by reaction C would not be inhibited. The failure of ribose to form suggests that reaction C, if it occurs, is very slow relative to reactions A and B.

The formation of secondary products is substantially reduced when the dioxobis(2,4-pentanedionato-*O,O′*)molybdenum(VI) complex is used and DMF is the solvent.[16] This is the preferred method for the interconversion of pentoses and tetroses (Table IV).

Trioses and Tetroses. DL-[1-^{13}C]Glyceraldehyde gives only small amounts of DL-[2-^{13}C]glyceraldehyde when incubated with molybdate; [1-^{13}C]dihydroxypropanone is the major product.[32]

D-[1-^{13}C]Threose in aqueous molybdate rearranges rapidly to give D-[2-^{13}C]erythrose and other products (16%) that were not identified. The reaction gives only the expected 1,2 inversion in DMF. The facile rearrangement of tetroses and the limited reaction of glyceraldehyde provide further evidence of the importance of four aldose oxygens in the formation of the reactive molybdate–sugar complex.

Summary

The C-2 epimerization of aldoses catalyzed by molybdate occurs with exchange of C-1 and C-2 by inversion of the C-1–C-2 aldol fragment. The nature of the skeletal rearrangement and an examination of the reactivity of analogues of aldoses suggest that the reactive complex involves two molybdate moieties and four oxygens of the aldehyde form of the aldose. Structural features that interfere with complex formation inhibit the reaction. Rates of conversion are strongly influenced by the formation of stable and unreactive molybdate complexes with ring forms of the aldoses. Secondary reactions that involve the simultaneous inversion of configuration of adjacent trans hydroxyl groups occur more slowly and by a different mechanism.

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Registry No. MoO$_2$(acac)$_2$, 17524-05-9; molybdic acid, 11099-00-6; D-[1-^{13}C]mannose, 70849-16-0; D-[2-^{13}C]glucose, 70849-17-1; D-[1-^{13}C]talose, 70849-29-5; D-[1-^{13}C]galactose, 70849-30-8; D-[1-^{13}C]glucose, 40762-22-9; 6-deoxy-L-[1-^{13}C]talose, 83379-33-3; 6-deoxy-L-[2-^{13}C]talose, 83379-34-4; D-[1-^{13}C]xylose, 70849-21-7; D-[1-^{13}C]arabinose, 70849-23-9; D-[2-^{13}C]galactose, 83379-35-5; D-[2-^{13}C]talose, 83379-36-6; D-[2-^{13}C]mannose, 70849-16-0; L-[2-^{13}C]fucose, 83379-37-7; L-[1-^{13}C]fucose, 83379-38-8; D-[2-^{13}C]xylose, 83379-39-9; D-[2-^{13}C]ribose, 83379-40-2; 3-deoxy-D-[1-^{13}C]-*arabino*-hexose, 83379-41-3; 4-deoxy-D-*lyxo*-hexose, 74164-24-2; 4-deoxy-D-*xylo*-hexose, 7286-46-6; mannitol, 69-65-8; D-[1-^{13}C]glucosamine, 83379-42-4; 4,6-*O*-ethylidene-D-galactose, 6207-17-6; 4,6-*O*-ethylidene-D-glucose, 13403-24-2; 4-*O*-β-D-galactopyranosyl-D-[1-^{13}C]glucopyranose, 83379-43-5; 4-deoxy-4-fluoro-D-[1-^{13}C]glucose, 83379-44-6; D-[1-^{13}C]threose, 70849-20-6; D-[2-^{13}C]erythrose, 83434-88-2; D-[1-^{13}C,^{2}H]mannose, 83379-45-7; D-[2-^{13}C,^{2}H]glucose, 83379-46-8; ammonium molybdate, 11098-84-3.

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Mechanism of the Aminolysis of Alkyl Benzimidates[1]

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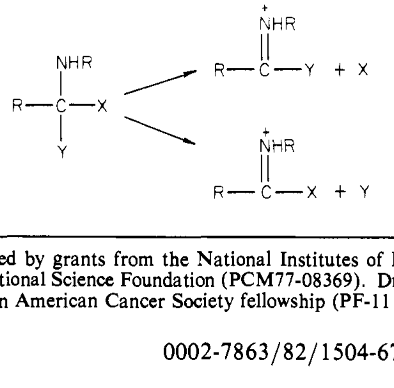
Contribution No. 1429 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254. Received March 26, 1982

Abstract: The aminolysis of a series of ring- and alkyl-substituted benzimidates proceeds through a mechanism involving the formation and decomposition of a tetrahedral intermediate as evidenced by a change in rate-determining step with changing pH. On the alkaline side of the pH–rate profile, formation of the tetrahedral intermediate from the free amine and protonated benzimidate is rate determining. Structure reactivity correlations for this step show a late (intermediate-like) transition state with $\beta_{nuc} = 0.61$, $\beta_0 = -0.47$ (for O-substituted benzimidates), and $\rho = 1.49$. There is no evidence for a kinetically significant proton-transfer step. The addition of water to alkyl benzimidates follows $\beta_0 = -0.56$. On the acidic side of the pH–rate profile for aminolysis, the breakdown of the intermediate with expulsion of alcohol is the rate-determining step, as evidenced by the observation of an exchange reaction of methoxyamine for ammonia. The neutral tetrahedral intermediate (T$_0$) partitions between acid-catalyzed expulsion of alcohol, ammonia, and methoxyamine with partition ratios of approximately 1/1/300, respectively. The expulsion of alcohol also occurs by a spontaneous (water catalyzed) reaction characterized by $\beta_0 = -1.30$ and $\rho = -0.01$, suggesting a late (product-like) transition state for this reaction. The expulsion of alcohol through a general-acid-catalyzed reaction is characterized by relatively low Brønsted α values of 0.40–0.49. The decrease in α with decreasing p*K* of the leaving alcohol can be described by an interaction coefficient $p_{xy'} = 1/c_5 = \delta\alpha/\delta pK_{lg} = 0.05$. This reaction can be described on a structure–reactivity diagram by a diagonal reaction coordinate that represents concerted proton transfer and C–O bond cleavage in the transition state. The effect of structure on the direction of acid-catalyzed expulsion of alcohols and amines from addition compounds is reviewed briefly.

Most imine-forming elimination reactions[3-11] consist of the following types:



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in which X and Y are R, OR, or NHR. In order to provide a more complete picture of these reactions, we have studied the

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formation and breakdown of the intermediate formed during the aminolysis of benzimidates (X = OR, Y = NHR). Hand and Jencks[11] have previously shown that the aminolysis of alkyl benzimidates proceeds through the formation of a tetrahedral intermediate, as evidenced by a change in rate-determining step with pH.

We were interested in determining the characteristics of the transition state structure for both the formation and breakdown of this addition intermediate in order to determine (1) the relative leaving abilities of alcohols and amines from the intermediate, (2) the mechanism of the observed buffer catalysis, and (3) the variation in the structure of the transition state for the buffer-catalyzed reaction with the structure of the alcohol leaving group. In addition, we wished to examine the effect on transition-state structure of the increase in stability by a factor of $\sim 10^{16}$ of the amidine product compared with the immediate product of acetal cleavage.

Experimental Section

Materials. Substituted alkyl benzimidate hydrochlorides and ring-substituted benzimidate hydrochlorides were prepared by the method of Pinner[12] as previously described.[13] All other organic reagents were purified by distillation or recrystallization prior to use. Deionized, glass-distilled water was used throughout.

Kinetics. The decrease in benzimidate concentration upon reaction with various amines was monitored by the decrease in absorbance at 245 nm, or the increase in benzamidine absorbance at 265 nm for some experiments at high pH values, on a Zeiss PM-II recording spectrophotometer equipped with a thermostated cell compartment maintained at 25.0 ± 0.1 °C. Reactions were initiated by adding a small aliquot of a freshly prepared solution of the appropriate benzimidate hydrochloride in the parent alcohol to a buffered, temperature-equilibrated solution of the amine. Initial benzimidate concentrations were in the range $(0.4-1.6) \times 10^{-3}$ M, and observed absorbance changes were generally 0.2–0.5 at the analytical wavelength. Ionic strength was maintained constant at 1.0 M by the addition of KCl.

In most cases, first-order rate constants were evaluated from linear plots of $\ln(A - A_\infty)$ or $\ln(A_\infty - A)$ against time. These plots were generally linear for at least 3 half-lives. Under conditions in which imidate hydrolysis was significant (at low pH), the observed first-order rate constants were corrected for hydrolysis by subtracting the first-order rate constant for the disappearance of benzimidate absorbance in the absence of amine. This correction was generally small (<20% of the observed rate in the presence of amine).

Reaction of Ethyl Benzimidate with Methoxyamine. At low pH (<4), the reaction of methoxyamine with ethyl benzimidate led to a biphasic disappearance of absorbance at 245 nm. At pH 3.7 (0.3 M methoxyamine) the fast decrease in absorbance occurred with a rate constant of 2.8×10^{-4} s^{-1} while the slower process was characterized by a rate constant of 5.1×10^{-5} s^{-1}.

The disappearance of ethyl benzimidate was measured by an alternate method that relies on the hydroxide-catalyzed elimination of ethoxide ion from ethyl benzimidate at alkaline pH.[13] The aminolysis reaction was initiated by adding 0.02 mL of a solution of ethyl benzimidate (5.0 mg/mL) to a solution of 0.3 M methoxyamine at the appropriate pH. At various times, a 0.05-mL aliquot was removed from the reaction mixture and added to 3.0 mL of 0.25 M potassium hydroxide. The absorbance change at 240 nm due to the conversion of ethyl benzimidate to benzonitrile[13] was found to be proportional to the concentration of ethyl benzimidate remaining in the original reaction mixture. The change in extinction coefficient for the elimination reaction was found to be 6.5×10^3 M^{-1} cm^{-1}, and the rate constant for the decrease in absorbance at 240 nm in 0.25 M potassium hydroxide was identical with that measured in independent experiments with ethyl benzimidate. A rate constant of 2.4×10^{-4} s^{-1} for the disappearance of ethyl benzimidate in the reaction with 0.3 M methoxyamine (pH 3.7) that was measured by the elimination assay corresponds to the fast phase of the reaction measured spectrophotometrically.

A rapid initial decrease in absorbance at 240 nm was observed in the elimination assay at pH <4 due to hydrolysis of ethyl benzoate that is formed during the hydrolysis of ethyl benzimidate. Authentic ethyl benzoate reacted with the same rate constant of 9.7×10^{-3} s^{-1} and $\epsilon = 5 \times 10^3$ M^{-1} cm^{-1}. Ethyl benzoate was ≤15% of the reaction products in the aminolysis experiments.

The product of the exchange of methoxyamine for ammonia, ethyl *N*-methoxybenzimidate, was prepared on a preparative scale by the procedure of Hand and Jencks[11] by reaction of ethyl benzimidate with methoxyamine at pH 3.6 for 1.5 h, followed by separation of the ethyl *N*-methoxybenzimidate from starting material and the amidine product by chromatography on silica gel. The NMR spectrum corrected for contamination by approximately 20% ethyl benzoate (from hydrolysis) was consistent with the assigned structure for ethyl *N*-methoxybenzimidate ($CDCl_3$); δ 1.33 (2.1 H, t, J = 7 Hz), 3.98 (3.0 H, s), 4.27 (2.0 H, q, J = 7 Hz), 7.2–7.8 (5.0 H, m). A small peak at δ 3.79 was observed, which could either be an impurity or could reflect the presence of an *EZ* isomeric mixture of ethyl *N*-methoxybenzimidates with ≤20% of the minor component.

The rate constant of 5.8×10^{-5} s^{-1} for the reaction of ethyl *N*-methoxybenzimidate with methoxyamine (0.3 M, pH 3.7, 0.05 M methoxyacetate buffer) corresponds to the slow phase of the reaction of ethyl benzimidate under the same conditions. The observed absorbance changes were also found to be consistent with reaction of methoxyamine with ethyl *N*-methoxybenzimidate that was formed by exchange of methoxyamine for ammonia in the fast phase of the reaction with ethyl benzimidate.

Partitioning between Exchange of Amine and Aminolysis. The initial products of the reaction of methoxyamine with ethyl benzimidate were analyzed by following the change in absorbance at 255 nm that is due to hydrolysis of ethyl *N*-methoxybenzimidate by using aliquots of reaction mixtures that were transferred to 1 M hydrochloric acid. Authentic ethyl *N*-methoxybenzimidate was found to undergo hydrolysis with $k = 1.1 \times 10^{-2}$ s^{-1}, whereas ethyl benzoate and *N*-methoxybenzamidine are stable under these conditions.

Ethyl *N*-methoxybenzimidate hydrochloride[11] was found to give a change in extinction coefficient at 255 nm of 4.0×10^3 M^{-1} cm^{-1} upon hydrolysis. In a typical experiment, a solution of known concentration of ethyl benzimidate hydrochloride in ethanol was added to 1.0 mL of the appropriate solution of methoxyamine. After 5–7 half-lives of the reaction, a 0.08-mL aliquot of the reaction mixture was removed and injected into 0.92 mL of 1.0 M HCl, and the decrease in absorbance at 255 nm was monitored to completion. The concentration of ethyl *N*-methoxybenzimidate was calculated from the decrease in absorbance at 255 nm. From the known concentration of starting ethyl benzimidate hydrochloride and the observed concentration of ethyl *N*-methoxybenzimidate, the concentration of the aminolysis product (*N*-methoxybenzamidine) could be determined. Above pH 4, the amount of ethyl benzoate formed from hydrolysis of the ethyl benzimidate was insignificant (<5%) and was ignored.

At pH values greater than 4.4, the kinetics of the reaction of methoxyamine and ethyl benzimidate observed at 245 nm were not biphasic. Ethyl *N*-methoxybenzimidate was shown to be stable at pH >4.7 ($k \leq 4 \times 10^{-5}$ s^{-1} in 0.9 M methoxyamine at pH 4.7) by measuring the change in absorbance at 255 nm and by hydrolysis of aliquots in 1 M HCl. Products from the reaction of ethyl benzimidate and methoxyamine were determined after 5–7 half-lives at pH >4.7 and after 37% and 65% reaction at pH 3.7, which should give <8% and <18% hydrolysis of ethyl *N*-methoxybenzimidate, respectively. The concentrations of ethyl benzoate and remaining ethyl benzimidate were determined in 0.25 M potassium hydroxide and the concentration of ethyl *N*-methoxybenzimidate by hydrolysis in 1.0 M HCl; the concentration of benzamidine was determined by difference.

The formation of ethyl *N*-methoxybenzimidate at low pH was confirmed by NMR spectroscopy. A reaction mixture containing ethyl benzimidate and 0.3 M methoxyamine was incubated at pH 3.6 for 1.5 h at 20 °C and was extracted with ether immediately after neutralizing to pH 6. After the ether had been evaporated, the product mixture was dissolved in $CDCl_3$.

Results

At pH values below neutrality, ethyl benzimidate reacts in the presence of methoxyamine to give the exchange product ethyl *N*-methoxybenzimidate, the aminolysis product *N*-methoxybenzamidine, and the hydrolysis product ethyl benzoate. The exchange reaction is observed because alcohol expulsion is rate determining,[11] and the further reaction of ethyl *N*-methoxybenzimidate is relatively slow under these conditions. The concentration of ethyl *N*-methoxybenzimidate was determined by measuring the absorbance change upon hydrolysis of aliquots of the reaction mixtures in 1 M HCl. The rate constants for hydrolysis were found to be identical with those for the hydrolysis

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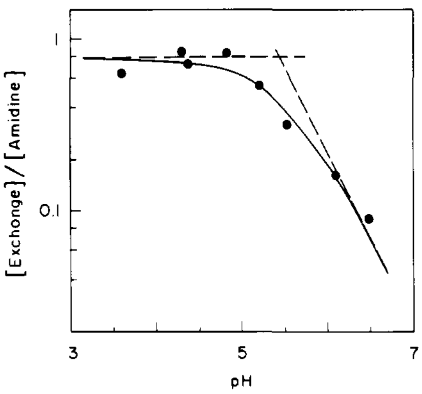


Figure 1. Dependence on pH of the ratio of the concentration of ethyl *N*-methoxybenzimidate (exchange) to the concentration of *N*-methoxybenzamidine (amidine) formed upon reaction of ethyl benzimidate with methoxyamine at 25.0 °C, μ = 1.0 M (KCl).

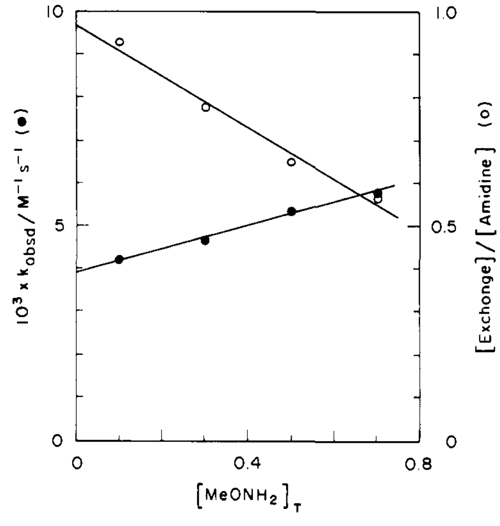


Figure 2. Variation of the observed second-order rate constant for methoxyaminolysis of ethyl benzimidate, and the ratio of concentration of products [exchanged imidate]/[amidine] with total methoxyamine concentration at pH 4.72, μ = 1.0 M (KCl). (●), k_{obsd}, left axis; (O), [exchange]/[amidine], right axis.

of authentic ethyl *N*-methoxybenzimidate.

The variation with pH of the ratio of exchanged imidate to *N*-methoxybenzamidine is shown in Figure 1. At pH values less than 5, the ratio is constant at a value of approximately 0.8, indicating a composition of 55% amidine and 45% exchanged benzimidate. As the pH increases, the extent of the exchange reaction decreases markedly, reaching a composition of approximately 8% exchanged benzimidate at pH 6.5.

The formation of ethyl *N*-methoxybenzimidate was confirmed by NMR spectroscopy, which showed approximately 10% ethyl benzoate, 20% *N*-methoxybenzamidine, and 70% ethyl *N*-methoxybenzimidate product at pH 3.6 and 80% *N*-methoxybenzamidine and 20% ethyl *N*-methoxybenzimidate at pH 6.2.

The extent of the exchange reaction is also dependent on the total concentration of methoxyamine, declining as the total concentration of methoxyamine increases at pH 4.7. This decrease in the extent of exchange with increasing methoxyamine concentration is accompanied by a corresponding increase in the second-order rate constant for the overall reaction (Figure 2), suggesting that both the formation of amidine and the overall reaction are catalyzed by methoxyamine acting as a general-acid–base catalyst.

The observed second-order rate constants for the reaction of methoxyamine with alkyl benzimidates follow bell-shaped pH–rate profiles with maxima at pH 6.2, 5.9, 4.5, and 4.1 for methoxyethyl, chloroethyl, propargyl, and trifluoroethyl benzimidates, respectively (not shown). These bell-shaped curves reflect the change in rate-determining step and the p*K* values of methoxyamine and the benzimidates that occur in this pH region.[11]

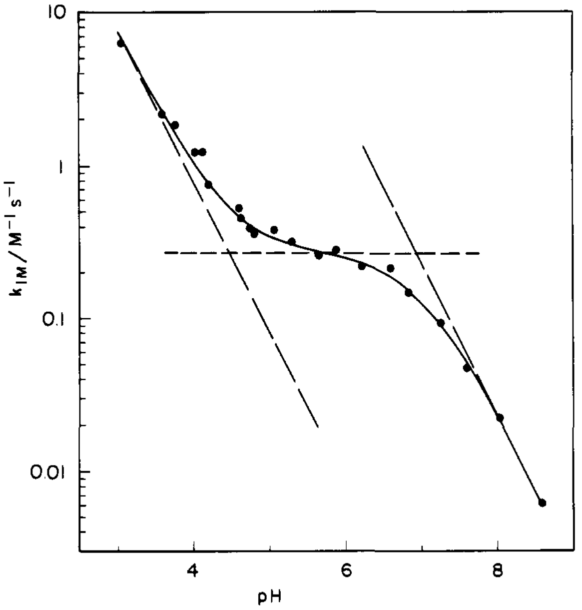


Figure 3. Dependence on pH of the second-order rate constant (k_{IM}) for the reaction of methoxyamine-free base with neutral methoxyethyl benzimidate at 25.0 °C, μ = 1.0 M (KCl). The value of k_{IM} was calculated from k_{obsd} as described in the text. The solid line was calculated from the values of k_1, k_2, and k_3 given in Table I by using eq 9. Dashed lines show individual components (k_1, k_2, k_3) used to calculate the overall curve.

It is useful to express the second-order rate constants in terms of defined ionic species. Figure 3 shows the dependence on pH of the second-order rate constants for the reaction of methoxyamine with 2-methoxyethyl benzimidate when the second-order rate constants are evaluated according to the rate law of eq 2,

$$v = k_{IM}[IM][RNH_2] \qquad (2)$$

in which k_{IM} is the observed second-order rate constant for the reaction when the reactant concentrations are expressed in terms of the concentrations of uncharged benzimidate ([IM]) and methoxyamine ([RNH_2]). The relation between k_{IM} and the observed second-order rate constant k_{obsd} at any pH is given by eq 3, in which f_{IM} and f_{RNH_2} represent the fraction of benzimidate

$$k_{IM} = k_{obsd}/(f_{IM}f_{RNH_2}) \qquad (3)$$

and methoxyamine present as the free base at a given pH.

On the acidic side of the pH–rate profile, the pH–rate behavior at low buffer concentration can be described by the rate law of eq 4, in which k_1 is the third-order rate constant for the acid-

$$v = k_1[IM][RNH_2][H^+] + k_2[IM][RNH_2] + k_0[IMH^+] \qquad (4)$$

catalyzed reaction observed at low pH, k_2 is the second-order, "water" reaction observed at intermediate pH, and k_0 is the first-order rate constant for hydrolysis of protonated benzimidates to the corresponding ester. All rate constants were corrected for k_0, which was determined in the absence of methoxyamine. These reactions are followed by slow, secondary reactions of the exchanged benzimidate, at low pH, that were not examined quantitatively.

As the pH increases, the rate constant for the reaction becomes much smaller than expected from the pH behavior observed at lower pH (Figure 3). This observation requires the existence of at least one intermediate and the occurrence of a change in rate-determining step at high pH.[11] On the alkaline side of the pH–rate profile, the reaction may be described by the rate law of eq 5, in which k_3 is the third-order rate constant for the

$$v = k_3[IM][RNH_2][H^+] \qquad (5)$$

acid-catalyzed reaction observed on the alkaline side of the pH–

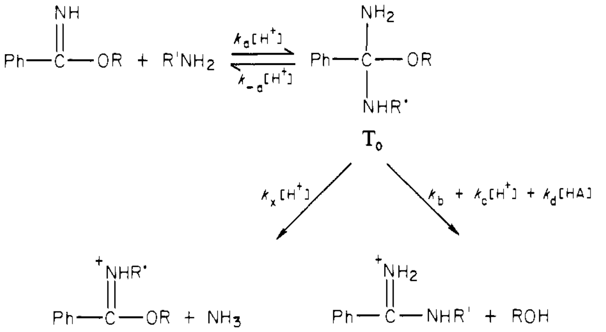
Table I. Rate Constants for the Methoxyaminolysis of Alkyl Benzimidates (PhC(=NH)OR) at 25.0 °C, μ = 1.0 M (KCl)[a]

alcohol (ROH)	pK_{ROH}[b]	pK_{IMH^+}[c]	$10^5 k_0$,[d] s^{-1}	$10^{-3} k_1$,[e] $M^{-2}\ s^{-1}$	k_2,[f] $M^{-1}\ s^{-1}$	$10^{-6} k_3$,[g] $M^{-2}\ s^{-1}$
CH_3CH_2OH	16	6.37	4.7	24	0.038	3.1
$CH_3OCH_2CH_2OH$	14.8	5.65	19	7.4	0.27	2.3
$ClCH_2CH_2OH$	14.31	5.36	27		2.9	2.8
$HC{\equiv}CCH_2OH$	13.55	4.82	55		19 ± 5	0.86
CF_3CH_2OH	12.43	3.75	610		1500	0.44

[a] Rate constants were derived from the pH–rate profile of the observed first-order rate constants for the reaction of the amine and benzimidate. Amine concentrations were in the range of 0.05–0.9 M. In cases where the amine might also serve as a general-acid base catalyst, the second-order rate constants were extrapolated to zero amine concentration. Under conditions where the amine itself had no buffering capacity, the pH was maintained by the addition of 0.02–0.05 M of an appropriate buffer. The rate constants reported were based on at least ten independent measurements of k_{obsd}. [b] Reference 40. [c] Reference 13. [d] First-order rate constant for hydrolysis of benzimidate hydrochloride. [e] $v = k_1[IM][RNH_2][H^+]$ on acidic limb of pH–rate profile. [f] $v = k_2[IM][RNH_2]$ on acidic side of pH–rate profile. [g] $v = k_3[IM][RNH_2][H^+]$ on basic side of pH–rate profile.

rate profile. Values for k_1, k_2 k_3, and k_0 are given in Table I for the various alkyl benzimidates.

The entire pH–rate profile can be described by considering a mechanism involving an uncharged tetrahedral intermediate (T_0) in which formation of the intermediate is rate determining on the basic side of the pH–rate profile and breakdown of the intermediate is rate determining on the acidic side of the pH–rate profile (eq 6). The steady-state treatment[14] gives eq 7 for this



(6)

mechanism at low buffer concentrations.

$$k_{IM} = \frac{k_a[H^+](k_b + k_c[H^+] + k_x[H^+])}{k_{-a}[H^+] + k_b + k_c[H^+] + k_x[H^+]} \tag{7}$$

At high pH, where formation of T_0 is rate determining and $k_{-a}[H^+] \ll k_b + k_c[H^+] + k_x[H^+]$, eq 7 simplifies to $k_{IM}[H^+] = k_a[H^+] = k_3[H^+]$. At low pH, where breakdown of T_0 is rate determining and $k_{-a}[H^+] \gg k_b + k_c[H^+] + k_x[H^+]$, eq 7 simplifies to eq 8. In terms of observable rate constants, $k_{IM} = k_1[H^+] +$

$$k_{IM} = \frac{k_a}{k_{-a}}(k_b + k_c[H^+] + k_x[H^+]) \tag{8}$$

k_2, where $k_1 = k_a(k_c + k_x)/k_{-a}$ and $k_2 = k_a k_b/k_{-a}$ (k_1 and k_2 are the observed rate constants at low pH). Substitution of the expressions for k_1, k_2, and k_3 into eq 7 yields eq 9. This equation

$$k_{IM} = \frac{k_3[H^+](k_1[H^+] + k_2)}{k_3[H^+] + k_1[H^+] + k_2} \tag{9}$$

and the values of k_1, k_2, and k_3 in eq 1 accurately describe the observed pH–rate profile at all values of pH (Figure 3).

Buffer catalysis of the aminolysis of benzimidates is significant only on the acidic side of the pH–rate profile, where expulsion of alcohol from the addition intermediate is rate determining.[11] Catalysis of the methoxyaminolysis of methoxybenzimidate by acetate buffers was found to be significant at pH 4.11 and 4.64, but not at pH 5.06, for example. Under conditions in which there is only a small amount of exchange of methoxyamine for ammonia, the observed first-order rate constant increases with increasing buffer concentration and with increasing concentration of the basic form of the buffer; there is no apparent general-acid catalysis.

Table II. General-Acid Catalysis of the Methoxyaminolysis of Alkyl Benzimidates at 25.0 °C, μ = 1.0 M (KCl)

acid	pK_a	total buffer, M	pH	no. of points	k_{HA}, $M^{-2}\ s^{-1}$
		Ethyl Benzimidate			
cyanoacetic	2.39	0–0.7	4.06	8	33
methoxyacetic	3.53	0.02–0.4	3.74	3	9.7
acetic	4.60	0–0.5	5.10	6	2.4
methoxyamine hydrochloride	4.72				0.49
cacodylic	6.20	0.02–0.5	6.21	6	0.46
		Methoxyethyl Benzimidate			
cyanoacetic	2.39	0–0.70	4.02	8	36
methoxyacetic	3.53	0.02–0.67	3.57	6	10.4
acetic	4.60	0.0–0.7	4.60	8	2.9
		0–0.75	4.12	6	
		0–0.5	5.06	6	
methoxyamine hydrochloride	4.72	0.025–0.5	4.71	14	1.39
cacodylic	6.20	0.02–0.85	5.83	8	0.70
		0.045–0.64	6.59	8	
		Chloroethyl Benzimidate			
cyanoacetic	2.39	0–0.7	4.06	8	⩽56
methoxyacetic	3.53	0.02–0.66	3.74	6	30
acetic	4.60	0–0.7	4.11	6	6.3
		0–0.7	4.60	8	
		0–0.7	5.13	6	
methoxyamine hydrochloride	4.72	0.05–0.8	4.00	8	3.8
cacodylic	6.20	0.0–0.90	4.75	8	1.97
		Propargyl Benzimidate			
methoxyacetic	3.53	0–0.8	3.76	8	51
acetic	4.60	0–0.8	4.07	8	13.2
methoxyamine hydrochloride	4.72	0–0.9	3.26	8	8.8

However, the rate constants for the observed general-base catalysis of the protonated imidate can also be expressed in terms of general-acid catalysis of the reaction of neutral benzimidate with free methoxyamine according to the rate expression of eq 10, in which k_{HA} is the third-order rate constant for the general-acid-catalyzed reaction and [HA] is the concentration of the acidic form of the buffer. Rate constants for general-acid catalysis (k_{HA}) for the reactions of a series of alkyl benzimidates with methoxyamine are given in Table II.

$$v = k_{HA}[IM][RNH_2][HA] \tag{10}$$

For alkyl benzimidates in which the alcohol becomes a better leaving group, the breakdown of the intermediate becomes less significant kinetically in relation to the formation of the intermediate, so that it becomes increasingly difficult to observe the change in rate-determining step. For trifluoroethyl benzimidate, the formation of the intermediate is rate determining over most of the pH range examined experimentally.

The second-order rate constants for the reactions of a series of different amines with trifluoroethyl benzimidate and ethyl

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(14) Gilbert, H. F. J. Chem. Educ. 1977, 54, 492–493.

Table III. Rate Constants for the Aminolysis of Ethyl Benzimidate Hydrochloride and Trifluoroethyl Benzimidate Hydrochloride at 25.0 °C, $\mu = 1.0$ M, (KCl)[a]

imidate	amine	pK_{RNH_2}[b]	k_f,[c] $M^{-1}\ s^{-1}$
ethyl benzimidate	CH_3ONH_2	4.72	1.31
	$CF_3CH_2NH_2$	5.81	0.4 ± 0.1
	$CH_3OCH_2CH_2NH_2$	9.65	54
	CH_3NH_2	10.85	580
trifluoroethyl benzimidate	$NH_2CONHNH_2$	3.84	10
	CH_3ONH_2	4.72	76
	$CF_3CH_2NH_2$	5.81	9.3
	$H_2NCOCH_2NH_2$	8.22	200
	$ClCH_2CH_2NH_2$	8.81	530
	$CH_3OCH_2CH_2NH_2$	9.65	1020
	CH_3NH_2	10.85	7600

[a] Rate constants were obtained as described in Table I, footnote *a*. [b] Determined from the pH of partially neutralized solutions of the amine hydrochloride at 25.0 °C, $\mu = 1.0$ M (KCl). [c] Based on the second-order rate constant observed on the basic side of the pH–rate profile, $v = k_f[IMH^+][RNH_2]$ for the reaction of the benzimidate hydrochloride with neutral amine.

Table IV. Rate Constants for the Methoxyaminolysis of Ring-Substituted Ethyl Benzimidates (X–Ph–C(=NH)OEt) at 25.0 °C, $\mu = 1.0$ M (KCl)[a]

substituent (X)	pK_{IMH^+}[b]	10^2k_2,[c] $M^{-1}\ s^{-1}$	$10^{-6}k_3$,[d] $M^{-2}\ s^{-1}$
m-NO_2	5.30[e]	2.9	2.13
p-NO_2	5.11[f]	3.2[f]	2.32
p-Cl	6.09[e]	3.0	3.57
m-Cl	5.82[e]	2.6	3.30
H	6.37[f]	3.8[f]	3.05
p-OMe	7.01[e]	2.8	3.78

[a] Rate constants were obtained as described in Table I, footnote *a*. [b] p*K* of benzimidate hydrochloride. [c] Based on the observed second-order rate constant $v = k_2[IM][MeONH_2]$ on the acidic limb of the pH–rate profile. [d] Based on the observed third-order rate constant $v = k_3[IM][MeONH_2][H^+]$ on the basic side of the pH–rate profile. [e] Reference 13. [f] Reference 11.

benzimidate on the alkaline side of the pH–rate profile, expressed as the reaction of protonated benzimidate with neutral amine according to the rate law of eq 11, are given in Table III. Rate

$$v = k_f[IMH^+][RNH_2] \tag{11}$$

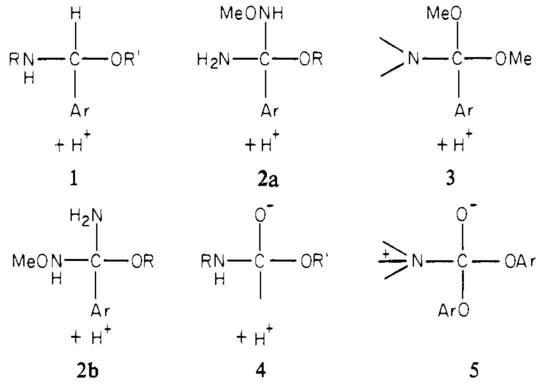
constants for rate-determining formation and breakdown of the addition intermediate in the methoxyaminolysis of a series of ring-substituted alkyl benzimidates are shown in Table IV.

Discussion

During the methoxyaminolysis of ethyl benzimidate on the acidic side of the pH–rate profile, two products are observed, *N*-methoxybenzamidine from the aminolysis reaction and ethyl *N*-methoxybenzimidate from an exchange of methoxyamine for ammonia. The intermediate formed during the reaction can partition between expulsion of alcohol leading to the formation of the amidine or expulsion of ammonia leading to the formation of the exchanged ethyl benzimidate (eq 6). The observation of a partial exchange of methoxyamine and methylamine[11] for ammonia only on the acidic side of the pH–rate profile shows that on the acidic side of the pH–rate profile, breakdown of the intermediate with expulsion of alcohol is the rate-determining step. The same behavior has been observed with phenyl and ethyl acetimidates.[15] The rate-determining step on the basic side of the pH–rate profile is formation of the intermediate.

Further confirmation of the relationship of rate- and product-determining steps comes from the variation of the partition ratio between exchanged imidate and amidine with methoxyamine concentration. With increasing methoxyamine concentration at constant pH, the second-order rate constant for the observed reaction increases with increasing methoxyamine concentration, indicating that the rate-determining step is catalyzed by the methoxyamine acting as a buffer catalyst in the low-pH region (Figure 2).[11] The ratio of exchange to amidine formation decreases with increasing concentration of methoxyamine buffer under these conditions (Figure 2). The observation that the rate-determining and product-determining steps show a comparable dependence on buffer concentration suggests that catalysis of the same step, the breakdown of T_0 to amidine, controls both the rate and the product ratio.

Chart I


1 2a 3

2b 4 5

The observed change in rate-determining step and the partitioning of the intermediate can be rationalized with reference to eq 6. The tetrahedral intermediate (T_0) can partition between expulsion of methoxyamine to regenerate starting materials ($k_{-a}[H^+]$), expulsion of ammonia leading to exchange ($k_x[H^+]$), or expulsion of alcohol leading to amidine formation ($k_b + k_c[H^+] + k_d[HA]$). According to eq 6, the partition ratio is given by eq 12, which adequately describes the observed behavior. At low

$$\frac{[\text{exchanged imidate}]}{[\text{amidine}]} = \frac{k_x[H^+]}{k_b + k_c[H^+] + k_d[HA]} \tag{12}$$

pH and buffer concentration, where $k_c[H^+] \gg k_b$, the partition ratio [exchange]/[amidine] reduces to the quantity k_x/k_c, a pH-independent ratio. At low pH, the value of [exchange]/[amidine] is approximately 0.8 (Figure 1), showing that the acid-catalyzed expulsion of alcohol from T_0 occurs with approximately the same second-order rate constant as the acid-catalyzed expulsion of ammonia from T_0. In addition, the decrease in the amount of exchange observed with increasing concentration of buffer species suggests that the step leading to amidine formation is catalyzed by buffer species while the step leading to exchange is not. The same buffer-mediated increase in the amount of alcohol expulsion from a tetrahedral addition compound has been observed directly in the cleavage of amide acetals.[16]

On the acid limb of the pH–rate profile where $k_{IM} = k_1[H^+]$, the observed value of k_1 is composed of two terms, one describing the aminolysis reaction (k_c) and one describing the exchange reaction (k_x). For the methoxyaminolysis of ethyl benzimidate, it is possible to separate the contributions of each process to k_1 by measuring the ratio of the products of the exchange reaction to the aminolysis reaction. In the region of the pH–rate profile where $k_{IM} = k_1[H^+]$, the ratio of exchanged imidate to amidine of 0.8 corresponds to $k_x/k_c = 0.8$. Since $k_1 = k_a(k_c + k_x)/k_{-a}$, the rate constant for the aminolysis reaction $k_{am} = k_ak_c/k_{-a}$ is given by $k_1/(1 + k_x/k_c)$. Given that $k_1 = 2.4 \times 10^4\ M^{-2}\ s^{-1}$ (Table I) and $k_x/k_c = 0.8$, the rate constant for the aminolysis reaction (k_{am}) is $1.3 \times 10^4\ M^{-2}\ s^{-1}$.

At high pH, where attack (k_a) becomes the rate-determining step, the observed rate constant is $k_{IM} = k_3 = k_a$. Thus the ratio $k_3/k_{am} = k_{-a}/k_c = 230$. The acid-catalyzed expulsion of methoxyamine from T_0 is then approximately 230-fold faster than the acid-catalyzed expulsion of ethanol from T_0. Since $k_x = 0.8k_c$,

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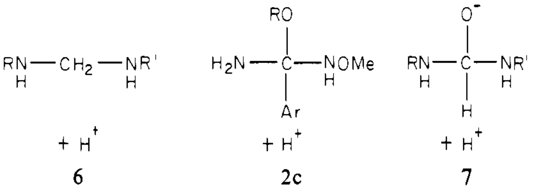
[15] Brown, D. T.; Kent, S. B. H. *Biochem. Biophys. Res. Commun.* **1975**, *67*, 126–132. Pocker, Y.; Beug, M. W.; Stephens, K. L. *J. Am. Chem. Soc.* **1974**, *96*, 174–180.

[16] McClelland, R. A. *J. Am. Chem. Soc.* **1978**, *100*, 1844–1849.

Chart II



the acid-catalyzed expulsion of methoxyamine from T_0 is approximately 300-fold faster than the acid-catalyzed expulsion of ammonia from T_0 ($k_{-a}/k_x = 300$).

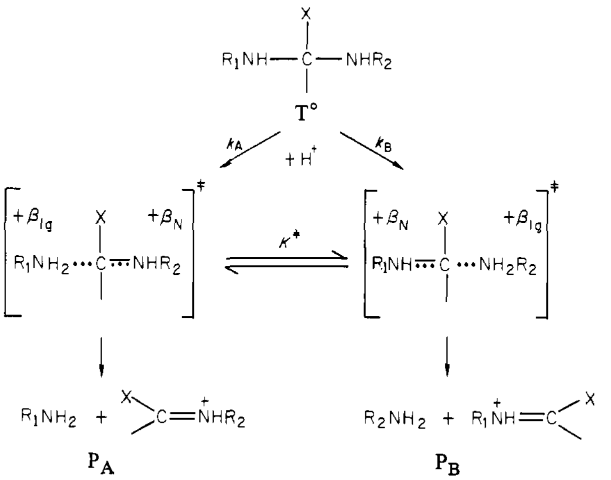
Relative Leaving-Group Ability. The relative rates of approximately 300:1:1 for the acid-catalyzed expulsion of methoxyamine, ammonia, and ethanol from the addition intermediate T_0 fit an overall pattern of leaving-group abilities for C–O and C–N cleavage, as shown in Charts I and II. The groups being compared are on either side of the central carbon atom, and additional groups that may donate electrons to assist the expulsion of both groups are above or below the central carbon atom in these charts. In most cases C–N cleavage involves equilibrium protonation of the amine followed by its expulsion, and C–O cleavage occurs through concerted protonation and heavy-atom rearrangement. The conclusion from these sequences is that the preferred leaving group in these compounds depends primarily on the *push* from the group(s) that remain behind; the leaving ability per se is usually of secondary importance. The moral may be that God helps those who help themselves, but electron donation helps those groups that need help the most.

Carbinolamines and related compounds (**1**) undergo preferential cleavage of the C–O bond in the presence of acid to give the imine and ROH.[17] This means that the strong push provided by electron donation from the remaining nitrogen atom is more important than the high basicity of nitrogen that facilitates its protonation and expulsion and the relatively small push provided by electron donation from oxygen. However, addition of the weakly basic methoxyamine group in **2a** provides enough help to the weakly electron-donating oxygen atom so that ammonia is expelled at a rate comparable to that of the alcohol. This help is less important for the expulsion of alcohol because alcohol expulsion is already driven by the strongly electron-donating $-NH_2$ group.

It is perhaps surprising that electron donation from two RO groups in **3** is enough to make dimethylamine expulsion competitive with alcohol expulsion in amide acetals.[16] Again, an additional push from electron-donating substituents on the benzene ring favors amine expulsion. With the less basic *N*-methylaniline leaving group, there is less push for alcohol expulsion, and only the aniline leaves.[18] The strong electron donation of the $-NH_2$ group in **2b** favors expulsion of methoxyamine, a weakly basic amine, over alcohol by 230-fold. The still more basic oxygen anion of **4** provides sufficient electron donation that C–N cleavage through the dipolar intermediate $T^{\pm}$ is almost always observed when this intermediate is generated in ester aminolysis or imidate hydrolysis.[19]

The amine is also expelled much faster than a phenolate ion of comparable pK from the dipolar intermediate **5** that is formed in the reactions of carbonate esters with tertiary amines. However, electron-donating groups on the nonreacting ArO– group in **5** increase the rate of oxygen expulsion relative to that of nitrogen. In this case the additional electron donation favors oxygen expulsion because there is no electron donation from the tertiary amine to push oxygen expulsion, but there is electron donation from oxygen to push amine expulsion.[20] All of these reactions represent examples of the nonadditivity of resonance effects; resonance is most important when the demand for it is greatest.[21]

Scheme I



The direction of the acid-catalyzed cleavage of geminal diamines (**6**, Chart II) depends on the basicity of the leaving group, the amount of leaving of the protonated amine, and the amount of electron donation from the remaining amine in the transition state. It is easiest to evaluate this problem by considering only the initial uncharged diamine and the amount of charge development on the two nitrogen atoms in the transition state, as indicated by β_{lg} and β_N (Scheme I).[20] The reaction ordinarily will proceed through the lowest energy transition state in which the *largest positive charge develops on the more basic nitrogen atom*, which has substituents that stabilize this charge. For an early transition state, there will be a large positive charge on the protonated leaving amine (large β_{lg}) and the more basic amine will leave. For a late transition state, there is little charge left on the leaving group but a large charge on the remaining nitrogen atom (large β_N), so that the more basic amine will remain. The value of β_{lg} is defined here relative to the initial uncharged diamine, so that it includes the effects of both protonation and the amount of C–N bond cleavage.

The acid-catalyzed cleavage of geminal diamines of formaldehyde (**6**) results in expulsion of the less basic amine, because the push provided by the remaining amine develops a large positive charge on this amine and is more important than the combination of protonation and leaving ability of the departing amine.[22] The same result is found for the imidate addition of compound **2c**, in spite of the additional electron donation from the RO– group and benzene ring. This addition compound expels methoxyamine 300 times faster than ammonia as a consequence of the strong electron donation from the remaining NH_2 group. However, the strongly electron-donating oxygen anion of **7**, the intermediate that is formed in the hydrolysis of amidines, expels the more basic amine preferentially.[9] This is because the push provided by the remaining amine is now relatively unimportant and increased basicity increases leaving-group ability in most acid-catalyzed reactions if the push from the remaining groups is approximately constant. The concentration of protonated amine increases with increasing basicity, with $\beta_N = 1.0$, while the leaving ability of the protonated amine decreases with increasing basicity, with $\beta_{lg} < 1.0$. Consequently, protonation is more important than leaving group ability, there is a net positive charge on the leaving amine in the transition state, and electron-donating substituents on the amine stabilize this positive charge to increase the observed leaving ability.

Cleavage of unsymmetrical imidazolidines[23] and the reduction of methylenetetrahydrofolic acid and its analogues[24] also occur

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(17) Jencks, W. P. *J. Am. Chem. Soc.* **1959**, *81*, 475–481. Jencks, W. P. *Prog. Phys. Org. Chem.* **1964**, *2*, 63–128.

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(22) Moad, G.; Benkovic, S. J. *J. Am. Chem. Soc.* **1978**, *100*, 5495–5499.

(23) Fife, T. H.; Pellino, A. M. *J. Am. Chem. Soc.* **1981**, *103*, 1201–1207.

(24) Barrows, T. H.; Farina, P. R.; Chrzanowski, R. L.; Benkovic, P. A.; Benkovic, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 3678–3689. Benkovic, S. J. *Acc. Chem. Res.* **1978**, *11*, 314–320.

with departure of the less basic amine as a consequence of the dominant role of electron donation and positive-charge development on the remaining amine. However, these reactions are complicated by the presence of general-acid catalysis of imidazoline cleavage, which has been attributed to a concerted reaction mechanism,[23] and the probability that the preferred direction of reduction reflects the equilibrium constants rather than the rate constants for bond cleavage,[24] which would certainly favor formation of the iminium ion of the more basic amine. The methoxyaminolysis of formamidines gives expulsion of the more basic amine, but in this reaction the product-determining step is the protonation of the amine, not C–N cleavage, so that the more basic amine is preferentially protonated and expelled.[10] The transiminations of *p*-methoxybenzaldehyde and benzophenone imines with hydroxylamine proceed with rate-determining proton removal from $HONH_2^+$ in the addition intermediate. Again, the more basic amine is expelled preferentially from the uncharged addition intermediate because it is protonated more rapidly.[7,8]

The 300-fold preference for expulsion of the weakly basic methoxyamine compared with ammonia from **2c** is most easily analyzed by considering the "effective charges" on the two nitrogen atoms in the transition states (Scheme I, X = -OEt). The preferred expulsion of the less basic amine means that there is more positive charge development on the remaining amine, so that the transition state with less positive charge on methoxyamine is favored. The effective charges in the transition state are defined by the values of β_{lg} and β_N for the leaving and remaining nitrogen atoms, respectively, and the dependence of the product ratios on amine p*K* is given by eq 13, in which pK_1 and pK_2 refer to $R_1NH_3^+$

$$\log (k_B/k_A) = \log K^{\ddagger} = \beta_{lg}(pK_2 - pK_1) + \beta_N(pK_1 - pK_2) = (\beta_N - \beta_{lg})(pK_1 - pK_2) \quad (13)$$

and $R_2NH_3^+$ (Scheme I). This equation was obtained as described previously for cleavage of the addition intermediates in ester aminolysis,[20] taking into account that the product ratio is 1.0 for the symmetrical reaction with $pK_1 = pK_2$. The ratio of 300:1 for the expulsion of methoxyamine and ammonia from **2c** corresponds to a value of $\beta_N - \beta_{lg} = 0.5$. The products from the breakdown of three diamines of formaldehyde formed from substituted anilines[22] give $\beta_N - \beta_{lg} = 0.9$.[25] These large values could correspond to values of $\beta_{lg} = 0.5$ and $\beta_N = 1.0$ for **2c** and $\beta_{lg} = 0.2$ and $\beta_N = 1.1$ for the formaldehyde compounds (**6**), for example. The large values of β_N suggest that β_N for the equilibrium formation of the iminium ion products must be >1.0. This is presumably a reflection of the sp^2 character of the product and is consistent with the value of $\beta_N = 0.26$ for the equilibrium formation of uncharged aliphatic imines of isobutyraldehyde.[26]

The role of an additional electron-donating group, such as the oxygen anion in **7**, is to decrease the electron demand from the remaining group, so that there is less development of positive charge and a smaller value of β_N for this group. This increases the relative amount of charge development on the leaving group until β_{lg} becomes larger than β_N and departure of the more basic amine is favored.

These values of $\beta_N - \beta_{lg}$ provide a useful way to examine the behavior of these reactions, but the particular numerical values of $\beta_N - \beta_{lg}$ should not be taken as representative of those to be expected from reactions of simple aliphatic amines because the leaving ability of both "α-effect" compounds[27] and ammonia[11] is less than expected for amines of comparable p*K* and electron donation by resonance from anilines to the developing double bond may provide additional stabilization to the transition states for the formaldehyde compounds. The result for **2c** cannot be attributed to stereoelectronic control[28] because the expulsion of methoxyamine requires protonation of the weakly basic nitrogen atom, which should allow ample time for rotation or inversion of the $-NH_2$ group to provide antiperiplanar electrons for the expulsion of methoxyamine.

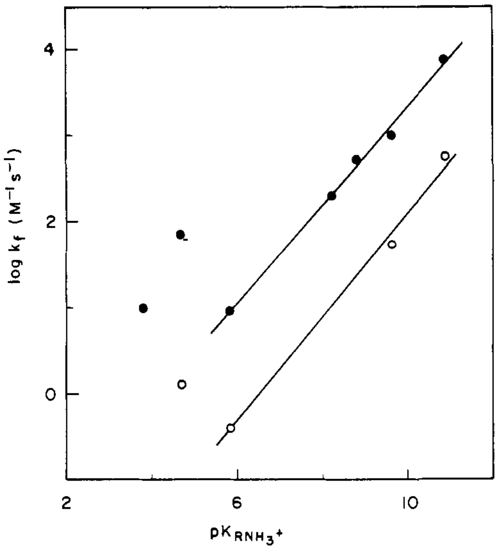

Figure 4. Brønsted-type correlation between the rate constant for formation of the tetrahedral intermediate during the aminolysis of alkyl benzimidates and the p*K* of the amine hydrochloride. The values of k_f are reported according to the rate law $v = k_f[IMH^+][RNH_2]$ observed on the alkaline side of the pH–rate profile. The line for aminolysis of trifluoroethyl benzimidate (●) is drawn with slope $\beta_{nuc} = 0.54$, and the line for ethyl benzimidate (○) is drawn with slope $\beta_{nuc} = 0.61$. Points for α-effect nucleophiles show positive deviations from the lines and were omitted from the least-squares treatment.

Formation of the Tetrahedral Addition Intermediate and Proton Transfer. On the basic side of the pH–rate profile, the formation of the tetrahedral intermediate is the rate-determining step in the overall reaction. The reaction is acid catalyzed, and the rate constants shown in Tables I and IV are based on the rate law $v = k_3[IM][RNH_2][H^+]$. However, the reaction involves attack of the free amine on the protonated imidate,[5,11] and in order to use structure–reactivity correlations to assess the changes in charge on the reacting atoms in the transition state for formation of the addition intermediate, the reaction can be described by the kinetically equivalent rate law $v = k_f[IMH^+][RNH_2]$.

A Brønsted-type plot of the second-order rate constants (k_f) for the addition of a series of substituted aliphatic primary amines gives slopes of $\beta_{nuc} = 0.54$ and 0.61 for trifluoroethyl and ethyl benzimidate, respectively (Figure 4). These values of β_{nuc} indicate that an unusually large amount of positive charge has developed on the nitrogen atom of the attacking amine in the transition state for formation of the intermediate. Rate-determining attack of amines on esters, for example, exhibits $\beta_{nuc} = 0.2 \pm 0.2$.[29] Part of the large value for the imidates may represent an electrostatic interaction of substituents on the amine with the net positive charge of the imidate.[30] However, the values are much larger than the value of $\beta_{nuc} = 0.1$ for addition of a series of secondary amines to a phthalimidium cation[5] and slightly larger than values of $\beta_{nuc} = 0.4$–0.5 for addition of amines to carbocations[31] and $PhC{\equiv}NO^{\pm}$.[32]

The rate constants for nucleophilic attack by the α-effect nucleophiles methoxyamine and semicarbazide are increased by 15–30-fold compared with those of ordinary primary amines (Figure 4). This is of interest because the best known examples of enhanced reactivity of α-effect nucleophiles are in ester aminolysis under conditions in which breakdown of the tetrahedral intermediate or proton transfer is rate determining.[19,33] Therefore,

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(25) This conclusion differs from that of an earlier report.[22]

(26) Hine, J.; Via, F. A. *J. Org. Chem.* **1977**, *42*, 1972–1978.

(27) Morris, J. J.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2*, **1980**, 220–224.

(28) Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463–2490.

(29) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018–7031.

(30) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948–7960.

(31) Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 3248–3254. Ritchie, C. D.; Virtanen, P. O. I. *Ibid.* **1973**, *95*, 1882–1889.

(32) Dignam, K. J.; Hegarty, A. F.; Quain, P. L. *J. Chem. Soc., Perkin Trans. 2*, **1977**, 1457–1462.

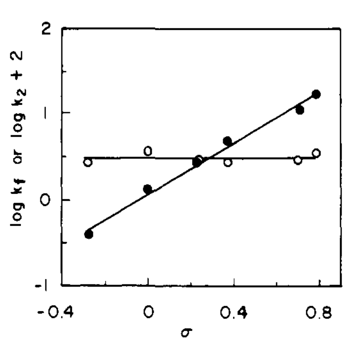


Figure 5. Hammett plots for rate-determining formation and breakdown of the tetrahedral intermediate formed on methoxyaminolysis of ring-substituted ethyl benzimidates at 25.0 °C, μ = 1.0 M (KCl). Rate constants (k_2) for rate-determining breakdown of the intermediate were evaluated from the rate law $v = k_2[\mathrm{IM}][\mathrm{MeONH_2}]$ observed on the acid side of the pH–rate profile. The line for the rate constants k_2 (○) is drawn with slope $\rho = -0.01$. Rate constants (k_f) for the formation of the intermediate were evaluated from the rate law $v = k_f[\mathrm{IMH^+}][\mathrm{MeONH_2}]$ observed on the basic side of the pH–rate profile ($k_f = k_3K_{\mathrm{IMH^+}}$; where k_3 is given in Table IV and $K_{\mathrm{IMH^+}}$ is the acid dissociation constant of the benzimidate hydrochloride). The line for the rate constants k_f (●) is drawn with slope ρ = 1.49.

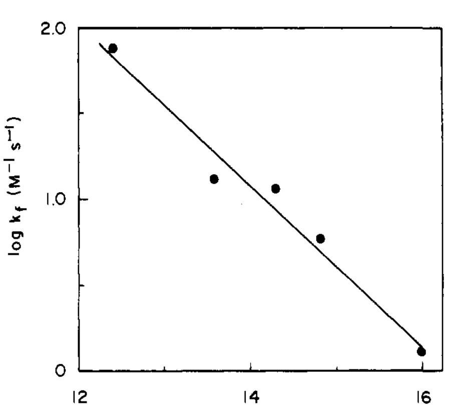
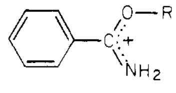


Figure 6. Brønsted-type correlation between the second-order rate constant for formation of the tetrahedral intermediate and the pK_a of the alcohol leaving group for the methoxyaminolysis of alkyl benzimidates at 25.0 °C, μ = 1.0 M (KCl). Rate constants k_f are evaluated from the rate law $v = k_f[\mathrm{IMH^+}][\mathrm{MeONH_2}]$ observed on the basic side of the pH–rate profile ($k_f = k_3K_{\mathrm{IMH^+}}$; k_3 is given in Table I, and $K_{\mathrm{IMH^+}}$ is the acid dissociation constant of the benzimidate hydrochloride). The line is drawn with slope β_0 = –0.47.

the rate increase is the result of an especially favorable equilibrium constant for nucleophile addition[31,34] or rate constant for intramolecular general-acid–base catalysis,[35] rather than an increased rate constant for nucleophilic attack by α-effect nucleophiles.

A late, product-like transition state is also indicated by the increase in rate from electron-withdrawing substituents on the benzene ring, with ρ = 1.5 for the addition of methoxyamine to a series of protonated, ring-substituted ethyl benzimidates (Figure 5). This value is as large as the value of ρ = 1.5 for the acid dissociation of protonated ethyl benzimidates,[13] with loss of a full positive charge. However, there is presumably an additional contribution to the observed value of ρ from the change from sp^2 to sp^3 hybridization in the addition reaction that does not occur in the acid dissociation. The addition of water in the hydrolysis of protonated ethyl benzimidates gives a similar ρ value of 1.4.[36]

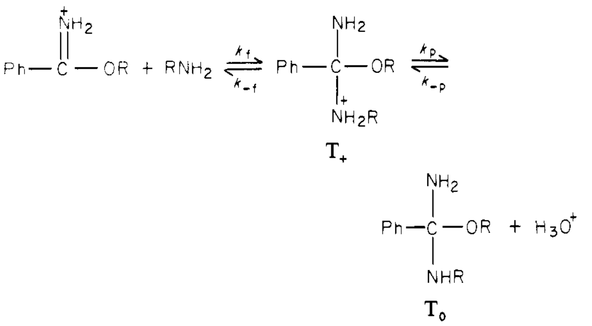
The addition of methoxyamine shows no negative deviation of the rate constant for the p-CH_3O compound from the correlation with σ that might suggest a large loss of resonance stabilization from the benzene ring in the transition state. Rate constants for the hydrolysis of ethyl benzimidates[36] show a small negative deviation for the p-CH_3O compound from the σ correlation, but the addition of methoxyamine and water to protonated benzhydrylidenemethylamines show a larger deviation from σ and follow the σ^+ scale with values of ρ^+ = 0.96 and 1.1, respectively,[37] which suggest a significant loss of such resonance stabilization in the transition state. Electron donation from the benzene ring in benzimidates may be less important than in the corresponding protonated imines because of the strong electron donation by resonance from the oxygen atom in the imidate (**8**).



8

The rate constants for addition of methoxyamine to protonated alkyl benzimidates show a value of β_0 = –0.47, based on the pK_a values of the parent substituted alcohols (Figure 6). The rate constants in Table I for the addition of water to these benzimidates follow β_0 = –0.56 (plot not shown). The value of β_0 for the complete loss of the net positive charge of protonated benzimidates upon acid dissociation is –0.74.[13] These values confirm the large amount of positive charge on the oxygen atom in protonated benzimidates (**8**) and show that a major fraction of this charge is lost in the transition states for the addition of water or amines.

There is no evidence for kinetically significant proton transfer (k_p, eq 14), and the attack of amine on the protonated imidate appears to be rate determining in the addition reaction (k_f, eq 14).



(14)

The pK_a of T$_+$ formed from the addition of methoxyamine to ethyl benzimidate was estimated[38–40] to be approximately 0.1, 4.6 units below the pK_a of the parent amine, and the pK_a values of T$_+$ formed from more basic amines will be correspondingly higher. Rate-determining proton transfer from T$_+$ formed from these amines to water, a weak base, would then be thermodynamically

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[38] The pK values of the protonated nitrogen atoms of T$_+$ were estimated by the method of Fox and Jencks[39] as follows. For T$_{+,1}$ in which the nitrogen derived from ammonia is protonated, the pK was estimated by beginning with the pK of benzylamine (9.34).[40] With a ρ_I of –8.4 and the appropriate σ_I values, substitution of OEt (σ_I = 0.27) and NH_2 (σ_I = 0.12) at the methylene carbon would decrease the pK to 9.34 – 8.4 (0.12 + 0.27) = 6.1 for the species bearing two identical amine substituents. With a falloff factor of 0.2 and the pK difference between methylamine (10.6) and N-methylmethoxyamine (4.7), the effect of substituting OMe for H on the nonionizing amino group would be to reduce the pK to 6.1 – 0.2(10.6 – 4.7) = 4.9. Thus the pK for the protonated primary amino group of T$_{+,1}$ would be 4.9. For T$_{+,2}$ in which the nitrogen derived from methoxyamine is protonated, the pK can be estimated beginning with N-methylmethoxyamine (4.7) and correcting for the substitution of H by phenyl by subtracting the difference in pK between methylamine (10.6) and benzylamine (9.34), so that the estimated pK of N-benzylmethoxyamine is 4.7 – 1.3 = 3.4. A ρ_I of –8.4 and values of σ_I = 0.12 for NH_2 and σ_I = 0.27 for OMe gives an estimated value of 0.1 for the pK of T$_{+,2}$ for the dissociation of the protonated nitrogen atom derived from methoxyamine.

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unfavorable and would follow a Brønsted slope of $\alpha = 1.0$, which corresponds to $\beta_{nuc} = 0$.[41] Rate-determining proton transfer from T_+ to most buffer bases would be thermodynamically favorable and would give $\beta_{nuc} = 1.0$ and general-base catalysis.[41] These requirements are inconsistent with the observed value of $\beta_{nuc} = 0.6$ and the first-order dependence of the rate on amine concentration in the region in which the addition step is rate determining.[11] Kinetically significant proton removal from the attacking amine would be catalyzed by a second molecule of amine and would give a second-order dependence of the observed rate constants on amine concentration.[8] Furthermore, the fact that methoxyamine leaves 300 times faster than ammonia from T_0 is inconsistent with kinetically significant proton transfer to the methoxyamine or ammonia moieties of T_0, because such proton transfer would give preferential expulsion of the more basic ammonia.[7,8,10]

The rate constant for proton transfer to water from T_+ formed from methoxyamine is approximately $k_p = 0.8 \times 10^{10}\ s^{-1}$, from the relation $K_a = 10^{-0.1} = k_p/k_{-p}$ and assuming a value of $10^{10}\ M^{-1}\ s^{-1}$ for k_{-p}.[41] Buffer catalysis of proton transfer would not be expected to compete successfully against a rate constant of this magnitude for proton transfer to water. General-base catalysis by buffer or a second molecule of amine would be expected for proton transfer from T_+ formed from more basic amines if it were kinetically significant, but such catalysis has not yet been observed.

The conclusion that amine attack is rate determining means that proton transfer is faster than the reversion of T_+ to reactants, i.e., $k_p > k_{-f}$ (eq 14). Thus, for the methoxyamine adduct, k_{-f} is $<10^{10}\ s^{-1}$. Since there is no term second order in amine for the addition of *n*-butylamine at 0.1 M RNH_2,[11] the value of k_{-f} for the butylamine adduct must be $<0.1 \times 10^9 = <10^8\ s^{-1}$, assuming a second-order rate constant of $10^9\ M^{-1}\ s^{-1}$ for proton abstraction from T_+ by *n*-butylamine.[41] It is possible that kinetically significant proton transfer could be detected at lower concentrations of basic amines, because proton transfer to water from the weakly acidic T_+ formed from such amines will become relatively slow, with $k_p \sim 10^4\ s^{-1}$.

Proton removal from T_+ is kinetically significant in the reactions of hydroxylamine with benzhydrylidenedimethylammonium ion[8] and of methoxyamine with a formamidine,[10] for which the values of k_{-f} are $>10^9\ s^{-1}$ and $\geq 10^{10}\ s^{-1}$, respectively. The two benzene rings in the former adduct, which provide steric crowding as well as electron donation, and the two aniline nitrogen atoms in the formamidine evidently give larger values of k_{-f} than are found in the imidate addition compounds. Proton transfer is not kinetically significant in the methoxyaminolysis of a series of benzylideneanilines.[42] The intermediate T_+ in this reaction has only a single aniline nitrogen atom to push the expulsion of methoxyamine, and proton transfer to the solvent is expected to be fast.

Uncatalyzed Expulsion of Alcohol. On the acidic side of the pH-rate profile, the expulsion of alcohol from the addition intermediate is the rate-determining step for amidine formation and occurs through pH-independent and acid-catalyzed pathways (Figure 3).[11] These pathways represent the spontaneous expulsion of alkoxide ion from the uncharged addition intermediate and general-acid catalysis of the expulsion of alcohol, respectively.

The large negative value of $\beta_{lg} = -1.3$ means that there is a large negative effective charge on the leaving oxygen atom that is "seen" by polar substituents in the transition state of the uncatalyzed, pH-independent reaction (Figure 7). This value is slightly more negative than the values of $\beta_{lg} = -1.2$ for the base-catalyzed elimination of alkoxide ions from imidates to form nitriles[13] and $\beta_{lg} = -0.9$ for the pH-independent expulsion of alkoxide ions to form a phthalimidium ion.[6] The value of $\beta_{lg} = -1.3$, which is a measure of the change in effective charge between the reactants and the transition state, is larger than that seen on the ionization of the parent alcohol. Part of this may be attributed to a partial positive charge on the oxygen atom in the starting uncharged imidate. There is a large effective positive charge on the oxygen atom of esters in the ground state, with $\beta_{eq} = 0.7$,[43] but a smaller value is expected for imidates because the C=NH group is less electron withdrawing than C=O. A larger contribution is probably made by incomplete solvation of the leaving alkoxide ion in the transition state, for which there is more extensive evidence in the elimination of alkoxide ions from imidates[13] and other similar reactions.[4,44]

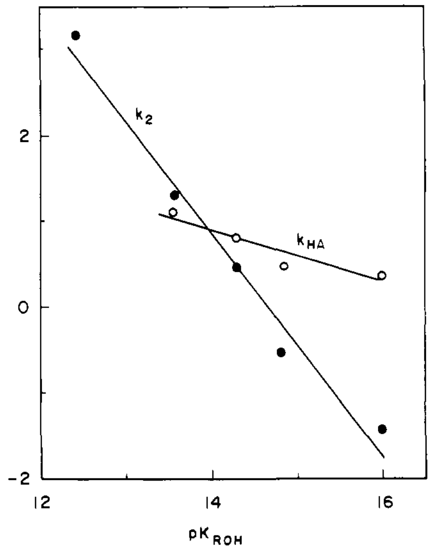
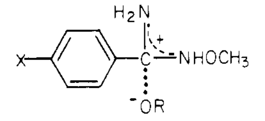


Figure 7. Brønsted-type correlation for the pH-independent and the acetic acid catalyzed breakdown of the tetrahedral intermediate formed during the methoxyaminolysis of alkyl benzimidates at 25.0 °C, $\mu = 1.0$ (KCl). Rate constants (k_2, k_{HA}) are evaluated from the rate law $v = k_2[IM][RNH_2]$ or $v = k_{HA}[IM][RNH_2][HA]$ observed on the acid limb of the pH-rate profile. The least-squares line for the "water" reaction (●) is drawn with slope $\beta_{lg} = -1.30$. The least-squares line for the acetic acid catalyzed reaction (○) is drawn with slope $\beta_{lg} = -0.31$.

The value of $\rho = -0.01$ for the pH-independent expulsion of ethoxide ion in the methoxyaminolysis of ring-substituted ethyl benzimidates (Figure 5) means that the effective charge on the central carbon atom in the transition state is essentially the same as in the starting uncharged imidate. This indicates that the electrostatic interactions from the developing positive charge on the nitrogen atoms, the negative charge on the leaving oxygen atom, and the relatively small contribution from the change in hybridization cancel each other almost completely in the transition state **9**.



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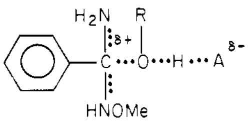
General-Acid Catalysis of Alcohol Expulsion and Structure-Reactivity Interactions. Rate-determining expulsion of alcohol from the addition intermediate in the acidic region of the pH-rate profile is subject to general-acid catalysis (Figure 2).[11] This reaction is assigned to a class-n mechanism of general-acid catalysis with concerted C-O bond cleavage and proton transfer to the leaving alcohol (**10**).[45] The reaction exhibits the characteristic



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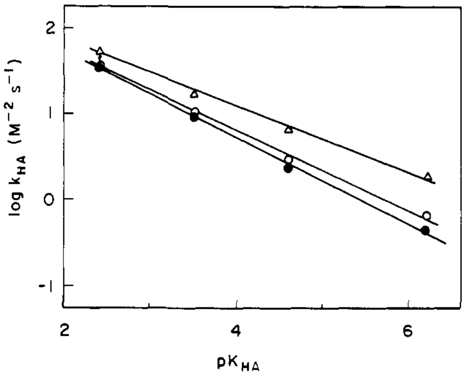

Figure 8. Brønsted plots for general-acid-catalyzed methoxyaminolysis of alkyl benzimidates at 25.0 °C, μ = 1.0 M (KCl). Data are shown for ethyl benzimidate (●), α = 0.49; methoxyethyl benzimidate (○), α = 0.45; and chloroethyl benzimidate (△), α = 0.40. The limited data available for propargyl benzimidate are not shown.

properties of this mechanism, which has been established for a number of related reactions[4,44–50] including the closely analogous general-acid-catalyzed expulsion of alcohols to give a phthalimidium ion.[6] The kinetically equivalent mechanism of general-base catalysis of the expulsion of protonated alcohol is excluded by the negative value of $\beta_{lg} = -0.31$ for the reaction catalyzed by acetic acid (Figure 7). The value of β_{lg} for this mechanism would be expected to be between the values of approximately +1.0 for a fully protonated alcohol and 0 for the alcohol product. Mechanism **10** has also been demonstrated by the observation of kinetically unambiguous general-acid–base catalysis for the analogous formation of a phthalimidium ion[6] and, in the reverse direction, for the addition of water to a formamidinium ion.[51]

The values of $\alpha = 0.4$–0.5 (Figure 8) are unusually small, and the value of $\beta_{lg} = -0.31$ is unusually negative compared with other reactions of this class. These parameters place the transition state in the right lower quadrant near the center of the reaction-coordinate diagram of Figure 9, which has axes that are defined by the observed structure–reactivity parameters for the reaction.[30] The negative value of β_{lg} may reflect, in part, a substituent effect on the equilibrium constant for formation of the addition intermediate. The rate constants for catalysis by the proton of the reactions of ethyl and methoxyethyl benzimidates fit an extrapolation of the Brønsted plot for catalysis by carboxylic acids in Figure 8. This suggests that the proton and other acids catalyze the reaction by the same mechanism; i.e., there is no evidence for an additional pathway of specific acid catalysis with protonation of the leaving alcohol in a fast equilibrium step.

There is a small but definite increase in the Brønsted coefficient α with increasing basicity of the leaving alcohol (Figure 8). The increase corresponds to a positive interaction coefficient ($p_{xy'}$) (eq 15)) that is characteristic of the diagonal reaction coordinate for

$$p_{xy'} = \frac{\delta\alpha}{\delta pK_{lg}} = \frac{\delta\beta_{lg}}{-\delta pK_{HA}} = \frac{1}{C_5} \tag{15}$$

this class of reaction with both C–O cleavage and proton transfer in the transition state (Figure 9).[6,30] The changing slopes result in a characteristic crossing of the Brønsted lines,[6] so that the reaction is faster with electron-withdrawing substituents on the leaving alcohol for weak-acid catalysts and with electron-donating substituents for catalysis by the proton (Figure 7, k_1, Table I). The increase in α corresponds to a value of $p_{xy'} = 0.05$, which is similar to values of $p_{xy'}$ ranging up to 0.12 for related reactions.[4,6,44,47,49] The α values for the hydrolysis of methyl substituted-phenyl benzaldehyde acetals give a value of $p_{xy'} = 0.20$,[30,46] but this may represent a special effect of the phenolic leaving groups because the α values for the hydrolysis of ethyl substituted-alkyl benzaldehyde acetals give a value of $p_{xy'} = 0.06$.[49]

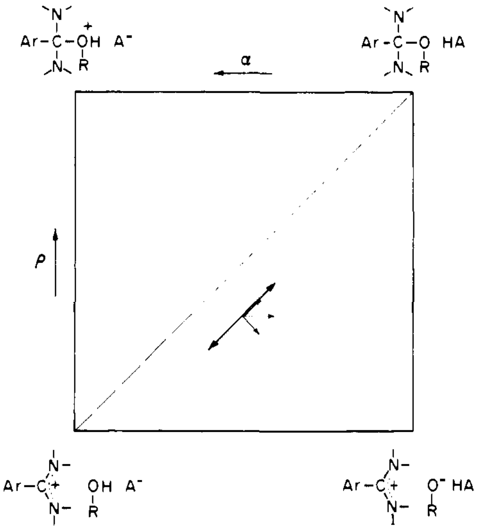

Figure 9. Gibbs free energy reaction-coordinate surface for the elimination of alcohol from tetrahedral intermediates. The extent of proton transfer (α) is represented by the horizontal location of the transition state on the diagram while the extent of C–O bond breakage is represented by the vertical location of the transition state. The resultant increase in α with increasing energy of species along the top of the diagram is shown for a concerted transition state with a diagonal component to the reaction coordinate.

The relatively small values of α are expected as a consequence of the stability of the amidinium ion product of the reaction. Stabilization of the product corresponds to a lowering of the energy of the bottom relative to the top of the reaction-coordinate diagram of Figure 9. This will tend to cause the transition state of a diagonal reaction coordinate to slide downhill toward the lower right corner, perpendicular to the reaction coordinate, and climb uphill toward the upper right corner, parallel to the reaction coordinate. The resultant of these two motions corresponds to a net movement toward the right and a decrease in the amount of proton transfer, as shown in Figure 9.[52]

This change in the amount of proton transfer in the transition state with changing stability of the product corresponds to a positive p_{xy} coefficient, which is defined by eq 16 when the change

$$p_{xy} = \frac{\delta\alpha}{\delta\sigma} = \frac{\delta\rho}{-\delta pK_{HA}} = \frac{1}{C_4} \tag{16}$$

in stability is brought about by changing substituents on a benzene ring.[30,53] The stability of the product in this reaction is brought about by the two nitrogen atoms of the amidine rather than by substituents in the benzene ring. Rate constants for the reaction of water with the central carbon atom range from approximately $<10^{-6}$ s^{-1} for amidinium ions,[10] 1 s^{-1} for phthalimidium cation,[7] and 10 s^{-1} for formaldehyde[44] to 10^{10} s^{-1} for the carbocation formed from benzaldehyde acetals.[54] This increase in stability over a range of $>10^{16}$ in the product corresponds to a decrease of ~0.5 in the value of α. It is not surprising, therefore, that α often does not change significantly with changing stability within a closely related reaction series with changing substituents on a benzene ring or other groups. However, there is a measurable decrease

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in α with electron-withdrawing substituents on the benzene ring (positive p_{xy} coefficient) for the cleavage of benzaldehyde acetals[46,49] and Meisenheimer complexes,[47] and there is evidence for a positive p_{xy} coefficient from α secondary-deuterium-isotope effects in the cleavage of formaldehyde hemiacetals.[55]

The larger change in α with substituents on the alcohol ($p_{xy'}$) than with substituents on the reacting carbon atom (p_{xy}) represents an apparent inconsistency or imbalance of the changes in transition-state structure if these are to be described by a single reaction-coordinate diagram. The imbalance represents a larger movement of the transition state toward the right side of the diagram when the upper left corner is raised than when the top is raised (increased in energy); there is no significant movement to the right when the left edge is raised ($\delta\alpha/\delta pK_{HA} = p_x \simeq 0$). Formally, the imbalance represents a failure of the normalized interaction coefficients to follow the relationship of eq 17. The

$$p_{xy} = p_{xy'} + p_x \tag{17}$$

same imbalance has been observed previously in the cleavage of carbinolamines and their ethers.[56] The positive p_{xy} coefficients that have been observed for the cleavage of benzaldehyde acetals,[46,49] Meisenheimer complexes,[47] and formaldehyde hemiacetals[55] also show imbalance according to eq 17. There is a similar imbalance between the effects of substituents in the alcohol on the amount of proton transfer ($p_{xy'}$) and the amount of C–O bond cleavage ($p_{y'y'}$) in the transition state for the cleavage of formaldehyde hemiacetals.[55]

These observations indicate that there is a greater tendency for change in the structure of the proton-transfer portion of the transition state, which involves three atoms and two partial bonds, than of the remainder of the transition state, which involves only two heavy atoms and one partial bond. A small part of the imbalance can be accounted for by a simple electrostatic contribution to the $p_{xy'}$ coefficient, but most of it can be explained if there is a net tightening of the transition state for proton transfer as the acid becomes stronger.[56] The imbalance means that the "effective charges" in different parts of the transition state may not be additive; the bond orders for the making and breaking of σ bonds in the different parts of the transition states of these complex reactions also may not be additive to give an integer. The characteristics of these reactions may be easier to understand if they are regarded as an electrophilic attack by the acid on oxygen that withdraws electrons from the C–O bond rather than as C–O cleavage that is assisted by proton transfer.[55]

Acknowledgment. We are grateful to J. Y. Loewenberg and D. Kolodrubetz for carrying out preliminary experiments that demonstrated general-acid catalysis with $\alpha \sim 0.5$ for the methoxyaminolysis of ethyl benzimidate.

Registry No. m-NO_2—Ph—C(=NH)OEt, 831-65-2; p-NO_2—Ph—C(=NH)OEt, 831-68-5; p-Cl—Ph—C(=NH)OEt, 827-72-5; m-Cl—Ph—C(=NH)OEt, 827-64-5; p-OMe—Ph—C(=NH)OEt, 829-48-1; CH_3ONH_2, 67-62-9; $CF_3CH_2NH_2$, 753-90-2; $CH_3OCH_2CH_2NH_2$, 109-85-3; CH_3NH_2, 74-89-5; $NH_2CONHNH_2$, 57-56-7; $H_2NCOCH_2NH_2$, 598-41-4; $ClCH_2CH_2NH_2$, 689-98-5; ethyl benzimidate, 825-60-5; methoxyethyl benzimidate, 72047-81-5; chloroethyl benzimidate, 72047-82-6; propargyl benzimidate, 41897-10-3; trifluoroethyl benzimidate, 72047-83-7; cyanoacetic acid, 372-09-8; methoxyacetic acid, 625-45-6; acetic acid, 64-19-7; methoxyamine hydrochloride, 593-56-6; cacodylic acid, 75-60-5.

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Communications to the Editor

^1H and ^{13}C NMR of Vinylketene and Its Dimerization by [4 + 2] Cycloaddition. Synthesis of Sibirinone and Bicyclo[4.2.1]nona-3,7-dien-2-one

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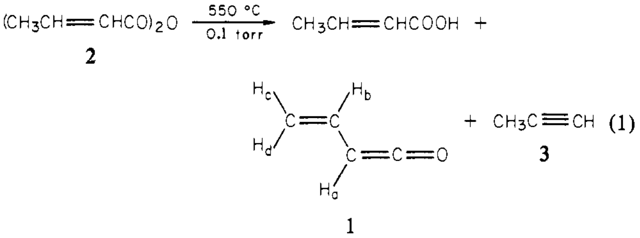
There have been several reports of the generation of vinylketene (**1**) from various sources.[2] In the earlier work **1** was postulated on the basis of trapping experiments, but recently it has been observed directly by mass,[2f] microwave,[2g,h] and infrared[2g,h] spectroscopy. On the basis of photoelectron spectroscopy and MNDO calculations, the vinylketene structure instead of the ethylideneketene structure was assigned to the product of thermolysis of crotonic acid derivatives.[2j] In this communication we report the low-temperature ^1H and ^{13}C NMR spectra of **1** and some chemistry of **1**.

The vacuum pyrolysis (eq 1) of crotonic anhydride[2h,j,3] was



carried out by using an apparatus with two product condensers, the first cooled to −20 °C and the second to −196 °C, in order to separate the crotonic acid from the more volatile products.[4] After pyrolysis, a mixture of CS_2 and $CDCl_3$ was distilled into the −196 °C condenser, the mixture was allowed to warm to −78 °C, and a standard was added. The ^1H NMR spectrum of the resulting solution at −70 °C showed a 22% yield of **1** [4.0 (H_a, d, J_{ab} = 11 Hz), 4.6 (H_c dd, J_{bc} = 11 Hz, J_{cd} = 1.5 Hz), 4.9 (H_d dd, J_{bd} = 18 Hz, J_{cd} = 1.5 Hz), 5.9 (H_b, ddd, J_{ab} = 11 Hz, J_{bc} = 11 Hz, J_{bd} = 18 Hz)], a 40% yield of methylacetylene[2g-i] (**3**) [1.89 (s, 1), 1.88 (s, 3)], and only 5% of minor products. No evidence for the cyclic isomer of **1**, cyclobutenone,[5] was obtained.

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