alberta Heritage Medical Research Foundation Summer Student, 1982.

(2) Curtis, N. J.; Brown, R. S. *J. Org. Chem.* **1980**, *45*, 4038-4040.

(3) (a) We have also explored the possibility of introducing dialkoxyethyl groups to the imidazole N by treatment with triethyl or trimethyl orthoacetate under the same conditions. This reaction is only successful for imidazole itself and fails when methyl substituents occupy the 2- and/or 4- and 5-positions, the only isolable products being the corresponding *N*-ethyl- or *N*-methylimidazoles in variable yield. (b) Brown, R. S.; Curtis, N. J.; Huguet, J. *J. Am. Chem. Soc.* **1981**, *103*, 6953-6959. (c) Brown, R. S.; Salmon, D.; Curtis, N. J.; Kusuma, S. *Ibid.* **1982**, *104*, 3188-3194.

(4) (a) Quinn, D. M.; Elrod, J. P.; Ardio, R.; Friesen, P.; Schowen, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5358-5365. (b) Pollack, E.; Hogg, J. L.; Schowen, R. L. *Ibid.* **1973**, *95*, 968-969. (c) Hamilton, S. E.; Zerner, B. *Ibid.* **1981**, *103*, 1827-1831 and references therein. (d) Fife, T. H.; Hutchins, J. E. C.; McMahon, D. M. *Ibid.* **1972**, *94*, 1316-1323. (e) Hubbard, C.; Kirsch, J. F. *Biochemistry* **1972**, *11*, 2483. (f) Walsh, C. "Enzymatic Reaction Mechanisms"; W. H. Freeman: San Francisco, 1979; pp 56-90. (g) Dugas, H.; Penney, C. "Bioorganic Chemistry": Springer-Verlag, New York, 1981; pp 208-226.

(5) (a) McClelland, R. A. *J. Am. Chem. Soc.* **1978**, *100*, 1844-1849. (b) McClelland, R. A.; Patel, G. *Ibid.* **1981**, *103*, 6908-6911 and references therein. (c) Gravitz, N.; Jencks, W. P. *Ibid.* **1974**, *96*, 507-515.

(6) (a) Reppe, W. *Justus Liebigs Ann. Chem.* **1955**, *596*, 1-224. (b) Schunack, W. *Arch. Pharm.* **1974**, *307*, 517-523. (c) Stensio, K.-E.; Wahlberg, K.; Wahren, R. *Acta Chem. Scand.* **1973**, *27*, 22-26.

0002-7863/83/1505-2382$01.50/0

combined, decolorized with charcoal, and stripped of solvent to yield a yellow-brown paste of the imidazole alcohol (which was used for protection without further purification). Protection involves refluxing the crude paste with triethyl orthoformate and a catalytic quantity of toluenesulfonic acid and removing ethanol as it is formed. Spinning-band distillation of **2** yields a faint yellow oil: bp 80–81 °C (0.08 torr); ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3 H, J = 7 Hz), 2.87–3.02 (m, 2 H), 3.82 (q, 2 H, J = 7 Hz), 4.45–3.26 (m, 2 H), 6.27 (s, 1 H), 6.85 (s (br), 1 H), 7.57 (s, 1 H); IR (neat) 2979.6, 2935.5, 2895.2, 1489.9, 1386.9, 1342.5, 1264.4, 1247.7, 1219.8, 1195.7, 1099.3, 1077.4, 1056.0, 1031 cm^{-1}; exact mass calcd for $C_8H_{12}N_2O_2$ m/e 168.0898, found 168.0898. Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.13; N, 16.45. Found: C, 57.11; H, 7.26; N, 16.38.

Rates of disappearance of **1a–c** and **2** were monitored at 25.0 ± 0.2 °C by observing the diminution of absorbance at 225, 235, 250, and 236 nm, respectively. Buffers were formulated to 0.3 M (except for pH <2.3) from commercially available materials: pH 0.5–2.3, $HClO_4$; pH 2.8–3.7, formic acid; pH 4–5, acetic acid; pH 5.5–6.5, MES [2-(*N*-morpholino)ethanesulfonic acid]; pH 6.8–7.8, HEPES [*N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid] or MOPS [3-(*N*-morpholino)propanesulfonic acid]; pH 8.4–9.2, CHES [cyclohexylaminoethanesulfonic acid]; pH 9.6–11.3, CAPS [cyclohexylaminopropanesulfonic acid]. Ionic strength throughout was maintained at 0.3 M (except in 0.5 and 1.0 M $HClO_4$) by the addition of the appropriate amount of $NaClO_4$. pH readings were made with a Radiometer TTT-2 titrator module using a Radiometer GK 2321C combination electrode standardized with Fisher Certified Buffers (pH 4.00, 7.00, 10.00) immediately before use.

Slower kinetic data (k_{obsd} < 10^{-1} s^{-1}) were obtained by using a Varian/Cary 210 UV/visible spectrophotometer interfaced to an Apple II microcomputer. This set up allows collection of absorbance/time data for up to five cells and analyzes the kinetic curves as being first order with a standard nonlinear least-squares method.[7] Reactions were initiated by injecting 100 μL of a stock (0.1–0.3 M in dry THF) solution of **1** or **2** into 3.0 mL of buffer held in 1-cm quartz cuvettes. pHs were monitored immediately following a kinetic run and found to be invariant. In cases where the total absorbance of sample and buffer was large (usually HEPES buffers and in N_3 trapping experiments) shorter path length cells of 0.5 and 0.1 cm were used and the amount of sample stock decreased accordingly.

Fast rates (k_{obsd} > 10^{-1} s^{-1}) were determined with a Durrum-Gibson stopped-flow instrument thermostated at 25.0 ± 0.2 °C. Absorbance/time traces were digitally stored on a TDI Model 1024-C transient recorder. Data manipulations and calculations were performed by a Commodore/PET Model 4032 microcomputer interfaced to the system, and k_{obsd} values were calculated to be the slopes of a standard linear regression of log Δ(abs) vs. time. One drive syringe contained the buffer solution while the second contained a sample of **1** or **2** (25 μL) dissolved 20 mL in 0.001 N NaOH to retard its decomposition. Rapid mixing of equal volumes of the two dilutes the final buffer concentrations to 0.15 M and causes a rapid pH jump. pHs were monitored by using retrieved effluent from the sample compartment and found to vary by 0.00–0.20 pH unit upward from the initial buffer values. Final measured values are those reported in Figure 1 and are assumed to have reached equilibrium prior to the hydrolysis reaction.

Product analyses were conducted in two ways. For the actual conditions of the kinetic runs, a final solution comprised of the buffer and anticipated imidazole products at the same concentration as the starting material was compared and found to be the same. However, since the UV spectra of these imidazoles are rather featureless and show only end absorption, NMR determination of products was undertaken. The NMR solutions consisted of D_2O–methanol-d_4 (60/40, v/v), and spectra were monitored at various time intervals. In all cases, products were those anticipated from the reaction schemes to follow.

Results and Discussion

Shown in Figure 1 are plots of log k_{obsd} vs. pH for ortho amides **1** and **2**. Inspection of the shapes of the plots for **1a–c** indicates two sections to the profile, one being first order in [H$^+$] at pHs >7–8 and a second being independent of [H$^+$] at pH <5–6. Each

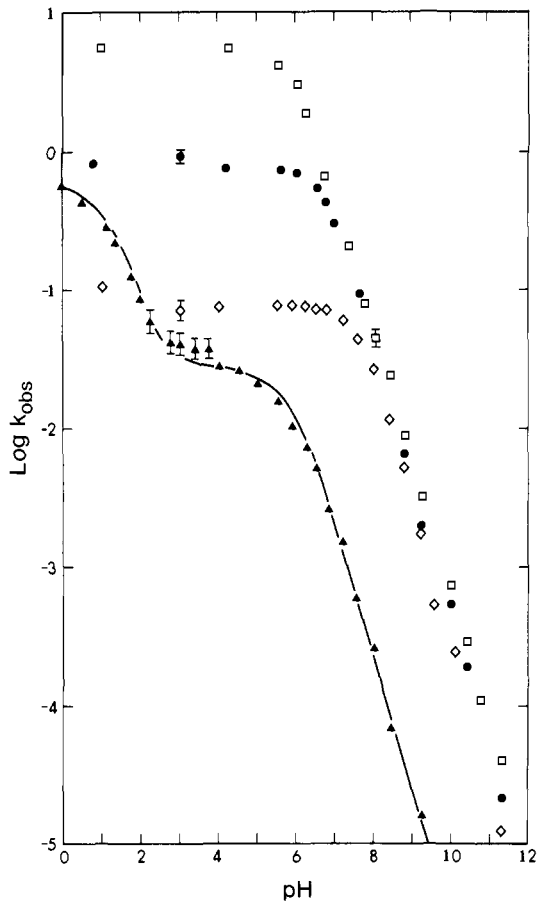


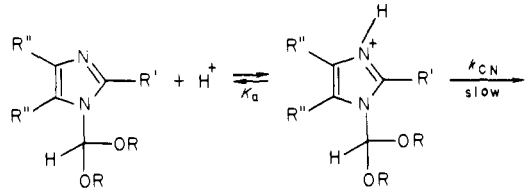
Figure 1. pH vs. log k_{obsd} profiles for **1a** (open squares), **1b** (closed circles), **1c** (open diamonds), and **2** (closed triangles). The theoretical pH profile based on the mechanism shown in Scheme I obtained by fitting eq 5 to the observed data is shown as the solid curve.

Table I. Equilibrium and Rate Constant Values for Amide Acetals 1a-c

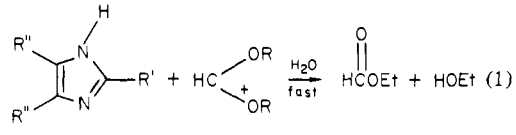
compd	pK_a[a]	$k_{C\text{-}N}$,[a] s^{-1}	p$K_{a_{IM}}$[b]	10^{-6} $k_{H^+,CN}$,[c] M^{-1} s^{-1}
1a	5.97	5.39	7.12	5.43
1b	6.75	8.4 × 10^{-1}	7.85	4.17
1c	7.66	7.75 × 10^{-2}	8.92	2.83

[a] Evaluated from the slopes and intercepts of plots of k_{obsd} vs. k_{obsd}/[H$^+$]; correlation coefficients >0.999. [b] pK_a of the parent imidazole.[9] [c] Evaluated from the linear first-order sections of the plots in Figure 1.

hydrolysis therefore appears to adhere to a common mechanism given in eq 1, where k_{obsd} is given in eq 2. Plots of k_{obsd} vs.



1a-c



3

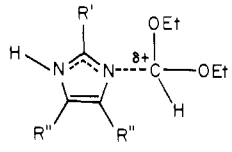
k_{obsd}/[H$^+$] yield straight lines, the slopes and intercepts of which are $-K_a$ and k_{CN} respectively, these values being given in Table

(7) We are indebted to Mr. Doug Greg, Varian Associates, Palo Alto, Calif., for providing us with the software for data acquisition and manipulation. The nonlinear least-squares program used in the above software is based on a program kindly provided by Prof. R. E. D. McClung of this department.

(8) This is evidenced by replacement of the methine signal of the initially formed orthoformate at δ 5.04 by first one and then a second signal, each shifted upfield from the other by 0.06–0.07 ppm.

$$k_{obsd} = \frac{k_{CN}[H^+]}{K_a + [H^+]} \quad (2)$$

I. Under no circumstances could buffer catalysis be detected for **1a–c**. This and the fact that the acid-dependent section of the pH/rate profile has a slope of −1.0 indicate that the reaction is specific acid catalyzed with the rate-limiting step being C–N cleavage. Although we have at hand only limited data, the kinetic (k_{CN}) data of Table I show a large dependence on the pK_a of the parent imidazole since a Brønsted plot of log k_{CN} against pK_a for the three imidazoles[9] has a slope of $\beta = -1.0$ ($r = 0.999$). Hence, those parent imidazoles having the lowest pK_a's liberate the dialkoxymethyl cation from the protonated substrate most readily. Such would suggest a late transition state with a large amount of C–N cleavage and almost complete transfer of (+) to the departing diethoxymethyl group as in **4**.[5c] Additional support

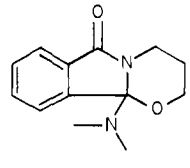


4

for the exclusive C–N cleavage comes from ^{1}H NMR studies of the decompsition of **1a–c** in 60/40 D_2O–methanol-d_4 containing small amounts of acetic acid-d_4. In the cases of **1a,b**, both of which hydrolyze relatively rapidly, disappearance of starting material leads immediately (without buildup of any detectable intermediates) to the parent imidazoles, ethanol, ethyl formate, and some methyl-d_3 diethyl orthoformate, the latter being formed by capture of the diethoxymethyl carbonium ion by methanol-d_4. Monitoring the reaction mixture after 24 h showed complete hydrolysis of ethyl formate and methyl-d_3 diethyl orthoformate to give formic acid and ethanol. For **1c** which reacts more slowly than **1a,b**, ethyl formate does not build up in the medium since it is hydrolyzed more rapidly than it is formed.

Finally, in pure methanol-d_4 containing a drop of acetic acid-d_4, the *only* cleavage products were the parent imidazoles and methyl-d_3 diethyl orthoformate. The observation of the latter indicates the ethoxy group replacement within the ortho amide starting materials does not occur and hence C–O cleavage prior to C–N is not important. Continued monitoring of the NMR spectra shows that the initially formed ortho ester slowly undergoes successive ethoxy replacement to yield finally tris(methyl-d_3) orthoformate and ethanol.[8]

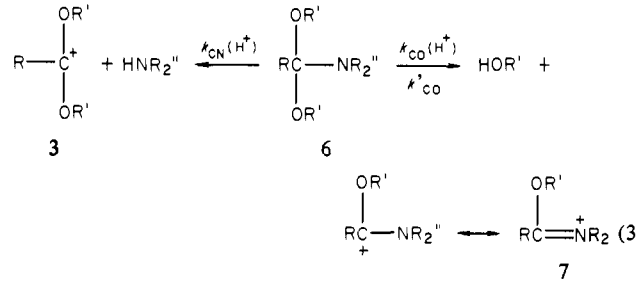
Two additional points that differentiate these species from simple amide acetals[5] are of note. First, for each of **1a–c** the pK_a of the imidazole is depressed by some 1.2–1.3 units relative to the parent.[9] Such a depression of pK_a in amide acetals is a general phenomenon,[10] but in the cases of $RC(OCH_3)_2NR_1R_2$, where $R_1 = R_2 = CH_3$ or $R_1 = CH_3$ and R_2 = phenyl, the amine pK_a is severely reduced by roughly 6 units[5a,b] due to the fact that the site of proton attachment is adjacent to the acetal carbon. Similar large reductions in pK_a's of amines attached to the related phthalamide nucleus **5** are also established[5c] wtih the exception



5

of bifunctional amines such as imidazole and *N,N'*-dimethylhydrazine. The difference between the latter two cases and the others is reasonably attributed to the fact that protonation occurs on the distal imidazole or hydrazine N and therefore does not transfer so much charge to the N directly attached to the aminal moiety.[5c] Clearly such a situation occurs in the imidazole amide acetals as well, and the kinetic consequences become predictable. Because of charge dispersion, the imidazole acetals will protonate more easily than simple amide acetals, but the same effect will make C–N cleavage slower because the (+) is not as completely localized on the proximal N as it is, for example, in protonated **5** or **6**. The latter statement may be verified by observations[5a,b] that C–N cleavage in simple amide acetals occurs in H_2O with a half-life of <1 s at all pH values.

Secondly, previously studied amide acetals **6** react simultaneously by competing routes involving C–N and C–O cleavage (eq 3).[5a,b] At high pH (>10) where little of the amine is protonated,



the dominant process is cleavage of alkoxide yielding **7** in a mode independent of pH. For **6** ($R'' = CH_3$) under more acidic conditions two kinetically indistinguishable processes both catalyzed by H^+ but involving C–N and C–O cleavage, respectively, are evident from product studies, which require formation of both **3** and **7**.[5a,b] The latter cleavage choices reflect a delicate balance of factors. Although N is the more basic site, which favors C–N cleavage, once oxygen is protonated (or partially so) it becomes a more potent leaving group[5a,11] and importantly yields a highly stabilized imidatonium ion **7**. The situation for anilide acetals is somewhat different since although the k_{obsd} values at pH >10 are independent of $[H^+]$ and indicate alkoxide cleavage, under acidic conditions, only C–N cleavage of the N-protonated substrate occurs[5b] such that elimination of a neutral aniline is much favored over elimination of HOR.[12]

The present situation for **1a–c** is different from either of the above cases. For reasons discussed above, the imidazoles are more basic than the corresponding secondary amines, thereby becoming more fully protonated at higher pHs which in turn has a net effect of bringing into play the kinetic term involving H^+ catalyzed C–N cleavage earlier. Since one observes no curvature of the $[H^+]$-dependent lines even as high as pH 11, alkoxide or imidazolate expulsion cannot be involved. The pH-independent section (6 > pH > 1) and lack of buffer catalysis in this region argues against a new term involving C–O cleavage although admittedly we have no way of directly probing the initial products of cleavage in the kinetic medium.[13] One NMR experiment in which **1a–c** are solvolyzed in CF_3COOD is however suggestive. Such spectra show that immediately upon dissolution, the parent imidazole is completely released with concomitant formation of ethyl formate, ethyl trifluoroacetate, and what appears to be the diethoxymethyl cation as evidenced by its sharp methine singlet at δ 9.3.[14] (This signal disappears within a few minutes to yield a final spectrum consisting

(9) pK_a's of imidazole, 2-methylimidazole, and 2,4,5-trimethylimidazole are 7.12, 7.85, and 8.92 respectively: Perrin, D. D. "Dissociation constants of organic bases in aqueous solution"; Butterworths: London, 1965.

(10) Guthrie, P. J. *J. Am. Chem. Soc.* **1974**, *96*, 3608–3615.

(11) Gravitz, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 499–506.

(12) (a) Kluger, R.; Chin, J.; Choy, W. W. *J. Am. Chem. Soc.* **1979**, *101*, 6976–6980. (b) Ewing, S. P.; Lockshon, D.; Jencks, W. P. *Ibid.* **1980**, *102*, 3072–3084.

(13) pH-independent C–O cleavage of a simple amide acetal has been reported[5a] between pH 1 and pH ~3 and apparently behaves as such since the substrate must be N deprotonated before O-protonation can occur on the neutral amide acetal.

(14) (a) The diethoxymethyl cation has been observed before in nonnucleophilic media; the methine singlet appears at δ 9.4[14b] and 9.1[14c] in 30% SO_3/H_2SO_4 and $CDCl_3/BF_3$ media, respectively. (b) Ramsey, B. G.; Taft, R. W. *J. Am. Chem. Soc.* **1966**, *88*, 3058–3063. (c) Borch, R. F. *Ibid.* **1968**, *90*, 5303–5305. (d) Ethanol itself is unstable in this medium and slowly (within 30 min) gives rise to ethyl trifluoroacetate. However, if ethanol had been an initial cleavage product of the amide acetal, it would have been observable since the initial reactions of **1a–c** in this medium are quite fast.

of ethyl formate, ethanol, and apparently ethyl trifluoroacetate.) Importantly, at the time when the imidazole is completely released from the ortho amide, there is no evidence of a substantial amount of ethanol produced which argues against significant C–O cleavage prior to C–N cleavage[14d] in a highly acidic medium.

The reason why C–O cleavage is not observed in **1a–c** even though the protonated imidazole is not as good a leaving group as a protonated seconary amine with which acid-catalyzed C–O cleavage *does* compete in the breakdown of **6** probably again reflects the high pK_a of the imidazole and delicate balance of factors in these systems. Likely, in the case of the imidazole acetals it might be envisioned that C–O cleavage might be retarded from **1a–c** since expulsion of the ethoxyl moiety leads to an imidatonium ion resembling **7** but not as highly stabilized since the nitrogen electrons form part of the aromatic imidazole π system and hence are not readily delocalized to the adjacent C^+.

Given a mechanism such as that in eq 4[5a,b] where both C–N

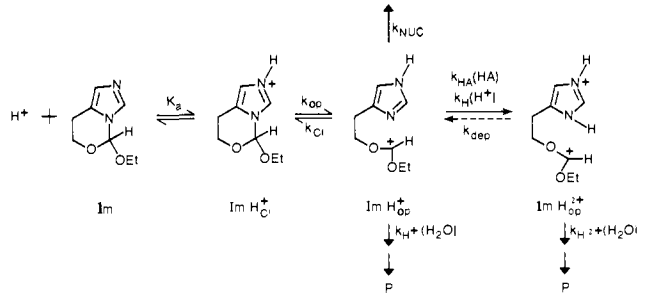
$$P' \xleftarrow{k_{CO}(H^+)} Im + H^+ \rightleftharpoons ImH^+ \xrightarrow{k_{CN}} P \qquad (4)$$

and C–O cleavage are acid catalyzed but are kinetically indistinguishable, if the pK_a and k_{CN} values for **1a–c** from Table I are used and k_{CO} $(H)^+$ is assumed to be 10^5 M^{-1} s^{-1} or less (this value being typical for acid-catalyzed C–O cleavage in related systems[15]), then the amount of C–O cleavage will always be 1% or less than the amount of C–N cleavage. The high imidazole pK_a effectively diverts larger amounts of **1a–c** into the N-protonated form such that the [free base] available for C–O protonation and cleavage is too small to provide a significant channel at any pH. Such an analysis also indicates that when the pK_a of the amine base is reduced, C–O cleavage can (and experimentally does)[5a] effectively compete with C–N cleavage if the latter's rate constant does not increase faster than the nitrogen basicity drops.

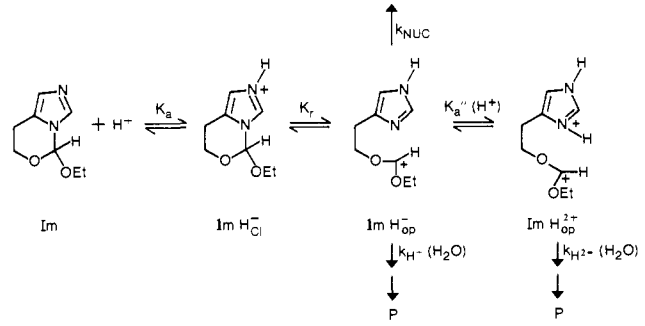
Bicyclic Amide Acetal 2. Refluxing of 4(5)-(hydroxyethyl)-imidazole[6] with triethyl orthoformate and removing 2 equiv of HOEt as it is formed yields **2** in which both the imidazole and hydroxyethyl groups are protected as well as a substantial quantity of nondistillable residue, which is assumed to be oligomeric material. Inspection of the pH/log k_{obsd} profile depicted in Figure 1 shows that the hydrolysis of **2** is quite different from that of **1a–c**. Three experimental observations are of note. First, at pHs >6, the observed rates are first order in $[H^+]$ which indicates a specific-acid-catalyzed C–N cleavage not unlike that seen for **1a–c**. However, in this region, the acid term ($k_{obsd}/[H^+] = k_{H^+,CN}$) = 2.36×10^4 M^{-1} s^{-1}, indicating this process is at least (1–2) × 10^2-fold slower than the comparable terms for **1a–c** (Table I). Buffer catalysis is not evident in this region.

Second, at pHs <5, one observes distinct sigmoidal shape to the profile that is indicative of an additional H^+-dependent equilibrium. When formate or acetate are used as buffers (2.3 < pH < 5), buffer catalysis is observed, the values depicted in Figure 1 being extrapolated to [buffer] = 0 with the appropriate error bars. This is likely a general-acid catalysis or an apparent specific acid–general base process since for a given buffer, dependence on [buffer] is greater at lower pHs. Finally, at pH <2, the kinetic traces show some biphasic character in which there is an initial rapid diminution of absorbance followed by a slower increase. Both processes are pH dependent. Monitoring the kinetics at 236 nm for disappearance of starting material minimizes the absorption due to the slower kinetic event, and values for k_{obsd} (Figure 1) are those determined at this wavelength. If the kinetics are monitored at 246 nm, the initial diminution of absorbance is minimized and the major (slower) kinetic event is easily monitored. Such observations indicate that an intermediate is generated whose rates of formation and disappearance are comparable. We believe the pH/log k_{obsd} profile and experimental observations can most simply be accommodated by the mechanisms shown in Scheme I[16a] or II[16b] with the observed rate constants being given by the expressions shown in eq 5[16a] or 5a,[16b]

Scheme I



Scheme II



$$k_{obsd} = \frac{\left(k_{H^+}\frac{k_{op}}{k_H}\right)[H^+] + k_{op}[H^+]^2}{K_a\left(\frac{k_{Cl} + k_{H^+}}{k_H}\right) + \left(K_a + \frac{k_{Cl} + k_{H^+}}{k_H}\right)[H^+] + [H^+]^2} \qquad (5)$$

respectively. Nonlinear least-squares fitting of the latter expressions to the experimental data generates the solid curve shown on Figure 1, which can be seen to fit the data points rather well. In point of fact the two mechanisms are conceptually the same with the same overall dependence on $[H^+]$; the major difference between the two stems from an assumption that in Scheme I the final protonation step is essentially irreversible ($k_H >> k_{dep}$) such that once ImH^{2+}_{op} forms, it is immediately captured by H_2O to yield products. In this case, at low pH, the event that controls the reaction rate is limited by k_{op}, the opening of ImH^+_{Cl} to form ImH^+_{op}. From the nonlinear least-squares analysis of eq 5, the following complex constants are given: $k_{op} = 0.64$ s^{-1}; $K_a[(k_{Cl} + k_{H^+})/k_H] = 1.414 \times 10^{-7}$; $k_{op}k_{H^+}/k_H = 2.89 \times 10^{-3}$; $K_a + (k_{Cl} + k_{H^+})/k_H = 0.107$, where the individual components are defined

(15) (a) Bergstrom, R. G.; Cashen, M. J.; Chiang, Y.; Kresge, A. J. *J. Org. Chem.* **1979**, *44*, 1639–1642. (b) Chiang, Y.; Kresge, A. J.; Young, C. I. *Finn. Chem. Lett.* **1978**, 13–18 (*Chem. Abstr.* **1978**, *88*, 135870). (c) Chiang, Y.; Kresge, A. J.; Salomaa, S.; Young, C. I. *J. Am. Chem. Soc.* **1974**, *96*, 4494–4499. (d) See also values reported in ref 4a,b and 17b.

(16) (a) Expression 5 is derived from assuming that ImH^+_{op} exists in low concentration as a steady-state intermediate and that the total imidazole is partitioned between Im and ImH^+_{Cl}. The steady-state assumption seems justified by the fact that although ImH^+_{op} is generated rather slowly from ImH^+_{Cl}, the former suffers three extremely rapid fates, namely, reclosure, capture by H_2O, or capture by H^+ to form ImH^{2+}_{op}. (b) Scheme II is kinetically equivalent to Scheme I and therefore the two can not be directly differentiated on the basis of the information given. Under equilibrium conditions assuming the total imidazole is partitioned between Im, ImH^+_{Cl}, ImH^+_{op}, and ImH^{2+}_{op}, eq 5a can be derived, with the constants being defined

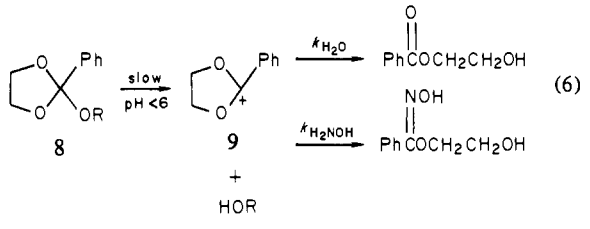
$$k_{obsd} = \frac{(k_{H^+}K_a'')[H^+] + k_{H^{2+}}[H^+]^2}{K_aK_rK_a'' + (K_rK_a'' + K_a'')[H^+] + [H^+]^2} \qquad (5a)$$

by the processes shown in Scheme II. Nonlinear least-squares analysis of the k_{obsd}/pH data points generates the following numerical values for the complex constants: $k_{H^+}K_a'' = 2.9 \times 10^{-3}$; $k_{H^{2+}} = 6.4 \times 10^{-1}$ s^{-1}; $K_aK_rK_a'' = 1.4 \times 10^{-7}$; $K_rK_a'' + K_a'' = 1.07 \times 10^{-1}$. Since $k_{H^{2+}}$, the rate of capture of the doubly charged ImH^{2+}_{op} by water, is (according to this analysis) only 0.64 s^{-1}, a value which seems far too low when compared to related processes involving H_2O capture of a dialkoxycarbonium ion (10^3–10^5 s^{-1}[5a,b,18]), the mechanism shown in Scheme I is more likely to be correct. We thank Prof. McClelland for bringing this point to our attention and suggesting the mechanism shown in Scheme I.

as in Scheme I. These can be solved to yield the following values: $K_a = 1.3 \times 10^{-6}$; $pK_a = 5.89$; $k_{H^+}/k_H = 4.5 \times 10^{-3}$; $k_{Cl}/k_H = 1.02 \times 10^{-1}$; $k_{H^+}/k_{Cl} = 4.4 \times 10^{-2}$. Moreover, if one makes the logical assumption that the final porton transfer step to form ImH^{2+}_{op} is essentially diffusion controlled ($k_H \simeq 10^{10}$ M^{-1} s^{-1}), then $k_{H^+} = 4.5 \times 10^7$ s^{-1} and $k_{Cl} = 10^9$ s^{-1}. With these data in hand, one can now turn to an analysis of the hydrolysis of **2** in comparison with that of **1a–c**.

(a) The fact that the section of pH/log k_{obsd} profile first order in $[H^+]$ is displaced toward lower pH by about 2 units relative to **1a–c** could arise from two possibilities: a reduced pK_a for **2** or a reduced C–N cleavage rate. It is, however, difficult to envision how the pK_a of **2** could be reduced so drastically relative to **1a** or **1b** since these are rather similar to **2** in terms of substitution. Moreover, the reported pK_a for the parent 4(5)-(hydroxyethyl)-imidazole is 7.26,[17] so if one reasonably assumes the same general reduction of 1.2–1.3 pK units in passing to the ortho amide, the pK_a or **2** should be roughly 6. It is evident from Figure 1 that a distinct curvature in the plot is seen at pH 6, and if the only kinetic events occurring for **2** were a simple protonation followed by rate determining C–N cleavage, the curve would be expected to plateau at pH ~4–5 as observed. Aside from the additional low pH sigmoidal section to the profile, the plateauing indicates that the pK_a for **2** is not abnormally low, consistent with the value of 5.89 derived from the kinetics. A more likely reason for the apparent reduction in the cleavage rate is that the opening of the cyclic species (ImH^+_{Cl}) to form ImH^+_{op} (Scheme I) is reversible with $K_r = k_{Cl}/k_{op} = [ImH^+_{Cl}]/[ImH^+_{op}]$. Opening of the ImH^+_{Cl} ring of **2** should be quite different from the analogous C–N cleavage in **1a–c**, since for these, the cleavage is unimolecular in the forward direction but bimolecular in the reverse. Hence at the concentrations employed in the study of **1a–c**, such reversal is minimized relative to solvent capture of the dialkoxymethyl cation.[18] For protonated **2** however, both opening and reclosure are unimolecular processes with the latter being favored by some 9 powers of 10 since the nascent dialkoxymethyl cation is held in close proximity to the imidazole. Analogously, hydrolyses of cyclic ketals are slower by 1.5–4.4 powers of 10 than their acyclic counterparts,[19a] the reason being dependent on the relative rates of unimolecular reclosure and bimolecular solvent capture.[19b]

Experimentally, there are two approaches to addressing the question of reversibility. The first and most definitive requires studying the rate of loss of optical activity of a chiral **2** which should (provided reversibility is present and slower than bond rotation in ImH^+_{op}) be faster than hydrolysis. However, since we are as yet unable to prepare **2** in an optically active form, this approach could not be utilized. A more convenient (but less definitive) route is a trapping experiment in which capture of ImH^+_{op} by a good nucleophile competes effectively with reversal and solvent capture. Such an approach has been used before[20a] and in a related example[20b] traps the dioxolenium ion formed during the hydrolysis of ortho ester **8** (eq 6). Although products



(6)

Table II. k_{obsd} Values for Disappearance of 2 in the Presence of Trapping Agents

pH	[added nucleophile], M		k_{obsd}, s^{-1}
5.5[a]	N_3^-	0.0	$(1.58 \pm 0.05) \times 10^{-2}$
	N_3^-	0.01	$(2.02 \pm 0.17) \times 10^{-2}$
	N_3^-	0.02	$(2.85 \pm 0.32) \times 10^{-2}$
	N_3^-	0.05	$(5.44 \pm 0.32) \times 10^{-2}$
6.8[b]	NH_2OH	0.0	2.67×10^{-3}
	NH_2OH	0.107	4.93×10^{-3}
	NH_2OH	0.214	8.27×10^{-3}
7.30[b]	N_3^-	0.0	$(1.15 \pm 0.02) \times 10^{-3}$
	N_3^-	0.05	$(1.79 \pm 0.20) \times 10^{-3}$

[a] MES buffer. [b] MOPS buffer.

were isolated that must have arisen from capture of **9** by hydroxylamine, the rate of hydrolysis of **8** remains unchanged since the rate-limiting step is the loss of HOR from **8**. For **2**, trapping experiments were conducted by using N_3^- and NH_2OH, and the results are tabulated in Table II. Because of its large absorbance, we could employ $[N_3^-]$ no greater than 0.05 M, but with hydroxylamine, concentrations of up to 0.214 M could be attained (this value representing the upper limit of NH_2OH·HCl that can be added to an 0.3 M MOPS, pH 6.8 solution such that the ionic strength does not exceed 0.3 M). Although the rate is not saturated to the point where increasing [trap] produces no further increase in k_{obsd}, the trend from Table II is clear. If analyzed according to the mechanism of Scheme I, added trapping agent introduces an additional pathway to ImH^+_{op} that prevents it from reversing back to ImH^+_{Cl} and hence produces an increase in the rate of loss of **2**. Although simply on the basis of these experiments, a possibility exists that the effect of added trapping agent is one of a general catalyst, we feel this is not so since buffer catalysis (and hence general catalysis from other species) does not appear to be important at pHs >6. Also, under the same trapping conditions, none of **1a–c** shows any enhancement in rate so that neither general catalysis of C–N cleavage nor reversibility is kinetically important for these.

(b) The additional sigmoidal trend seen in the profile of **2** at low pH can be rationalized by the mechanism shown in Scheme I (or Scheme II[16b]). Once C–N cleavage has occurred, ImH^+_{op} must itself undergo protonation although, due to the presence of the adjacent cationic center, the pK_a of that imidazole ring might reasonably be expected to be considerably depressed relative to that for **2**. From the profile, the apparent pK_a is roughly 1.8–2. Not only does the second H^+-dependent process lead to an additional species (ImH^{2+}_{op}), which can be diverted to products, but also at lower pHs where the $[ImH^+_{op}]$ is diminished by protonation, reversibility will be attenuated as well, so that k_{obsd} must increase as observed. In effect, according to this analysis H^+ acts as a "trap" of ImH^+_{op} preventing its reversal just as does N_3^- or NH_2OH, although not by the same mechanism. It can be shown that if the rate constant for protonation, k_H, is diffusion controlled, then at pH zero, the fate of ImH^+_{op} will be almost entirely determined by its partitioning to form ImH^{2+}_{op} such that the overall rate of hydrolysis of **2** is determined by the opening of ImH^+_{Cl}. In fact, the value of 0.64 s^{-1} computed for k_{op} compares favorably to the rate constants for C–N cleavage from the acyclic imidazoles (k_{CN}, Table I) for which reversibility does not occur.

Since one does observe some catalysis of the hydrolysis of **2** by formate and acetate buffer, one might infer that some additional process is occurring other than simple C–N cleavage. A priori, this could be a new term involving C–O cleavage, which should be (like that of ortho esters or acetals[15,19–21]) general acid catalyzed, although by spectroscopic analysis (vide infra) we have been unable to detect the expected products of such cleavage and tentatively reject this possibility. More likely, this buffer catalysis represents a general-acid-catalyzed protonation of ImH^+_{op} to again form ImH^{2+}_{op}. An obvious requirement of this latter event is that plots

(17) (a) Schneider, F. *Hoppe Seyler's Z. Physiol. Chem.* **1964**, *338*, 131–144. (b) Kleinsorge, R. Von; Löffler, H. G.; Schneider, F. Chimia **1975**, *29*, 385–388.

(18) (a) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7031–7036 and references therein. (b) Ahmad, M.; Bergstrom, R. G.; Cashen, M. J.; Chiang, Y.; Kresge, A. J.; McClelland, R. A.; Powell, M. F. *Ibid.* **1979**, *101*, 2669–2677.

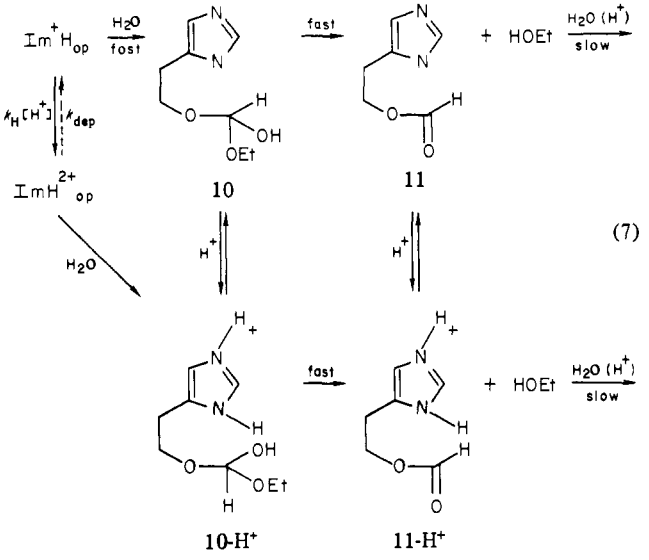
(19) (a) Willi, A. V. In "Comprehensive Chemical Kinetics"; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1977; Vol. 8, pp 49–52. (b) McClelland, R. A.; Ahmad, M.; Mandrapilias, G. *J. Am. Chem. Soc.* **1979**, *101*, 970–974.

(20) (a) Fullington, J. G.; Cordes, E. H. *J. Org. Chem.* **1964**, *29*, 970–972. (b) Chiang, Y.; Kresge, A. J.; Young, C. I. *Ibid.* **1979**, *44*, 619–622.

(21) (a) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425–432. (b) Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 464–474 and references therein. (c) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581–603.

of [buffer] vs. k_{obsd} should level off at high concentration as all ImH^+_{op} is converted to its protonated state. Unfortunately, we have insufficient data at hand to corroborate this expectation since we were unable to raise the [buffer] to values greater than 0.3 M.

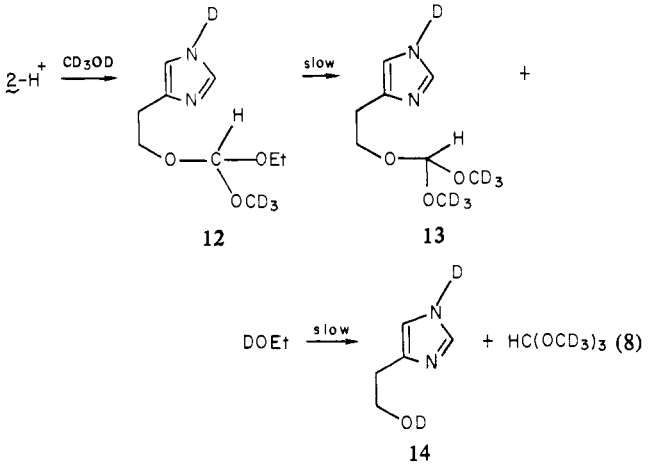
(c) Finally, we briefly address the question of the observed biphasic nature of the kinetics at pH <2 that indicates formation and subsequent hydrolysis of an intermediate. Since k_{obsd} is determined by monitoring the loss in absorbance of **2**, the initial rapid kinetic event requires C–N cleavage. For **1a–c**, once the imidazole N substituent is removed, no further change in absorbance at λ larger than that used to follow the kinetics is observed. On the other hand, the final stable UV spectrum of 4(5)-(hydroxyethyl)imidazole (generated by monitoring the UV spectrum of **2** several minutes after hydrolysis of the N substituent) shows a very intense end absorption at λ <240 nm, as well as a small shoulder with λ_{max} 250 nm ($\epsilon_{max} \simeq 190\ M^{-1}\ cm^{-1}$). At pH >2, continuous scanning of the UV spectra of **2** shows that the band at 250 nm increases with time in a mode dependent on pH. We believe these observations imply that the intermediate is likely the formate ester **11**, which is derived from solvent capture of ImH^+_{op} as in eq 7. Hydrolysis of ester **11** is not expected to be



(7)

a particularly facile process and therefore would not be observed during the time of C–N cleavage of **2** at mid range pHs since the corresponding acetate ester decomposes rather slowly (k_{obsd} = 10^{-4}–$10^{-3}\ s^{-1}$)[22b] from pH 6 to pH 8. On the other hand, at low pH the hydrolysis should show acid catalysis like that observed for other esters such that the slower acid-dependent process responsible for the biphasic kinetics observed at pH <2 likely corresponds to conversion of **11** into 4(5)-(hydroxyethyl)imidazole. It is well to consider that the adjacent imidazole is probably of little catalytic benefit to such ester hydrolysis other than perhaps as a general acid at low pH since it is completely protonated and hence cannot act as a general base or nucleophile.[22b]

Product Studies of 2. To a solution of **2** in methanol-d_4 was added acetic-d_4 acid. Continuous monitoring of the ^1H NMR spectrum showed that the set of peaks attributable to the ortho amide methine (δ 6.46) and imidazole 2- and 5-hydrogens (δ 7.84 and 6.84, respectively) disappeared and was replaced by signals at δ 5.16 (an ortho ester), 7.29, and 6.21. Judging by the relative intensities, the reaction responsible for these changes is ~70% complete in 5 min and can be explained by the sequence of events shown in eq 8. Further monitoring the NMR spectrum over a period of 24 h indicates the ethoxy group was released from intermediate mixed orthoformate (**12**) to yield **13** and ethanol. Subsequently, further solvolysis occurs to yield finally 4(5)-

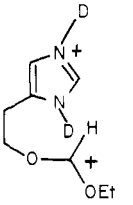


hydroxyimidazole and tris(methyl-d_3)orthoformate as evidenced by a methine singlet at δ 4.99.

The above experiments show that C–N cleavage is the fastest step in the sequence **2**-H^+ → **12** → **13** and that the alkoxyl group exchange reactions all occur more slowly. In this medium, no evidence for ethoxyl group exchange prior to C–N cleavage is obtained.

In methanol-d_4 containing two drops of trifluoroacetic acid, the overall reaction is very rapid to yield 4(5)-(hydroxyethyl)imidazole, ethanol, some tris(methyl-d_3) orthoformate and a singlet at δ 8.12 indicative of an HC(=O)OX group. After 24 h, the spectrum is unchanged except that the tris(methyl-d_3)orthoformate has solvolyzed to yield HC(=O)OX.

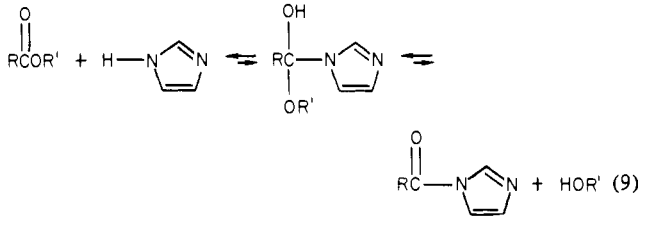
Even in pure trifluoroacetic acid-d, although the sequence of reactions is quite complicated and has not been fully analyzed, free DOEt is not immediately produced so that C–O cleavage does not occur. It is apparent, however, that in TFA, the open ion **15**



15

has some stability since the methine singlet at δ 9.03 disappears over ~1 h to yield $CH_3CH_2OC(=O)CF_3$ and HC(=O)OX, the latter formyl proton appearing at δ 8.2 in this medium.

Conclusions and Relevance to Serine Proteases. 1. The imidazole-containing amide acetals studies above hydrolyse by a common mechanism whereby an equilibrium protonation of the distal imidazole N precedes rate-determining C–N cleavage to produce the parent imidazole and a diethoxymethyl cation. The latter is rapidly captured by H_2O and ultimately produces ethanol and ethyl formate. In general, it is anticipated that C–N cleavage will predominate under all usual circumstances where the alkoxy group's pK_a is substantially larger than that of the imidazole. If **1a–c** are taken to be models for the tetrahedral intermediates formed by nucleophilic attack of imidazole on an ester (eq 9) or



HOR′ attack on an acylimidazole, then breakdown of the intermediate must involve only C–N cleavage.[22] Exceptions to this generality would arise when the pK_a of HOR′ is reduced to the

(22) (a) Fife, T. H. *Adv. Phys. Org. Chem.* **1975**, *11*, 1–22. (b) Pandit, U. K.; Bruice, T. C. *J. Am. Chem. Soc.* **1960**, *82*, 3386–3390. (c) Bruice, T. C.; Sturtevant, J. M. *Ibid.* **1959**, *81*, 2860–2870.

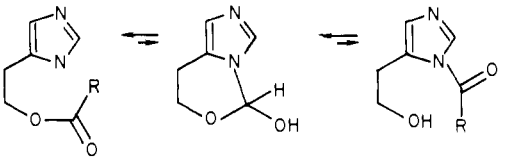
point where it becomes as good or better a leaving group than protonated imidazole.[22]

2. The values of k_{CN} from Table I represent the facility with which the protonated amide acetals undergo C–N cleavage. A Brønsted plot of log k_{CN} vs. pK_a of the parent imidazole (slope −1.0) indicates that the least basic imidazoles undergo C–N cleavage most rapidly.

3. Bicyclic amide acetal **2** at pHs >5 adheres to the general mechanism of hydrolysis common to the acyclic examples **1a–c** with the exception that the ring-opening process is a reversible one such that the rate of hydrolysis of **2** is (1–2) × 10^2-fold slower than that of **1a–c**. The reversibility can be demonstrated by the observation that added nucleophiles such as N_3^- or H_2NOH increase the rate of disappearance of **2** by trapping the intermediate open ion which prevents its reclosure to **2**-H^+.

The additional sigmoidal section to the pH/log k_{obsd} profile of **2** that is observed at pHs <5 is attributable to a second protonation of the imidazole of the open dialkoxymethyl cation (apparent pK_a ≃ 1.8–2) which also effectively prevents the reversal back to **2**-H^+. The net effect is an observed increase in k_{obsd} at low pH to a limiting value dependent on the rate of opening of the protonated imidazole. The observation of buffer catalysis between pH 2 and pH 5 stems from a general-acid catalysis of the protonation of the open ion. Although the overall kinetic behavior is consistent with both H^+-catalyzed C–N and C–O cleavage (the latter being observed in the hydrolyses of some related amide acetals[5]), since no products corresponding to C–O cleavage can be observed, we feel the dominant process is C–N cleavage in both **1** and **2**.

4. Bicyclic **2** can be taken as a model for the tetrahedral intermediate formed from intramolecular attack of imidazole on an ester with an alkoxy group having a high pK_a or intramolecular attack of an alcohol on an acylimidazole as in eq 10. The latter



(10)

process is of direct relevance to the situation in some serine proteases[4a,c] in which nonideal substrates appear to acylate the histidine N, which subsequently undergoes intramolecular acyl transfer to the adjacent serine OH group. The above study indicates that the ultimate fate of such an intermediate is breakdown to form the ester and furthermore implies that nucleophilic attack by histidine–imidazole on the serine ester is completely reversible such that the process cannot simply be kinetically important in regeneration of the active enzyme. This leaves the role of histidine to be the generally accepted one of general-base catalysis of H_2O attack on the acylserine.[4]

Acknowledgement is made to the Alberta Heritage Medical Research Fund, Natural Sciences and Engineering Research Council of Canada, University of Alberta, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. In addition, we are grateful to Dr. Z. Frackman for the preparation of **2**. In particular we wish to acknowledge the invaluable advice of Prof. R. A. McClelland for suggesting the mechanism in Scheme I to us.

Registry No. 2, 84802-87-9.

Proton-Transfer Reactions. 3.[1] Differences in the Protonation of Localized and Delocalized Carbanion Intermediates

Heinz F. Koch,* Judith G. Koch, Nanci H. Koch, and Andrew S. Koch

Contribution from the Department of Chemistry, Ithaca College, Ithaca, New York 14850.
Received December 31, 1981. Revised Manuscript Received November 1, 1982

Abstract: Rates, activation parameters, and product distributions are reported for the reaction of methanolic sodium methoxide with $XC_6H_4CH{=}CF_2$ (V) and $C_6F_5CH{=}CF_2$ (IX) and compared to previously reported results for $C_6H_5C(CF_3){=}CF_2$ (I). A ρ = 3.5 was calculated and substituents studied were X = *m*-, *p*-OCH_3, *m*-, *p*-CH_3, H, *o*-, *m*-, *p*-F, *m*-, *p*-Cl, *m*-, *p*-Br, and *m*-, *p*-NO_2. Products obtained for reaction of V (except *p*-NO_2-V) were fairly uniform and varied little with temperature (−15 to 65 °C). A saturated ether, $XC_6H_4CH_2CF_2OCH_3$, was the major product (56 ± 3%). Two vinyl ethers, (*E*)- and (*Z*)-$XC_6H_4CH{=}CFOCH_3$, were formed with *E* at 40 ± 3% favored over *Z* at 5 ± 1%. At higher temperatures slightly more of the saturated ether was observed. However, *p*-NO_2-V showed a large temperature effect on the amount of saturated ether formed, 96% at −77 °C vs. 42% at 28 °C, and yielded equal amounts of *E* and *Z* vinyl ethers. A product isotope effect (PIE) was calculated from product distributions observed when reaction was carried out in MeOD compared to MeOH. Values of PIE (k^H/k^D) are between 1.1 and 1.5 for reaction of I, *m*-NO_2-V, and IX and show little variance with temperature. On the other hand, PIE values for *p*-NO_2-V change in a manner similar to normal primary kinetic isotope effects and range from 15 (−77 °C) to 5.9 (28 °C). The differences in behavior are attributed to the fact that the carbanion *p*-$NO_2C_6H_4C^-HCF_2OCH_3$ is highly delocalized whereas the other carbanions remain largely localized on the benzylic carbon.

When a proton is transferred from oxygen to neutralize a carbanion, a question regarding the nature of the negative charge can arise. Is that charge localized on one carbon, or is it delocalized to other parts of the molecule? Does it matter if that charge is localized or delocalized? Kresge[2] has reviewed the effects that delocalization can have on the rate of proton transfer and concludes that delocalization of charge slows the rate of proton transfer to carbon. We recently proposed a mechanism that features two types of carbanion intermediates along the reaction

(1) Part 2: Koch, H. F.; Tumas, W.; Knoll, R. *J. Am. Chem. Soc.* **1981**, *103*, 5423–5429.

(2) Kresge, A. J. *Acc. Chem. Res.* **1978**, *8*, 354–360.

0002-7863/83/1505-2388$01.50/0