Carboxylic Acid Participation in Amide Hydrolysis. Reactivity of Intermediates in the Internally Catalyzed Hydrolysis of N-Substituted 2,3-Dimethylmaleamic Acids[1]

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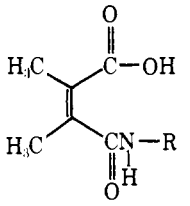
Abstract: Analysis of the pH–rate profiles for hydrolysis of *N*-alkyl-2,3-dimethylmaleamic acids (**1–4**) permits determination of the reactivity and stability of the tetrahedral adduct formed in the internal addition reaction. The dependence of rate on solution acidity for conversion of **1–4** to the corresponding amine and 2,3-dimethylmaleic anhydride between pH 5 and 1 M acid was measured at 15 °C. The complex variation of the observed first-order rate constant with acidity is due to changes in rate-determing steps and changes in mechanism due to proton transfer processes. Kinetic analysis, based on steps being competitive with proton transfer and estimates of pK_a of intermediates, reveals that: (1) expulsion of amine from the zwitterion form of the intermediate occurs with a rate constant of ca. 10^7 to 10^9 s^{-1}, the weakest base leaving fastest ($\beta_{LG} = -0.61$); (2) conversion of the zwitterion to the uncharged intermediate by a "proton switch" occurs with a rate constant of ca. 10^7 s^{-1} ($\beta_{LG} = 0$); (3) cyclization of the amic acid to the intermediate occurs with an equilibrium constant of ca. 10^{-4} to 10^{-5}, with the least basic compound most favorable toward cyclization ($\beta_{LG} = -0.50$). The nature of the elimination process, which is stepwise in this series, is compared with that in the reaction of anilic acids (aniline leaving groups), which is concerted. It is proposed that delocalization of electron density into π orbitals permits bypassing the zwitterion in the latter case.

Carboxylic acids catalyze the hydrolysis of neighboring amides by a reaction pathway involving nucleophilic addition by the carboxyl group.[2,3] The rate-determining step in this reaction involves conversion of the addition intermediate to the amine and anhydride.[4,5] It has been shown that monoamides derived from 2,3-dimethylmaleic acid are highly reactive and that, under certain circumstances, proton transfer from the intermediate can be rate determining.[6] This kinetic behavior can be used as a basis for experiments which measure the reactivity of intermediates. Changes in rate-determining steps occur when another process becomes comparable to proton transfer.

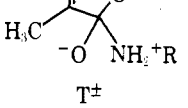
We have been able to analyze quantitatively the acidity dependence of the rate of conversion of 2,3-dimethylmaleamic acids **1–4** to the corresponding amine and an equilibrium



1–4

1, R = $-CH_2CH_2CH_3$
2, R = $-CH_2CH_2OCH_3$
3, R = $-CH_2CH_2F$
4, R = $-CH_2\overset{O}{\overset{\|}{C}}OC_2H_5$

mixture of 2,3-dimethylmaleic anhydride and acid. Kinetic competition between steps involving only proton transfer and those involving explusion of the leaving group from the addition intermediate $T^{\pm}$ are directly related to the response of observed



$T^{\pm}$

rates of reaction to changes in the acidity of the hydrolysis medium. This yields rate constants and substituent effects for the specific processes which determine the reaction patterns of the tetrahedral intermediates.

Combination of these data and estimates of the acidity of intermediates permits evaluation of the magnitudes of rate constants for intramolecular proton transfer and leaving group expulsion as well as equilibrium constants for formation of the intermediates. Relationships between these data and leaving group basicity permit the energetics of the reaction to be analyzed directly in terms of free energy relationships which could only be estimated previously.

Experimental Section

Materials. Alkyl-substituted 2,3-dimethylmaleamic acids were prepared from the reaction of 2,3-dimethylmaleic anhydride and the appropriate amine as described by Kirby et al.[6] The products were most readily handled when prepared as salts of the amine from which the amide is derived.

Kinetics. Ionic strength was maintained at 1.0 with potassium chloride. Reactions were followed by monitoring the UV absorbance change due to hydrolysis of the amide at the isobestic point of 2,3-dimethylmaleic acid and the 2,3-dimethylmaleic anhydride, 247 nm (since the subsequent reaction of anhydride to acid complicated the observed reaction). No spectral shift for this isobestic occurred with addition of buffers. Temperature was maintained at 50.0 ± 1 °C in the cell holder of a Unicam SP 1800 A spectrophotometer equipped with an AR 25 recorder and a Heto constant temperature circulator. First-order rate constants were obtained from the slope of log [OD(t) − OD(∞)] vs. elapsed time. All data were fitted to a best least-squares line by using a Texas Instruments SR 56 calculator. Data were obtained for at least 5 half-lives with correlation coefficients in the least-squares analysis of at least 0.999. Extrapolation to the "no buffer" rate introduces an uncertainty of about 10%. Reactions were initiated by adding 5 μL of the substrate in acetonitrile to 3 mL of buffer which was contained in a quartz cell incubated in the sample holder of the spectrometer.

All pK_a values were taken from a published compilation.[7] For each compound, first-order rate constants were obtained under the following conditions: hydrochloric acid (1, 0.32, 0.1, 0.032, 0.010 M); for all other buffers, concentrations used were 0.05, 0.04, 0.03, 0.02, 0.01 M. The pH and buffers used were: 2.45, cyanoacetate; 2.73, 3.03, 3.33, chloroacetate; 3.60, 3.90, 4.20, formate; 4.30, 4.60, 4.90, acetate. A value of 4.0 for the pK_a of **1–4** was used. This is consistent with reported values[6] and our own measurements for *N*-alkylmaleamic acids. Variation of this value by ±0.2 unit does not affect the kinetic analysis.

Results

pH–rate profiles for conversion of primary alkyl dimethylmaleamic acids (**1–4**) to dimethylmaleic anhydride are presented in Figure 1. The data were obtained by extrapolation of first-order reaction rates measured as described in the Experimental Section. Low buffer concentrations were used to avoid problems associated with saturating buffer effects.[6]

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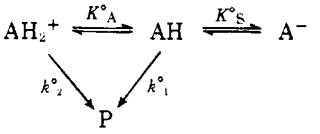
Table I. Kinetic Constants for Reactions of *N*-Alkyl-2,3-dimethylmaleamic Acids[a]

compound	1	2	3	4
pK_u (≡pK_S)	4.0	4.0	4.0	4.0
pK_u of leaving group	10.53	9.20	8.90	7.75
$K°_A$	2.48×10^{-3}	5.89×10^{-3}	1.1×10^{-2}	5.2×10^{-2}
$k°_1$, s^{-1}	9.15×10^{-2}	4.92×10^{-2}	4.24×10^{-2}	1.02×10^{-2}
$k°_2$, s^{-1}	1.64×10^{-1}	3.20×10^{-1}	3.50×10^{-1}	6.25×10^{-1}
K_1	7.6×10^{-6}	3.2×10^{-5}	4.6×10^{-5}	1.7×10^{-4}
K_S, M^{-1}	1.8×10^{4}	9.0×10^{2}	4.2×10^{2}	2.9×10^{1}
k_2, $M^{-1}\,s^{-1}$	1.2×10^{3}	2.2×10^{3}	2.0×10^{3}	2.5×10^{3}
k_{-2}, $M^{-1}\,s^{-1}$	1.5×10^{10}	1.5×10^{10}	1.5×10^{10}	1.5×10^{10}
k_4, s^{-1}	2.9×10^{4}	1.8×10^{3}	1.1×10^{3}	6.0×10^{1}
k_{-4}, s^{-1}	2.1×10^{7}	1.4×10^{7}	2.0×10^{7}	1.2×10^{7}
k_3, s^{-1}	1.7×10^{7}	7.5×10^{7}	1.5×10^{8}	7.7×10^{8}

[a] Experimental points were determined at 15 °C as described in the Experimental Section.

Scheme I



The rate-acidity behavior of **1–4** from pH 2 to 5 is more complex than the cases that Kluger and Lam observed for maleanilic acids[8] and norbornenylanilic acids.[9] In those series, the observed rate constants directly reflected a decrease in reaction rate that corresponded to dissociation of the carboxylic acid moiety. In the case of compounds **1–4**, the downturn in observed rate constant with decreased medium acidity does not simply follow a titration curve for the substrate.[6] This increased kinetic complexity yields information not available from more "well-behaved" systems.

In order to evaluate the data, we chose first to determine an empirical rate law and to optimize parameters for a best fit. The data for **4** roughly reflect two plateaus and two apparent dissociation constants. Such an empirical rate law is that for a reaction of a diprotic acid in which the diacid and monoacid forms may produce product. For **1–3**, the pH-rate profiles are also accommodated by this scheme, which explains why the "apparent pK_a" in Figure 1 (such as for **3**) is not the true pK_a. The rate equation for Scheme I is:

$$\frac{d[P]}{dt} = k°_2[AH_2^+] + k°_1[AH] = k_{obsd}[A_T] \qquad (1)$$

Defining $K°_A$ and $K°_S$ as acid dissociation constants and

$$[A_T] = [AH_2^+] + [AH] + [A^-] \qquad (2)$$

gives eq 3 if $K°_S \ll K°_A$

$$k_{obsd} = \frac{k°_1K°_A + k°_2[H^+]}{(K°_A + [H^+])} \cdot \frac{1}{(1 + K°_S/[H^+])} \qquad (3)$$

We define the observed value in 1 M HCl as $k°_2$. $K°_S$ is the macroscopic dissociation constant of the substrates (pK_a = 4.0).[6] Values for $K°_A$ and $k°_1$ were determined by iterative least-squares analysis of the data by using eq 3 with a standard curve fitting program, iterating with a digital computer. The results obtained are listed in Table I and were used to plot the curves in Figure 1 according to eq 3.

Relation of Data and Mechanism. Kirby et al. proposed a stepwise mechanism of reaction for these compounds in order to explain the phenomenon of saturating buffer catalysis and nonlinear Brønsted plots which they observed.[6] However, no rate law was derived. The Kirby mechanism is summarized in Scheme II.

This scheme can also explain qualitatively the response of the observed hydrolytic rate to variation of acidity. At high acidity, production of zwitterion $T^{\pm}$ is rapid due to the avail-

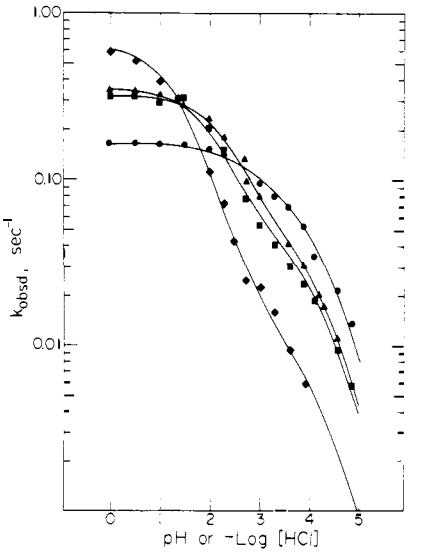
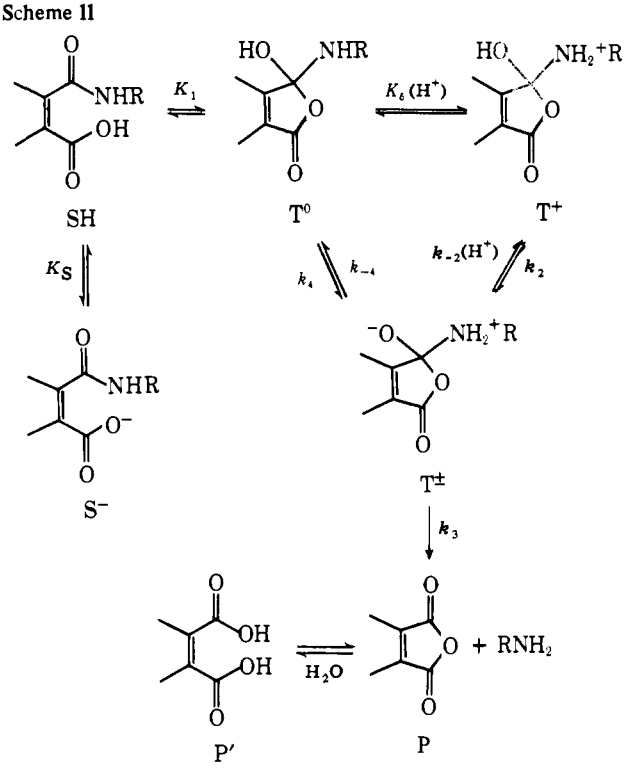


Figure 1. Observed first-order rate constants as a function of solution acidity for **1** (●), **2** (■), **3** (▲), and **4** (◆).

Scheme II



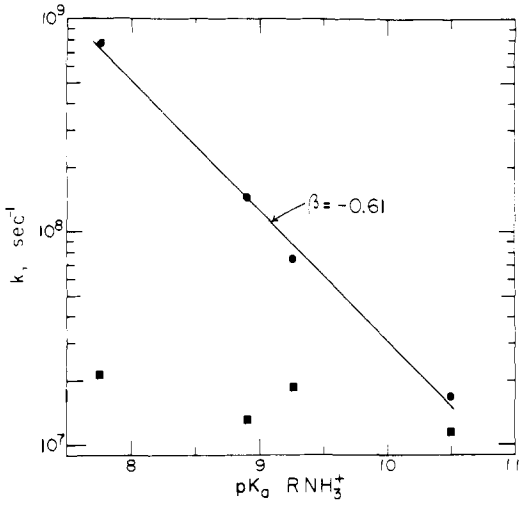


Figure 2. The variation of k_3 (●), amine explusion from T±, and k_{-4} (■), proton switch from T± to T⁰, as a function of leaving group conjugate acid pK_a for **1–4**. pK_a (**1**) = 10.53, pK_a (**2**) = 9.20, pK_a (**3**) = 8.90, pK_a (**4**) = 7.75.

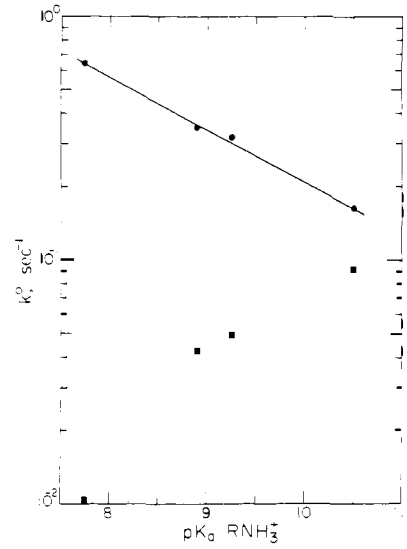


Figure 3. Observed rate constants $k°_2$ (●) and $k°_1$ (■) as a function of leaving group conjugate acid pK_a.

ability of an acid-catalyzed pathway via k_2. Hence, where $k_{-2}(H^+) > k_3(>k_{-4})$, the rate-determining step is k_3 and the overall reaction rate law is independent of acid. As acid concentration is decreased, the k_2 step becomes rate determining $[k_3 > k_{-2}(H^+)\ (>k_{-4})]$. The change in rate-limiting step causes a downward turn of the pH-k_{obsd} profile and an apparent dependence of observed rate on hydrogen ion. As acidity is decreased further, the "proton switch" step, k_4, becomes favorable compared with formation of T^+ from T^0 and conversion of T^+ to T± via k_2; that is, $k_3 > k_{-4} > k_{-2}(H^+)$. This change in mechanism is responsible for an apparent end to the decrease in rate with decreased acidity and a turn toward a level value. However, the dissociation of the substrate to an inactive form ($K°_S$) causes a net decrease in overall rate in the region where the leveling occurs, resulting in a further downturn.

The rate law for this system can be derived by using the fact that K_1 reflects an unfavorable equilibrium. T± can be treated as a steady-state intermediate. Under most circumstances, it is not in equilibrium with other reactive species (except when k_3 is rate determining). Defining:

$$K_1 = [T^0]/[SH] \tag{4}$$

$$K_5 = [T^+]/[H^+][T^0] \tag{5}$$

Then

$$\frac{d[P]}{dt} = k_3[T^\pm] = k_{obsd}([SH] + [S^-]) \tag{6}$$

$$\frac{d[T^\pm]}{dt} = 0 = k_4[T^0] + k_2[T^+] - (k_3 + k_{-2}[H^+] + k_{-4})[T^\pm] \tag{7}$$

Solving by substitution gives

$$k_{obsd} = \frac{(K_1k_3k_4/k_{-2}) + (K_1k_3k_4/k_{-4})[H^+]}{[(k_{-4} + k_3)/k_{-2}] + [H^+]} \times \frac{1}{(1 + K°_S/[H^+])} \tag{8}$$

Both the empirical equation (eq 3) and the mechanistic expression (eq 8) yield the same observed dependence on acid concentration for k_{obsd}. Thus, the empirical constants used to fit the data (Table I) can be related to the mechanistic constants, where $K°_S$ is the same quantity in both expressions:

$$k°_1K°_A = K_1k_3k_4/k_{-2} \tag{9}$$

$$k°_2 = K_1k_3k_4/k_{-4} \tag{10}$$

$$K°_A = (k_{-4} + k_3)/k_{-2} \tag{11}$$

In order to obtain values for k_3 and k_{-4}, a value for k_{-2} must be used. Since the step measured by k_{-2} involves transfer of a proton from hydronium ion to an alkoxide ion, the step must occur at or near the rate for diffusion of a proton in water. For simplicity, we take the value of k_{-2} to be $1.5 \times 10^{10}\ M^{-1}\ s^{-1}$.[10] Since k_3 and k_{-4} are determined relative to k_{-2}, any adjustment in the value of k_{-2} is readily incorporated and relative accuracy remains. Thus, from (9) and (10):

$$k_{-4} = 1.5 \times 10^{10} \times k°_1K°_A/k°_2 \tag{12}$$

$$k_3 = (1.5 \times 10^{10} \times K°_A) - k_{-4} \tag{13}$$

Values of k_3 and k_{-4} for compounds **1–4** are summarized in Table I. These are plotted logarithmically in Figure 2 as a function of leaving group pK_a. The linear plot for k_3 has a slope (β_{LG}) of −0.61. The value for k_{-4} appears to be independent of the substrate ($\sim 1.7 \times 10^7\ s^{-1}$).

Values for k_2 and k_4 can be obtained from the observed data if the equilibrium constants relating T^0, T^+, and T± can be evaluated. These equilibria involve only changes in protonation states and are thus accessible by conventional acidity estimation procedures. The *relative* values for log k_2 in the series of compounds are directly available from the β value for the pK_a of ionization of T^+ as a function of R, which we have previously estimated[9] to be 0.1.

Taking the logarithm of eq 10 and differentiating gives eq 14, where $K_4 = k_4/k_{-4}$:

$$\frac{\partial \log K_1}{\partial pK_a} + \frac{\partial \log k_3}{\partial pK_a} + \frac{\partial \log K_4}{\partial pK_a} = \frac{\partial \log k°_2}{\partial pK_a} \tag{14}$$

Microscopic reversibility in Scheme II requires that where $K_2 = k_2/k_{-2}$:

$$\frac{\partial \log K_4}{\partial pK_a} = \frac{\partial \log K_5}{\partial pK_a} - \frac{\partial \log K_2}{\partial pK_a} = 1.0 - 0.10 = 0.90 \tag{15}$$

Equation 14 becomes

$$\frac{\partial \log K_1}{\partial pK_a} = \frac{\partial \log k°_2}{\partial pK_a} - \frac{\partial \log k_3}{\partial pK_a} - 0.90 \tag{16}$$

A plot of log $k°_2$ vs. pK_a (Figure 3) gives a slope of −0.21.

Therefore

$$\frac{\partial \log K_1}{\partial pK_a} = -0.21 + 0.61 - 0.90 = -0.50 \qquad (17)$$

Discussion

The kinetic reaction patterns of *N*-alkyl-2,3-dimethylmaleamic acids are systematic and can be analyzed in terms of a common mechanism. A good fit of data to equations generated from the proposed mechanism (Scheme II) suggests that the mechanism is correct. Previously, no direct kinetic relationship between pH-rate profiles and mechanisms had been established for reactive alkylmaleamic acids. Most important is the observation that changes in rate-limiting step and changes in mechanism with pH permit direct analysis of rate and equilibrium constants.

Cyclization Equilibria. The formation of tetrahedral intermediate T^0 from the corresponding maleamic acid is an unfavorable process due to the loss of the resonance stabilization of the amide moiety. The proximity of the carboxylic acid to the amide overcomes most of any entropic barrier to the addition process. The enforced proximity of amide and carboxyl brought on by the rigid stereochemistry of the maleic backbone must lead to some undesirable steric effects in the acid-amide which are exacerbated by the presence of methyl groups on positions 2 and 3. The magnitude of K_1 and its dependence on the basicity of the amine substituent are quantities necessary for an analysis of the energetics of the system.

From rearranging eq 10, we can arrive at eq 18

$$K_1 = k^\circ_2/(k_3K_4) \qquad (18)$$

Values for k°_2 and k_3 are given in Table I. To estimate K_4, we need to estimate the two protonic equilibria, K_5 and K_2. The relative values of K_1 for different amine substituents have already been derived in eq 17. Therefore an estimate of K_1 for any compound can serve to generate a value for any of **1-4.**

The pK_a for T^+ going to T^0 should be accessible by considering the effect of the dioxyalkyl substituent upon the pK_a of the unsubstituted alkylammonium ion. Guthrie has shown[11] that, for ions of the type $RC(OH)_2NH(CH_3)_2^+$, the pK_a for loss of the amine proton is given by:

$$pK_a = 6.10 - 1.75\sigma^* \qquad (19)$$

Changing from dimethylamine to *n*-propylamine decreases the starting pK_a by 0.1 unit; therefore, for amines of the type $RC(OH)_2NH_2C_3H_7^+$, eq 20 should be used:

$$pK_a = 6.00 - 1.75\sigma^* \qquad (20)$$

The σ^* value for $HO_2CHC{=}CH-$ is 1.0;[12] therefore, the pK_a is about 4.25. That is, K_5 (for **1**) is about 1.8×10^4 M^{-1} since it is the inverse of the acid dissociation constant.

The pK_a for loss of a proton from the hydroxyl group of the same type of ion has been proposed by Guthrie[11] to follow eq 21:

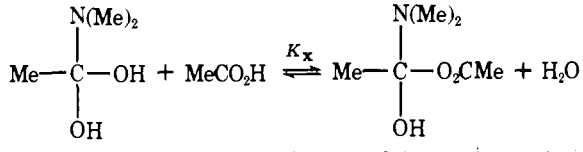
$$pK_a = 8.4 - 1.32\sigma^* \qquad (21)$$

Therefore, the pK_a for the loss of the hydroxyl proton of compound **1** is 7.1 by this approximation, or $K_2 = 7.9 \times 10^{-8}$ M. From the product of values for K_2 and K_5, K_4 is approximately 1.4×10^{-3}

We use values for k_3 and k°_2 from Table I and the value of K_4 estimated above to arrive at values of the cyclization equilibrium constant, K_1. Using the data for **1** and eq 18 yields a value for K_1 of 7.0×10^{-6}. Since $\partial \log K_1/\partial pK_a = -0.50$, for the least basic compound, **4**, K_1 will be larger by a factor of 25 ($K_1 = 1.8 \times 10^{-4}$), since the pK_as differ by 2.8 units. It is possible that a very weakly basic amine (such as dinitroaniline) could lead to a situation in which K_1 is sufficiently large to cause an observable amount of intermediate to form.

The internal addition of the carboxyl of **1** to its amide center has a K_1 value of 7.0×10^{-6}. The effective concentration of the internal carboxyl group can be determined by comparing this value with the corresponding bimolecular reaction.[13] The bimolecular data are not available but they can be estimated.

Guthrie calculated that the equilibrium constant for the addition of water to dimethyl acetamide is 4×10^{-16} M^{-1}.[11] The equilibrium constant (K_x) for conversion of an adduct formed by addition of water to an amide to that of a carboxylic acid and an amide is given by the value for the formation of the hypothetical ester:[14]



Since ester stability parallels the pK_a of the alcohol moiety,[15] and the alcohol in this case has a pK_a of about 14,[11] the value of K_x is ca. 10^{-2}. Therefore, the addition of acetic acid to dimethylacetamide has an estimated value of 10^{-18} M^{-1}. Since K_1 is about 10^{-6}, the "effective molarity" of the carboxyl in **1** would be 10^{12} M to the accuracy of our estimates.

Page and Jencks calculated that an intramolecular addition reaction which involves no decrease in translational or rotational entropy can be favored in solution over a bimolecular counterpart by a factor of 10^8 M at 25 °C.[16,17] Therefore, a large portion of the advantage for addition of the internal carboxyl is entropic, but a further factor of 10^4 remains to be accounted for.

Hine has discussed enthalpic effects in the cyclization of dicarboxylic acids to anhydrides.[18] The conversion of 2,3-dimethylmaleic acid to the corresponding anhydride is favored by a factor of about 500 when compared with the formation of maleic anhydride. This is due to an increase in $CH_3—C{=}C$ angle upon cyclization which relieves steric interactions between the adjacent methyl groups. The formation of an anhydride from a dicarboxylic acid involves retention of hybridization at carbon, whereas formation of T^0 from SH involves conversion of an sp^2 center to a more accommodating sp^3 center. Therefore, even more steric strain can be relieved in our case and a factor of 10^4 is not unreasonable. Thus, previously estimated entropic factors can account reasonably for the large "effective molarity" if the internal addition in this series is as favorable as possible.

Rate Constants. Values for k_3, conversion of zwitterion $T^\pm$ to products, are plotted in Figure 2. The derived values range from approximately 10^9 to 10^7 s^{-1}. Although very large rates are involved, no leveling is observed ($\beta_{LG} = -0.61$). This suggests that breakage of the C-N bond is relatively insensitive to the nature of the leaving group but the weakest base leaves more readily, as expected. The driving force for the reaction, formation of the carbonyl group, is powerful. Since a substituent effect is noticeable but small, the transition state must resemble the zwitterion. The large rate constant and high stability of the product also suggest that the transition state would resemble the zwitterion.

The rate constant for the "proton switch", k_{-4}, in the favorable direction, appears to be independent of substituent (1.7×10^7 s^{-1}). This is similar to what has been estimated to be the maximum rate for a related "proton switch" in other studies.[19] The proton transfer reaction may be a concerted process involving considerable solvent participation. This organization would be accompanied by an entropic barrier.[20]

Relationship of Empirical Behavior to That of Related Compounds. The pH-rate profiles observed for **1-4** are ac-

counted for by two "plateaus", $k°_2$ and $k°_1$, connected by an apparent acid-dependent term and ultimately decreased by the dissociation of the substrate at very low acid concentrations. The plateau rate constants are plotted as a function of leaving group pK_a in Figure 3.

The logarithm of the upper plateau rate constant, $k°_2$, decreases with increasing leaving group basicity in a straight line manner. In eq 10, $k°_2$ is dependent upon terms whose logarithms are linearly dependent upon pK_a, stated as a derivative:

$$\frac{\partial \log k°_2}{\partial pK_a} = \frac{\partial \log K_1}{\partial pK_a} + \frac{\partial \log k_3}{\partial pK_a} + \frac{\partial \log K_4}{\partial pK_a} \qquad (22)$$

By comparison, the lower plateau value, $k°_1$, increases with increasing pK_a. At the pK_a of the *n*-propyl derivative (**1**), the plateaus are extremely close. This closeness of plateau values has made a basis for analysis of data difficult to see in the past.

Equations 9 and 11 can be combined to give an expression for $k°_1$, the lower plateau, in terms of constants whose pK_a dependencies have been solved:

$$k°_1 = K_1k_3k_4/(k_{-4} + k_3) \qquad (23)$$

Since k_{-4} is independent of pK_a but k_3 is dependent and may be comparable to k_{-4}, the functional plot of $k°_1$ should be nonlinear, as observed in Figure 3.

The observed first-order rate constant at any pH therefore depends upon a combination of opposing effects. The result is that analysis of the dependence of k_{obsd} on leaving group basicity requires that the data be related first to the mechanism. Part of the cause of apparent irregular dependence in related studies[4,6] results from this phenomenon.

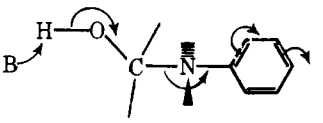
Concerted vs. Stepwise Elimination. The mechanism in Scheme II involves stepwise conversion of protonated intermediate T^+ to zwitterion $T^\pm$ by proton removal, followed by unimolecular conversion of the zwitterion to products, measured by k_3. Even as k_3 becomes very large, formation of the zwitterion, rather than elimination of the amine from T^+ is the preferred process. By comparison, maleanilic acids and related compounds with anilines as leaving groups do not show saturating buffer catalysis and have Brønsted slopes of ca. 0.6. This suggested a concerted elimination from T^+ occurs.[8,9] We can consider factors that might cause aliphatic derivatives to proceed stepwise and aromatic derivatives to undergo concerted eliminations.

In order for the concerted path to be preferable to reaction via the zwitterion, the transition state leading from T^+ to products must be lower in energy than a transition state leading to or from the zwitterion. The barriers between $T^\pm$ and T^+ or products must be on the order of no more than 2 or 3 kcal/mol in the case of **4** (k_{-2} measures a diffusion-controlled proton transfer and k_3 is estimated to be up to 10^9 s^{-1}). Therefore, those transition states are close in energy and structure to the zwitterion. Thus, it is most likely that the energy of the concerted reaction transition state will be below the energy of the corresponding $T^\pm$ [23]

What aspects of reactivity can contribute to the conversion of the stepwise to the concerted pathway? One possibility involves destabilizing the zwitterion toward C-N bond cleavage to make it so unstable as not to exist. Two major factors can contribute to this. The changes observed in rate-limiting steps in the reactions of **1–4** result because k_3 is comparable to k_{-2} or k_{-4}. In reactions of maleamides (compounds lacking substituents on C_2 and C_3), the step corresponding to k_3 remains slow compared with k_{-2} or k_{-4}.[4] Therefore, steric interactions between the adjacent methyl group and the tetrahedral center of $T^\pm$ promote k_3. Further steric interactions might accelerate k_3 and thus destabilize $T^\pm$. This effect is in the wrong direction to explain the concerted reaction of anilides derived from the unsubstituted acid.

Another effect that could promote k_3 is decreased basicity of the amine leaving groups weakening the C-N bond. In order to promote reaction of *N*-alkyldimethylmaleamides to the necessary instability, the intermediate would have to exist for less than one vibration ($\sim 10^{-13}$ s). Extrapolation of the line in Figure 2 requires the leading group to have a pK_a of 2 or less to reach $k_3 = 10^{13}$ $s.^{-1}$ This is even well below the pK_a where concerted reactions occur in the less reactive maleanilic acid system.[5,9] Therefore, this factor is an unlikely source for the observed dichotomy.

Finally, we propose that *stability* of the concerted transition state, rather than instability of the zwitterionic intermediate, accounts for the observed concerted reactions. The inaccessibility of a comparable source of stability then must account for reaction via the zwitterion. We suggest that the high energy aspect of the zwitterion is the result of its anionic oxygen center (a strong base in acidic solution). Therefore, with an aniline leaving group, stabilizing interactions of the incipient negative charge on proceeding from T^+ to the transition state are made possible by the π orbitals adjacent to the nitrogen center. This is qualitatively depicted below:



Alkylamines of comparable pK_a have no such stabilization of the incipient alkoxide in the transition state. Hence, the alkyl case is obliged to proceed via the zwitterion.

The stabilizing effect of an aromatic amine upon a developing *gem* alkoxide is seen only in the transition state of the elimination reaction. It is not a factor in determining relative pK_as and it is not a factor in elimination reactions which lead to cation formation, as in amide acetal reactions, since no anion develops.[22]

We are testing our hypotheses and the kinetic analytical procedures in related systems.

Acknowledgments. We thank Professors R. A. More O'Ferrall, J. P. Guthrie, and J. A. Berson for helpful discussions.

References and Notes

(1) Supported by an operating grant from the Natural Sciences and Engineering Research Council of Canada.
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(23) This is in contrast to the case for elimination reactions of carbon compounds. Since protonation of a carbanion is a much slower reaction than protonation of an alkoxide ion, the barriers to reversion of an E1CB intermediate remain high. The pathway for the E2 reaction is likely to involve a transition state that is higher in energy than the E1CB carbanion but lower than the E1CB transition states.[21]