Mechanism of the Base-Catalyzed Cleavage of Imido Esters to Nitriles[1]

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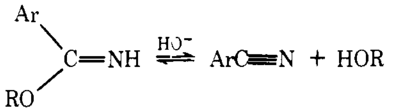
Abstract: The elimination of alcohols from alkyl benzimidates to give the corresponding nitriles is catalyzed by hydroxide ion with inverse solvent deuterium isotope effects of k_{HO}/k_{DO} = 0.66 and 0.86 for ethyl and trifluoroethyl benzimidates, respectively, fast exchange of the NH proton with water, and no detectable general base catalysis. It is concluded that the elimination proceeds through an E1cB mechanism with reversible formation of a nitrogen anion (pK_a < 23), followed by expulsion of the alcoholate anion ($k_2 \leqslant 10^7$ s^{-1} for ethyl benzimidate). Comparison with other reactions of this class suggests that the mechanism becomes concerted when the anionic "intermediate" becomes too unstable to exist. Electron-withdrawing substituents on the leaving alcohol cause a large rate increase, with $\beta_{lg} = -1.2$, but the reaction is slightly facilitated by electron-withdrawing substituents on the benzene ring, with $\rho = 0.5$. It is concluded that there is large amount of C-O cleavage in the transition state and that the negative charge on the leaving alcoholate anion has a strong electrostatic interaction with the carbon atom and a relatively weak interaction with the solvent. The dissociation constants of protonated alkyl benzimidates follow $\rho = 1.7$ for ring substitution and $\alpha = 0.74$ for alcohols of differing pK_a.

The experiments reported here were carried out with the goal of elucidating the mechanism and transition-state structure for the base-catalyzed elimination of alcohols from imido esters to give the corresponding nitriles.[2,3] In particular, we



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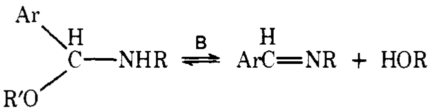
were interested in determining whether this elimination reaction proceeds through a concerted mechanism similar to that which has been proposed for the analogous base-catalyzed imine-forming elimination reaction of carbinolamines and carbinolamine ethers.[4,5]



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Experimental Section

Materials. All organic reagents were redistilled or recrystallized before use. Reagent grade inorganic reagents were used without further purification. Glass-distilled water was used throughout.

Ring-substituted ethyl benzimidates were prepared by published procedures.[6] Alkyl benzimidates were prepared by the reaction of equimolar quantities of the appropriate alcohol and benzonitrile in the presence of 1 equiv of dry hydrogen chloride[7] in a sealed tube at 0 °C for 24-72 h. After the addition of dry ether the solid benzimidate hydrochlorides were isolated by filtration, washed extensively with dry ether, and stored under dry nitrogen. ^{1}H NMR spectra of the alkyl benzimidate hydrochlorides in dry Me$_2$SO-d_6 are reported as chemical shift values in parts per million (δ) downfield from tetramethylsilane. **PhC(=NH$_2^+$Cl$^-$)OCH$_2$CH$_2$OCH$_3$:** δ 3.40, 3.1 H, s; 3.88, 2.0 H, m; 5.03, 2.0 H, m; 7.5-8.4, 5 H, m; 11.56, 1.7 H, broad.[8] **PhC(=NH$_2^+$Cl$^-$)OCH$_2$CH$_2$Cl:** δ 4.19, 2.0 H, t, J = 7 Hz; 5.01, 2.0 H, t, J = 7 Hz; 7.5-8.4, 6.9 H, m; 11.45, 2.1 H, broad.[8] **PhC(=NH$_2^+$Cl$^-$)OCH$_2$C≡CH:** δ 4.11, 1.0 H, t, J = 3 Hz; 5.52, 2.0 H, d, J = 3 Hz; 7.5-8.4, 5.9 H, m; 11.81, 2.0 H, broad. **PhC(=NH$_2^+$Cl$^-$)OCH$_2$CF$_3$:** δ 5.47, 2.0 H, q, J = 8.1 Hz; 7.7-8.2, 5.2 H, m; 10.20, 2.1 H, broad. Spectra were recorded immediately after dissolving the benzimidate hydrochloride; trace amounts of water resulted in hydrolysis of the benzimidate hydrochlorides within a few minutes and the appearance of the spectrum of the corresponding benzoate ester. Elemental analyses of some benzimidate hydrochlorides were unsatisfactory, presumably because of contamination with traces of hydrolysis products. However, all analyses were consistent with assigned structures if corrected for contamination with ammonium chloride (<10%). The NMR spectra are also consistent with assigned structures except for the strength of the bands in the aromatic region; traces of ammonium chloride probably account for the excess intensity observed with some compounds in this region (δ 7.50 for the NH protons of ammonium formate in Me$_2$SO-d_6). The benzimidates were judged to have the assigned structures and sufficient purity for kinetic measurements based on the NMR spectra, the method of synthesis,[6,7] the observation of first-order kinetics for over 3 half-lives, and the spectrophotometric identification of the corresponding benzonitriles as products of the elimination reactions.

Kinetics. The base-catalyzed decomposition of alkyl benzimidates, ~10^{-4} M, was followed spectrophotometrically by observing the decrease in absorbance at 240 nm. The reactions of ring-substituted ethyl benzimidates were followed at the wavelengths shown in Table II. The reactions were initiated by the addition of 10-20 μL of a solution of the benzimidate hydrochloride in the alcohol corresponding to the leaving group. Stock solutions of benzimidate hydrochloride were prepared immediately before each set of experiments and were stable for the duration of the experiments. The observed rate constants for the elimination reactions were different from the rate constants for hydrolysis of the corresponding benzoate esters under the same conditions. Pseudo-first-order rate constants, k_{obsd}, were determined from the slopes of ln ($A_\infty - A$) or ln ($A - A_\infty$) against time. The plots were linear for 3-4 half-lives except that some deviation was noted after 2 half-lives at very high concentrations of hydroxide ion, which was attributed to slow hydrolysis of the product nitrile. Values of A_∞ in these runs were calculated by adding 3% of the observed change in absorbance to the observed absorbance after 5 half-times. The ionic strength was maintained constant at 1.0 M by the addition of potassium chloride. The pH of the contents of each cuvette was determined after completion of the reaction. At low concentrations of potassium hydroxide or buffers, the pH was measured both before and after the kinetic runs and any run showing a change in pH of >0.04 unit was discarded. The pH was measured on a Radiometer 26 pH meter with a GK 2321C glass electrode standardized at pH 7 and 10.

The pK values of the protonated benzimidates were determined spectrophotometrically by adding a constant concentration of benzimidate to a series of buffered solutions at 25 °C, ionic strength 1.0 M. The pK_a was calculated from pK_a = pH − log [$f_A/(1 - f_A)$], in which $f_A = (A - A_b)/(A_a - A_b)$ and A is the observed absorbance at a given pH, A_b is the absorbance of the base form of the benzimidate obtained by adding an aliquot of benzimidate to a solution >3 pH units above the pK_a, and A_a is the absorbance of the acidic form of the benzimidate obtained by adding an aliquot of benzimidate to a solution >3 pH units below the pK. For each benzimidate, five to seven measurements were made between 20 and 80% acid. The pK_a of trifluoroethyl benzimidate hydrochloride was found to be 3.70 at ionic strength 1.0 (KCl) from the dependence on pH of the rate constants for hydrolysis between pH 2.2 and 4.2, determined at 245 nm, and the relation $k_{obsd} = k_h[H^+]/(K_a + [H^+])$, in which k_h (6.1×10^{-3} s^{-1}) is the rate constant for hydrolysis between pH 1 and 2.

Rate constants for trifluoroethyl benzimidate decomposition were determined in 0.02 M triethylamine buffers of different acid-base

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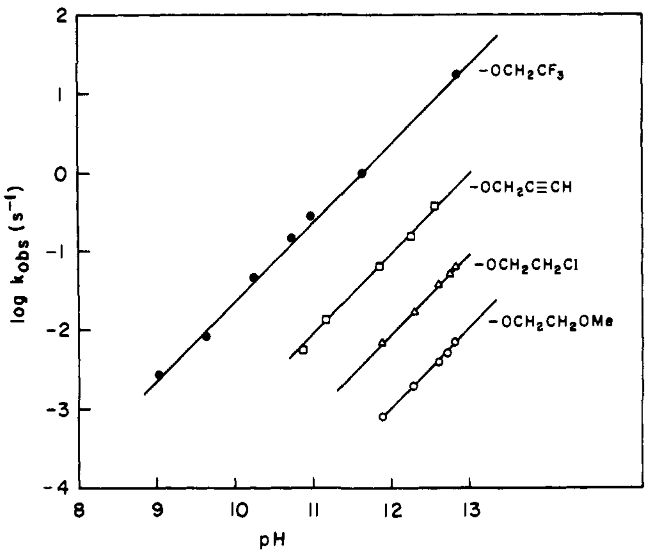


Figure 1. Dependence on pH of the pseudo-first-order rate constants for the cleavage of alkyl benzimidates at 25 °C, ionic strength 1.0 M (KCl). The substituent on the leaving alcohol is indicated.

ratios in water and deuterium oxide (μ = 1.0, KCl). The concentrations of hydroxide and deuteroxide ion were determined from measurements of pH and pD and the empirical relationships $[^-OH] = 1.3 \pm 0.1 \times 10^{(pH-14)}$ and $[^-OD] = 1.5 \pm 0.1 \times 10^{(pD-14.87)}$, respectively, which were determined by measuring the pH or pD of solutions of known hydroxide or deuteroxide concentrations (0.01-1.0 M) at ionic strength 1.0 M. The pD was determined by adding 0.40 to the observed pH meter reading and $10^{-14.87}$ is the ion product of deuterium oxide.[9] Rate constants for ethyl benzimidate decomposition were determined in solutions prepared by adding standardized potassium hydroxide to water and deuterium oxide. After all additions, the deuterium oxide solutions contained 98 ± 1 mol % deuterium oxide.

The slopes of structure-reactivity correlations were calculated by the method of least squares.

The cleavage of trifluoroethyl benzimidate was also examined by mixing a small volume of a solution of benzimidate in water or deuterium oxide buffered with 0.014 M phosphate buffer, pH 6.5, and a large volume of aqueous potassium hydroxide in a stopped-flow apparatus[10] fitted with two 1-mL syringes (for the potassium hydroxide solution) and a 0.1-mL syringe (for the benzimidate solution), such that the ratio of the volumes of the two solutions was 20:1. The block containing the two syringes was fitted into the thermostated cell compartment of a Gilford 2000 spectrophotometer. Each rate constant was measured with four to six runs. The solution of trifluoroethyl benzimidate in deuterium oxide was incubated at least 10 min before the first kinetic run to ensure complete exchange of the nitrogen proton for deuterium. A trifluoroethyl benzimidate solution in deuteriochloroform was prepared by mixing 2.0 mL of 0.7 M dipotassium phosphate in deuterium oxide with 0.14 g of protiotrifluoroethyl benzimidate hydrochloride (final concentration 0.3 M) followed by immediate (<30 s) extraction into $CDCl_3$. Integration of the N-H resonance (δ 8.12) of the ^1H NMR spectrum showed complete (>90%) exchange of deuterium for protium in the trifluoroethyl benzimidate free base.

The products of decomposition of all benzimidates were shown to have ultraviolet spectra identical with those of the corresponding benzonitriles. The decomposition of ethyl benzimidate in dilute potassium hydroxide solutions has been shown previously to yield benzonitrile.[3]

Results

The pseudo-first-order rate constants for the elimination of alcohol from alkyl benzimidates are directly proportional to the hydroxide ion concentration, with no indication of a pH-independent reaction (Figure 1). The second-order rate constants for these reactions are given in Table I. The pseudo-first-order rate constants for the decomposition of substituted ethyl benzimidates increase more rapidly than the concentration of hydroxide ion at high concentrations of hydroxide ion in the range 0.01-0.5 M, as has been observed previously for ethyl benzimidate,[3] and can be described by the rate law

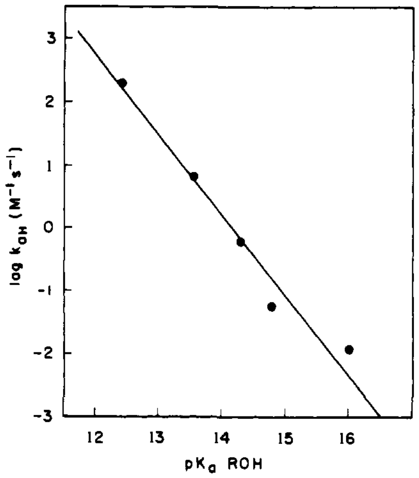


Figure 2. Dependence on the pK_a of the leaving alcohol of the rate constants for base-catalyzed cleavage of alkyl benzimidates at 25 °C.

Table I. Kinetic Constants for the Base-Catalyzed Elimination of Alcohols from Benzimidates at 25 °C, Ionic Strength 1.0 M (KCl)

leaving group	pK_{ROH}[a]	pK_{IMH^+}[b]	pH (D)	$k_{OH(OD)}$,[c] $M^{-1}s^{-1}$
CH_3CH_2O-	16	6.37[d]	12.9-13.6[e]	0.0116
			13.7-14.3[e]	0.0177[f]
$CH_3OCH_2CH_2O$-	14.8	5.65	11.9-12.8[e]	0.059
$ClCH_2CH_2O$-	14.31	5.36	11.9-12.8[e]	0.61
$HC\equiv CCH_2O$-	13.55	4.82	10.9-12.6[g]	6.5
CF_3CH_2O-	12.43	3.70	9.0-12.9[h]	190
			9.5-11.7[h]	220[f]

[a] Reference 15. [b] pK_a for the dissociation of protonated benzimidates. [c] Each rate constant is based on five to seven runs and the concentration of OH^-. [d] Reference 3. [e] The pH was maintained with dilute KOH. [f] In deuterium oxide solution. [g] The pH was maintained with 0.055 M potassium phosphate buffer, pH 10.9-11.2, and with dilute KOH, pH 11.0-12.6. [h] The pH was maintained at 9.0 with 0.006 M potassium borate, at pH 9.7 with 0.02 M potassium bicarbonate, at pH 10.3-11.0 with 0.01 M triethylamine buffer, and at pH 11.0-12.9 with dilute KOH; comparable buffers were used in deuterium oxide.

$$k_{obsd} = k_{OH}[OH^-] + k_s[OH^-]^2$$

Since there is no probable mechanism for the term second order in hydroxide ion and the cleavage of trifluoroethyl benzimidate is first order with respect to hydroxide ion in the range of pH 9-13, the increase in rate at high concentrations of hydroxide ion is attributed to a specific salt effect. Values of k_{OH} and k_s (Table II) were obtained from the intercepts and slopes, respectively, of plots of $k_{obsd}/[HO^-]$ against $[HO^-]$.

The rate constants show a large increase with electron-withdrawing substituents on the leaving alcohol, with a slope of $\beta_{lg} = -1.2$ for a plot of log k_{OH} against the pK_a of the alcohol (Figure 2). However, there is only a small dependence of the rate constants on polar substituents in the benzene ring, with $\rho = 0.5$ (Figure 3).

No evidence for general base catalysis was obtained for the cleavage of trifluoroethyl benzimidate in 0.02-0.50 M carbonate buffers, pH 9.7, nor for the cleavage of 2-methoxyethyl benzimidate in 0.05-0.28 M phosphate buffers, pH 10.7. Small increases of <50% were found for k_{obsd} before pH correction, but no increase was found after corrections for changes in the pH with increasing buffer concentration.

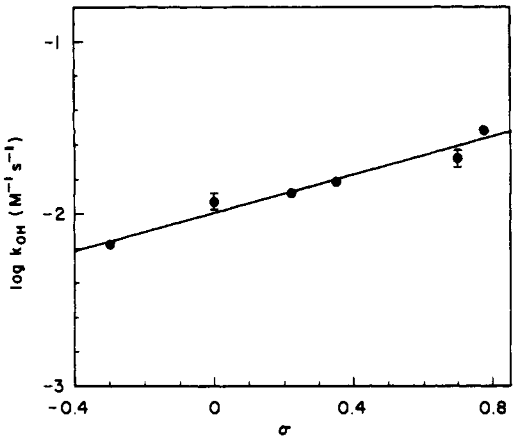


Figure 3. Hammett plot for the base-catalyzed elimination of ring-substituted ethyl benzimidates at 25 °C.

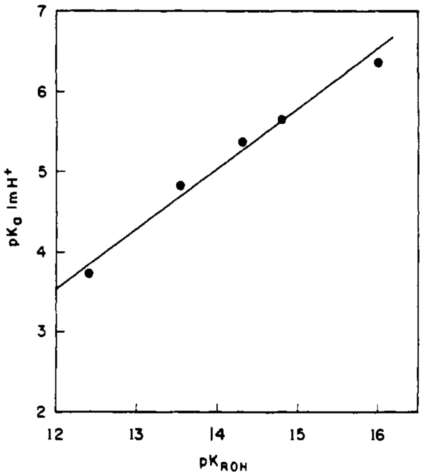


Figure 4. Dependence of the pK_a values of the protonated alkyl benzimidates on the pK_a of the parent alcohol.

The solvent deuterium isotope effect for the cleavage of ethyl benzimidate was found to be $k_{OH}/k_{OD} = 0.66 \pm 0.05$, from experiments in the range 0.1-0.5 M potassium hydroxide concentration. The solvent deuterium isotope effect for the cleavage of trifluoroethyl benzimidate was found to be $k_{OH}/k_{OD} = 0.86 \pm 0.08$ from experiments in a series of triethylamine buffers (Table I).

The primary isotope effect for the cleavage of trifluoroethyl benzimidate was examined by mixing a small volume of benzimidate, which had been equilibrated for 10 min in 0.014 M potassium phosphate buffer (pH 6.5) in water or deuterium oxide, with a large volume of aqueous potassium hydroxide in a stopped-flow apparatus. It was shown by ^{1}H NMR analysis that the NH proton of trifluoroethyl benzimidate free base was rapidly exchanged for deuterium upon incubation in deuterium oxide solution. Identical rate constants of 0.95 ± 0.02 s^{-1} in 0.006 M KOH and 16.5 ± 0.6 s^{-1} in 0.108 M KOH were found for benzonitrile formation with the solutions that had been equilibrated in water and in deuterium oxide. From the absence of a detectable isotope effect it was concluded that exchange of hydrogen for deuterium had occurred immediately upon mixing the deuterium oxide and aqueous potassium hydroxide solutions, before the elimination reaction had proceeded to a measurable extent.

The pK_a values for dissociation of protonated alkyl benzimidates follow $\alpha = 0.74$, based on the pK_a values of the corresponding alcohols (Figure 4). The pK_a values of three alkyl acetimidates[11] give a value of $\alpha = 0.6$. The difference between the value of $\alpha = 0.74$ and the value of $\alpha \simeq 0.2$ that is expected from the additional two atoms between the substituent and the ionizing atom[12] reflects a delocalization of positive charge onto the oxygen atom of the alcohol that may be attributed to the contributing resonance structure **1**. The acid dissociation constants of protonated ring-substituted ethyl benzimidates follow $\rho = 1.7$ (Figure 5). Omitting the points for para substituents (the *p*-methoxy group presumably stabilizes the protonated benzimidate by resonance) the value of ρ is 1.5. These values are considerably larger than the value of $\rho = 1.0$ for the ionization of benzoic acids, possibly because the positive charge of the protonated benzimidate can be delocalized into the benzene ring by resonance.

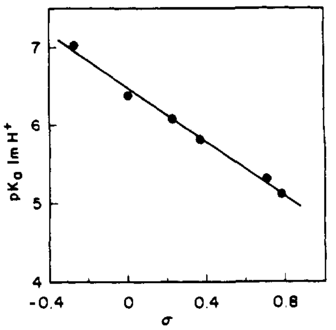
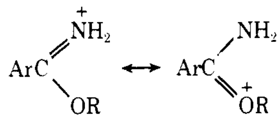


Figure 5. Hammett plot for the pK_a values of protonated ethyl benzimidates.

Table II. Kinetic Constants for the Base-Catalyzed Elimination of Ethanol from Substituted Ethyl Benzimidates [XPhC(=NH)-OCH$_2$CH$_3$] at 25 °C, Ionic Strength 1.0 M (KCl)[a]

substituent	pK_{IMH^+}[b]	10^2k_{OH},[c] $M^{-1}s^{-1}$	10^2k_s, $M^{-2}s^{-1}$	wavelength nm
m-NO$_2$-	5.30	2.1	1.5	240
p-NO$_2$-	5.11	3.0	1.9	290
m-Cl-	5.82	1.5	0.33	240
p-Cl-	6.09	1.3	0.83	250
H	6.37[d]	1.16	0.2	240
p-OMe-	7.01	0.66	0.18	265

[a] The rate constants were obtained from five runs for each compound in 0.01-0.50 M KOH. [b] pK_a for dissociation of the imidate cation. [c] Based on the concentration of added KOH. [d] Reference 3.



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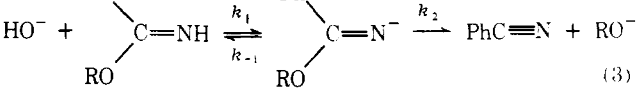
Discussion

Reaction Mechanism. We conclude that the reaction proceeds through an E1cB (reversible) mechanism, in which proton removal occurs in an initial equilibrium step (specific base catalysis) followed by rate-limiting elimination of alkoxide anion.



$$\mathrm{HO^- + Ph(RO)C{=}NH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Ph(RO)C{=}N^- \xrightarrow{k_2} PhC{\equiv}N + RO^-} \qquad (3)$$

(1) The absence of a primary isotope effect for the base-catalyzed cleavage of the >C=NH and >C=ND compounds in water means that exchange of H for D occurs rapidly, as expected for a reversible E1cB mechanism. The H-D exchange is expected to occur entirely by base catalysis in dilute potas-

sium hydroxide, by analogy with the NH exchange of amides.[13] Assuming that exchange is more than tenfold faster than the observed rate of base-catalyzed cleavage for trifluoroethyl benzimidate and[14] that $k_{-1} = 10^{11}$ s^{-1}, then $k_1/k_{-1} = >1900/10^{11} = >1.9 \times 10^{-8}$ M^{-1}, $K_a = k_1K_w/k_{-1} = >1.9 \times 10^{-22}$, and the p$K_a$ of the imidate is <22. An analogous calculation gives pK_a = <26 for ethyl benzimidate, but a more realistic estimate is pK_a = <23, based on the difference of 3.6 units in the pK of ethanol and trifluoroethanol[15] and a fall-off factor for two intervening atoms of 0.2.[12] Limiting values of k_2, the rate constant for cleavage of the imidate anion, are then $k_2 = k_{OH}k_{-1}/k_1 = <10^{10}$ s^{-1} for the trifluoroethyl compound and $k_2 = <10^7$ s^{-1} for the ethyl compound.

(2) The large inverse solvent deuterium isotope effect of $k_{OH}/k_{OD} = 0.66$ for ethyl benzimidate means that the proton is largely or completely transferred from NH to HO$^-$ in the transition state, as expected for a reversible E1cB mechanism, and is inconsistent with a concerted or irreversible E1cB mechanism, which would be expected to exhibit a normal isotope effect.[16] Similar inverse isotope effects of k_{OH}/k_{OD} = 0.56 for the cleavage of aryl carbamates and k_{OH}/k_{OD} = 0.42–0.80 for the cleavage of aryl phenylmethanesulfonates through a reversible E1cB mechanism have been reported previously.[17] The isotope effect for trifluoroethyl benzimidate of $k_{OH}/k_{OD} = 0.86$ is also inverse, but less so than for the ethyl compound. This difference might possibly reflect an earlier transition state with stronger hydrogen bonding of the nitrogen anion to water for the trifluoroethyl compound.

(3) There is no detectable general base catalysis of the elimination reaction. An E2 or irreversible E1cB elimination reaction would be expected to proceed with general base catalysis because proton transfer takes place in the rate-determining step. The absence of general base catalysis also means that there is no detectable general acid catalysis of the expulsion of alkoxide ion from the intermediate anion, which is kinetically equivalent to general base catalysis.

$$v = k_B[B][Ph(RO)C{=}NH] = k_{BH^+}[BH^+][Ph(RO)C{=}N^-] \quad (4)$$

This kind of catalysis is a general mechanism for the elimination and addition of alcohols and water, but is usually overshadowed by the uncatalyzed elimination–addition of alkoxide and hydroxide ions at high pH values.[18]

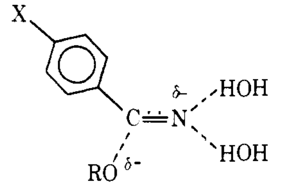
From the absence of significant buffer catalysis (<50% rate increase) of the elimination of trifluoroethoxide ion from trifluoroethyl benzimidate in bicarbonate buffer (0.02–0.5 M, 50% base, pH 9.69) a limit of $\beta \geqslant 0.7$ (or $\alpha \leqslant 0.3$ for general acid catalysis) can be set using

$$\beta_{min} = \frac{14 - pH - \log f + \log [B]}{15.74 - pK_{BH}} \quad (5)$$

in which f is the fractional increase in the observed rate constant which could have been detected on increasing the concentration of the basic form of the buffer from zero to [B], and pK_{BH} is the pK of the conjugate acid of B.[19] For this reaction f is taken as 0.5 at 0.25 M carbonate. However, eq 5 is based on the assumption that hydroxide ion falls on the same Brønsted line as other bases; if it fell above the line general base catalysis with $\beta < 0.7$ could exist for other bases and still be undetected.

The rate constants in the range $k_2 = 10^7$–10^{10} s^{-1} for breakdown of the imidate anion are small enough so that a concerted mechanism of catalysis is not enforced by the absence of a significant lifetime for this intermediate. However, the fact that no leveling of the observed rate constants is observed with increasing concentrations of hydroxide ion means that proton transfer from the imidate to hydroxide ion and buffer bases is thermodynamically unfavorable. The N-protonated benzonitrile that would be formed by elimination without proton transfer is strongly acidic, with an estimated[20] pK_a of −11, so that there is a change in pK of the NH proton of some 30 units in this reaction and proton transfer to hydroxide ion or buffer bases from this product is strongly favored thermodynamically. Therefore, a concerted reaction mechanism is not excluded by the requirement that a proton-transfer step should change from unfavorable to favorable during the course of the reaction in order to provide a driving force for concerted catalysis.[21] Evidently this reaction chooses the common course of proceeding through a stepwise rather than a concerted mechanism when the intermediate is stable enough that a stepwise mechanism is possible; i.e., when a concerted mechanism is not enforced by the nonexistence of the intermediate. Similarly, general acid and base catalysis of the cleavage of formaldehyde hemiacetals is enforced, in at least some cases, by the negligible lifetime of the dipolar "intermediate", T$^{\pm}$, that would be required for stepwise reaction mechanisms, but the anionic intermediate T$^-$ has a significant lifetime and the hydroxide ion catalyzed reaction proceeds through this intermediate in a stepwise mechanism.[18] It should be emphasized that the requirement that a proton-transfer step change from unfavorable to favorable is a necessary but not a sufficient condition for a concerted reaction mechanism, as is illustrated by this nitrile-forming elimination reaction.

Structure and Properties of the Transition State. The data are consistent with a transition state i in which proton removal from the imidate is complete or almost complete, the nitrogen anion is weakly hydrogen bonded to solvent molecules, there is a large amount of C–O bond cleavage and charge development on the leaving oxygen atom, and a considerable amount of negative charge is still "seen" by substituents on the benzene ring.



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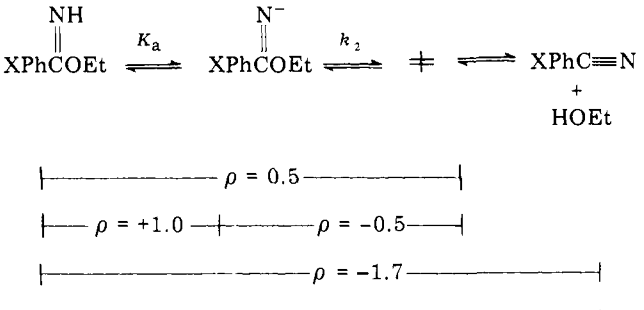
There is a nonadditivity or imbalance of the substituent effects on the leaving alkoxide ion and the central carbon atom. On the one hand, the value of $\beta_{lg} = -1.2$ means that there is a large change in charge on the leaving alkoxide ion that is seen by polar substituents on going from the imidate to the transition state, even larger than that for the ionization of the alcohol. This means that there is a large negative charge on the leaving oxygen atom and a large amount of C–O bond cleavage in the transition state. Similar behavior is found for the E1cB elimination of esters of acetoacetate and *N*-phenylcarbamate, which have values of β_{lg} in the range of −1.2 to −1.4.[22] The more negative values of β_{lg} for some of these compounds do not imply a later transition state than for imidate decomposition because β_{lg} measures the *change* in charge on the leaving oxygen atom between the starting material and the transition state and there is a large positive charge (β_{eq} = 0.7) on this oxygen atom in esters;[23] this charge is presumably smaller in imidates because C═NH is less electron withdrawing than C═O. The large inverse solvent deuterium isotope effect for the cleavage of ethyl benzimidate means that proton transfer from nitrogen to hydroxide ion is almost complete.[16] If the nitrogen anion were still strongly basic in the transition state, the transition state should be stabilized by hydrogen bonding of this anion to an acid BH$^+$, which would appear kinetically as general base catalysis (eq 4). The absence of such catalysis is consistent with a late transition state in which most of the negative charge has been transferred to the leaving alkoxide ion.

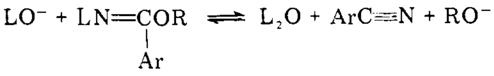
On the other hand, the small rate *increase* with electron-withdrawing substituents on the central carbon atom, with $\rho = +0.5$, and the large inverse solvent isotope effect suggest an early transition state for C–O bond cleavage; these results appear to be inconsistent with a late transition state in which C–O cleavage and formation of a solvated alkoxide ion are almost complete. The overall reaction is aided by electron donation ($\rho = -1.7$ for the equilibrium constant in methanol)[24] so that a late transition state should also be stabilized by electron-donating substituents, contrary to the experimental result. The substituent effects on this system may be summarized as follows:



$$\overset{\overset{\mathrm{NH}}{\|}}{\mathrm{XPhCOEt}} \xrightleftharpoons{K_a} \overset{\overset{\mathrm{N^-}}{\|}}{\mathrm{XPhCOEt}} \xrightleftharpoons{k_2} \ddagger \rightleftharpoons \mathrm{XPhC{\equiv}N} + \mathrm{HOEt}$$

The value of ρ for the initial dissociation of benzimidates to the anion is expected to be close to 1.0, based on $\rho = 1.0$–1.1 for the dissociation of trifluoroacetophenone hydrates[25] and benzoic acids and on the linear correlation of the rate constants for base-catalyzed exchange of the NH proton of amides with the dissociation constants of the parent carboxylic acids[13] (this reaction involves rate-limiting exchange after formation of the amide anion). The ρ value of 0.5 for k_{OH} then gives $\rho = -0.5$ for k_2, the rate constant for elimination of alkoxide ion from the benzimidate anion. This value of $\rho = -0.5$ is only a small fraction of the value of $\rho = -2.7$ for complete conversion of the benzimidate anion to the nitrile (based on $\rho = 1.0$ for K_a and $\rho = -1.7$ for the overall reaction). Thus, there is an apparent imbalance or nonadditivity of the substituent effects on the central carbon atom, which suggest an early transition state, and those on the leaving group, which suggest a very late transition state.

Formation of the basic anions LO^- and RO^- is approximately twofold less favorable in deuterium than in protium solvent, so that the complete formation of RO^- from LO^- should exhibit little or no solvent isotope effect.[16,26] The large observed inverse isotope effect of $k_{OH}/k_{OD} = 0.66$ for ethyl



$$\mathrm{LO^- + LN{=}\underset{\displaystyle \mathrm{Ar}}{C}OR \rightleftharpoons L_2O + ArC{\equiv}N + RO^-}$$

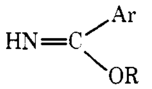
benzimidate cleavage means, therefore, that the alkoxide ion in the transition state does not resemble the alkoxide ion product. This is an apparent contradiction with the large value of $\beta_{lg} = -1.2$.

We suggest two complementary explanations for this imbalance. (1) The large substituent effect and inverse solvent isotope effect can both be accounted for by incomplete solvation of the leaving alkoxide ion in the transition state. If the developing negative charge on oxygen is incompletely solvated, a larger charge development will be seen by substituents on the alcohol for a given amount of C–O bond cleavage, with a correspondingly more negative value of β_{lg}. The large solvent deuterium isotope effect on the formation of lyoxide and alkoxide ions is caused by solvation of the basic oxy anion through hydrogen bonding to the solvent.[26] The large inverse solvent isotope effect for the cleavage of ethyl benzimidate catalyzed by hydroxide ion requires, therefore, that most of the solvation of the hydroxide ion be lost and that little or no solvation of the leaving alkoxide ion be developed in the transition state. The same explanation has been proposed previously for the large negative values of β_{lg} and the imbalance of substituent effects in the base-catalyzed expulsion of alkoxide and hydroxide ions from RNHCHR″OR′ and HOCHROR′.[5,18] In the reverse direction, the much smaller values of β_{nuc} for the attack of alkoxide than of phenoxide anions on esters and thiol esters has been ascribed, at least in part, to a larger requirement for desolvation of alkoxide than of phenoxide ions for attack on the carbonyl group (desolvation is aided by electron-withdrawing substituents and will therefore decrease the observed value of β_{nuc}).[27]

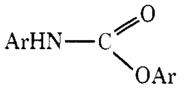
(2) Even if C–O bond cleavage is almost complete, a negative charge will still be seen by a polar substituent on the benzene ring as long as the leaving alkoxide ion has not diffused away, so that the value of ρ for formation of the transition state will always be more positive than that for formation of the separated products. The ρ value of 1.1 for the ionization of trifluoroacetophenone hydrates[25] provides a measure of the approximate magnitude of the substituent effect that would be expected from the introduction of a localized negative charge next to the central carbon atom in the transition state. A similar electrostatic effect has been proposed to account for the observed substituent effects on the addition of sulfite dianion to substituted acetophenones and on reactions of anionic nucleophiles with substituted benzyl halides.[28] In the reverse, addition direction the solvation of the anion by water in the ground state has been partially replaced by "solvation" by the electrophilic carbon atom in the transition state, which is aided by electron-withdrawing substituents on this atom. The situation is analogous to that for "reaction complexes," which also have been proposed to exhibit significant substituent effects on their formation,[29] except that the transition state is at a potential maximum rather than a minimum along the reaction coordinate.

These solvation and electrostatic effects mean that values of β_{nuc}, β_{lg}, and ρ for reactions of oxy anions cannot be interpreted directly as quantitative measures of the percent of C–O bond formation or cleavage in the transition state. Comparisons of the effects of substituents on the different reacting atoms and determination of isotope effects may permit an estimation of the relative amounts of bond cleavage and formation, solvation, and electrostatic effects in the transition state.

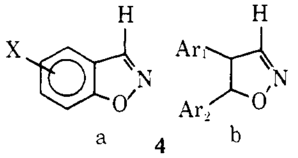
Comparison with Other Systems. It is of interest to compare the nitrile-forming elimination of imido esters, **2**, with the related elimination reactions of **3–6**. Benzimidate and carbamate



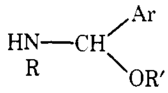
2



3



a **4** b



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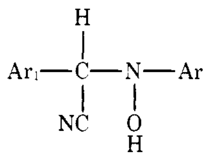

6

esters undergo elimination through a (reversible) E1cB mechanism. This mechanism is made possible by the stability of the intermediate anion, which is formed with a pK_a of <23 for benzimidates and 12–15 for carbamates,[22] and decomposes with a rate constant of 10^7–10^{10} s^{-1} for benzimidates. However, deuterium isotope effects, structure-reactivity relationships, and estimated lifetimes of 10^{-15} s for the "intermediates" that would be required for a stepwise elimination of HOR′ from **5** provide evidence for a concerted mechanism for elimination from isoxazoles (**4**)[30] and carbinolamines (**5**).[4,5] The anionic "intermediates" in these reactions are less stable as a consequence of the pK_a of ~27 for several carbinolamines (**5**), the good leaving ability of the phenolate anion in **4a**, and the estimated lifetime of 10^{-15} s for the anion of **5**. It has been estimated that the carbinolamine addition compound of acethydrazide and *p*-chlorobenzaldehyde undergoes elimination $>10^3$ faster than a proton can be removed from the nitrogen atom, so that it appears that the compound falls apart through a concerted reaction mechanism before proton transfer to give the anion is completed.[4,5] Thus, the available data for this series of reactions are consistent with the hypothesis that the reaction proceeds through a concerted mechanism when the anion becomes so unstable that a stepwise mechanism through an anionic intermediate with a significant lifetime is not possible. The absence of a significant lifetime for an intermediate species is a sufficient, but perhaps not a necessary, condition for a concerted reaction mechanism (in contrast to the development of a thermodynamically favorable proton transfer,[21] which is a necessary but not sufficient condition for a concerted mechanism).

The anion of the carbinolamine **5** decomposes to the imine much faster than the anion of **2** decomposes to the nitrile in spite of the fact that the nitrogen atom of **5** is attached to a strongly electron-withdrawing substituent that stabilizes the anion, i.e., the amide group of acethydrazide or similar groups of other hydrazides. This difference may reflect the fact that the difference in the bond energies of the C–N and C=N bonds favors elimination by 10 kcal mol^{-1} more than the difference between the C=N and C≡N bonds.[31] The absence of a similar difference in the overall rates of olefin-forming and acetylene-forming elimination reactions may be a consequence of the easier removal of the more acidic proton from sp^2 carbon in the latter reaction.

The dehydration of **6** exhibits a large primary isotope effect and probably proceeds through an irreversible E1cB mechanism, with rate-determining proton abstraction, although an E2 mechanism is possible for at least some compounds in this series.[32] This reaction can be regarded as an intermediate case, in which the greater acidity and poorer leaving group of **6** compared with **4** stabilize the intermediate anion sufficiently to overcome the higher intrinsic reactivity of the elimination to form C=N.

References and Notes

(1) Supported by grants from the National Science Foundation (BG-31740) and the National Institutes of Health (GM20888). H.F.G. was an American Cancer Society Postdoctoral Fellow.

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$$>\mathrm{C{=}NH} \underset{k_{-e}}{\overset{k_e}{\rightleftharpoons}} >\mathrm{C{=}NH_2^+} + \mathrm{OH^-}$$

$k_e = k_{-e}K_w/K_a$. Taking $k_{-e} = <5 \times 10^{10}$ M^{-1} s^{-1}, $k_e = <2.5$ s^{-1} and $k_{OH}/k_e = 190/>2.5$ s^{-1} = >75.

(14) This kind of calculation is sometimes made[13] assuming a value of $k_{-1} = 10^{10}$ s^{-1}, by analogy with the second-order rate constant close to 10^{10} M^{-1} s^{-1} for thermodynamically favorable proton abstraction by hydroxide ion (Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1–19). Although the exact value of k_{-1} remains uncertain, we prefer the estimate of 10^{11} s^{-1} for the first-order rate constant of a thermodynamically favorable proton transfer to the solvent. This can be regarded as equivalent to the assumption that the "effective molarity" of solvent around the base is ~10 M for a diffusion-controlled proton transfer.

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