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# Rate-Determining Processes in the Hydrolysis of Maleanilinic Acids in Acidic Solutions[1]

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**Abstract:** Aryl-substituted maleanilinic acids hydrolyze via intramolecular participation of the carboxyl group. In dilute acid, the rate of hydrolysis increases with acidity but in concentrated acid ($H_0 > 3$), the rate decreases with acidity. In dilute acid, the rates of hydrolysis parallel the basicity of the leaving group, while in concentrated acid the order of reactivity is reversed. Quantitative evaluation of these observations permits the establishment of a set of rate equations which can explain these results. These equations can be related to a detailed mechanism describing the behavior of these compounds in acidic solutions in general. The observations are accommodated by equations incorporating these features: (1) specific acid–general base catalyzed decomposition of intermediates, (2) acidity of protonated substrates and intermediates, (3) activity of water in the reaction solutions.

Amides adjacent to undissociated carboxylic acids undergo extremely rapid hydrolysis in comparison to unsubstituted amides. Evidence has been accumulated that indicates this facilitation is due to nucleophilic catalysis by the carboxylic acid.[3-14] Reaction proceeds via an addition intermediate from which the amine is expelled, producing a cyclic anhydride as the second product. This route circumvents the high barrier to hydration of the amide.[15] The reaction is of particular interest because it can be compared with catalytic routes provided by many proteolytic enzymes since the enzymes also function by a nonhydrated addition intermediate.[16,17]

It has previously been shown that the hydrolysis of maleanilinic acids is general acid catalyzed.[14] By evaluating the behavior of these compounds in strongly acidic solutions,
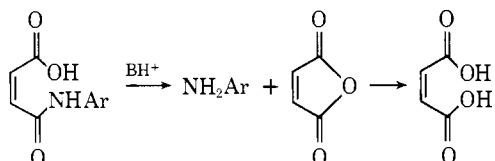
we could expect protonation of the substrate and intermediate might lead to a change in observed kinetic behavior in which C–N bond strength (rather than a combination of basicity and bond strength[14]) would become the rate-controlling feature. We have observed that in strong acid the rate of hydrolysis of

maleanilinic acids does depend directly on C–N bond strength, and as a result of effects related to a decrease in water activity, observed rates *decrease* with increasing acid strength. Rate equations can be derived which suggest that the breakdown of a protonated cyclic intermediate is concerted with loss of its hydroxylic proton in the rate-determining process in strong acid and in dilute acid. The implications of these results can be extended to other reactions involving nucleophilic assistance of amide hydrolysis (including enzymatic cases).

## Experimental Section

**Materials.** Aryl-substituted maleanilinic acids were prepared and purified according to published procedures.[14] Reagent grade sulfuric acid was obtained from Corco Chemical Corp.

**Kinetic Methods.** Sulfuric acid solutions were prepared on a molarity basis (up to 10 M) and were standardized against sodium hydroxide. For sulfuric acid concentrations above 10 M, percentage-weight was used. The reagent was determined to contain 96.4% sulfuric acid. For more dilute solutions, a measured weight of the reagent acid was diluted with measured weight of distilled water. Values of $H_0$ and water activities were taken from literature compilations.[18,19]

The hydrolysis of maleanilinic acid was followed by monitoring the decrease in absorbance of the amide band in the uv. Wavelengths used are: 4′-nitromaleanilinic acid, 320 nm; 3′-nitromaleanilinic acid, 270 nm; 4′-chloromaleanilinic acid, 280 nm; maleanilinic acid, 275 nm; 4′-methoxymaleanilinic acid, 300 nm. Temperature was maintained at 30.0 ± 0.1 °C in the sample compartment of a Unicam SP 1800A
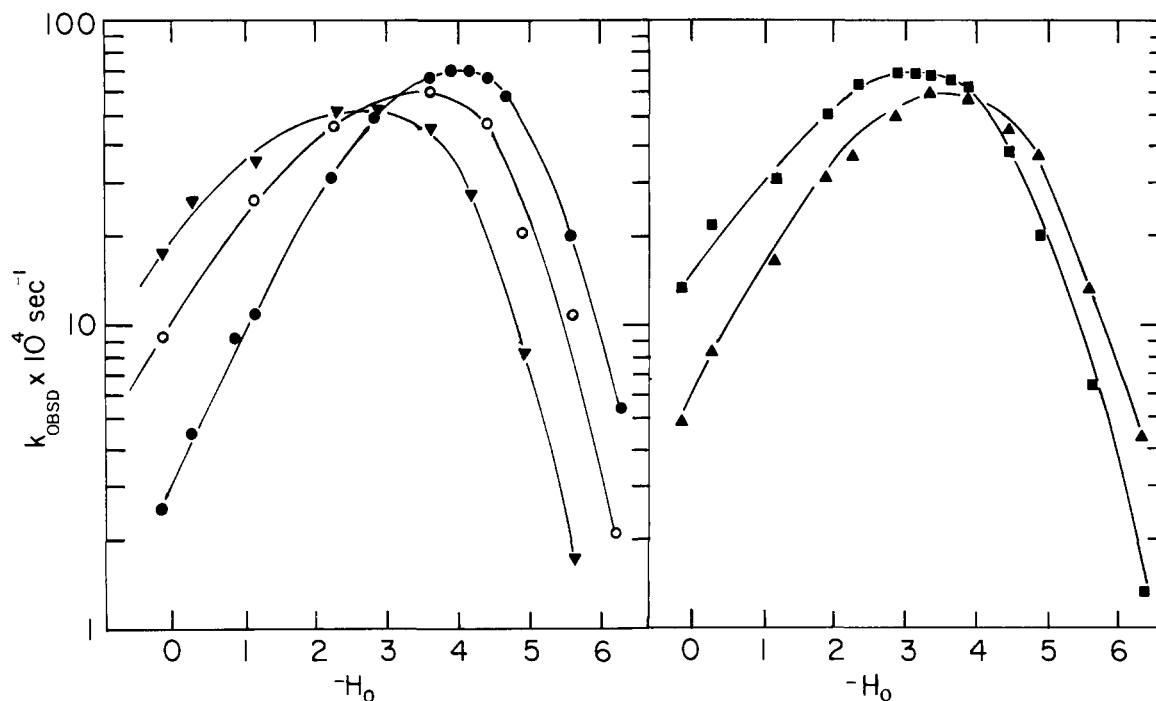
**Figure 1.** The observed first-order rate constant for hydrolysis of maleanilinic acids (H, ■; 4-OCH$_3$, ▼; 4-Cl, O; 3-NO$_2$, ▲; 4-NO$_2$, ●) as a function of $H_0$ at 30 °C.
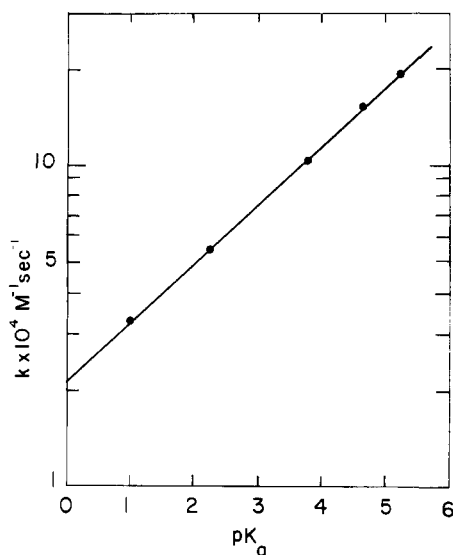


**Figure 2.** The values of log $k_{obsd}$ at $H_0$ = 0 in Figure 1 plotted against the p$K_a$ of the conjugate acid of the departing amine for the compounds in Figure 1.
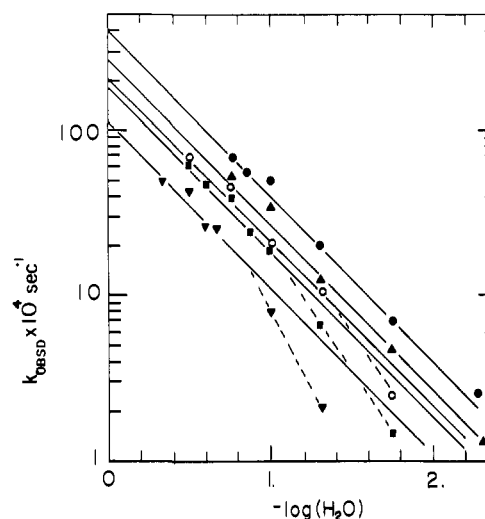


**Figure 3.** The values of log $k_{obsd}$ for hydrolysis of the compounds in Figure 1 as a function of the logarithm of water activity in strongly acid solutions.

spectrophotometer. First-order rate constants were obtained from the slopes of plots of log [OD($t$) − OD ($\infty$)] vs. elapsed time where the values were obtained from data on the associated Unicam AR 25 recorder. Straight lines were obtained for at least four half-times in all cases and OD($\infty$) values were obtained after intervals of over ten half-times. Solutions (3 ml) were incubated in quartz cells (10-mm pathlength) for 15 min at reaction temperature before 5 μl of a saturated solution of the substrate in dioxane was added.

## Results

Figure 1 relates the observed first-order rate constant for hydrolysis of maleanilinic acid derivatives to the Hammett acidity parameter, $H_0$, which in dilute acid approaches pH or −log [acid] as appropriate. The family of compounds undergo increasingly rapid hydrolysis as the concentration of sulfuric acid increases. The rates eventually level out and then decrease

in more concentrated acid. Comparison of the individual curves in Figure 1 reveals that in dilute acid, the compounds' relative reactivity parallels the basicity of the amine leaving group. In concentrated acid, the order of reactivity is reversed. There is no obvious pattern to the shape or location of the rate maxima. Since in dilute acid it appears that $k_{obsd} = k_{H^+}[H^+]$, we have plotted the apparent log $k_{H^+}$ (from the intercept of log $k_{obsd}$ on the $H_0$ axis) as a function of p$K_a$[14] of the conjugate acid of the departing amine (Figure 2).

It is likely that the decrease of rate of disappearance of maleanilinic acids in strong acid is a result of decreased activity of water in these solutions.[20] In Figure 3 we have plotted the observed rate constant as a function of water activity for the region in which rate decreases. We have noted that the order of reactivity in dilute acid is the reverse of that in strong acid.
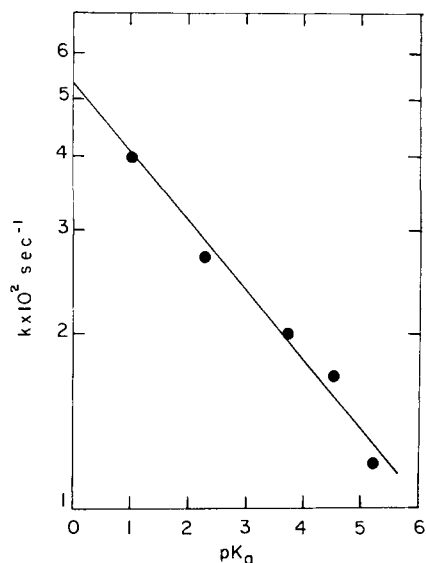
**Figure 4.** The extrapolated values of the plots in Figure 4 at unit activity of water as a function of the $pK_a$ of the conjugate acid of the departing amine.

In order to compare the situations, we have plotted the intercepts of plots of Figure 3 on the axis where $(H_2O)$ is unity as a function of the basicity of the departing amine (Figure 4). The results in Figures 2 and 4 can thus be compared. Whereas in Figure 2, there is a positive slope in the correlation between the basicity of the leaving group and observed rate ($\alpha \cong 0.15$), the slope is negative in Figure 4 ($\alpha \cong -0.12$).

## Discussion

We have previously shown that the hydrolysis of maleanilinic acids is subject to general acid catalysis.[14] It was suggested that hydronium ion catalysis probably could be considered in

**Scheme I**
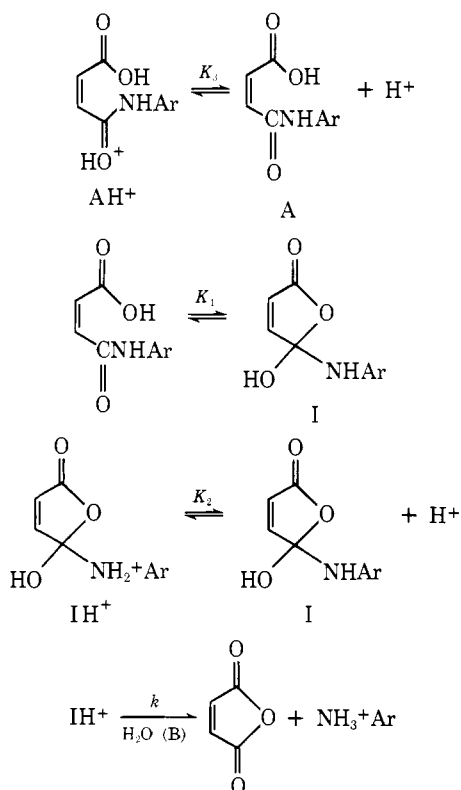


the context of that mechanism. In order to include the behavior we observe for maleanilinic acids in more strongly acidic solutions, we can ascribe the observed general acid catalysis to a kinetically equivalent path involving general base catalyzed decomposition of a protonated intermediate. By this mechanism, the "hydronium ion catalysis" term arises from water acting as a general base toward the protonated intermediate. Scheme I summarizes a set of equations that can accommodate our results.

Intermediates I and $IH^+$ are assumed to be present in very low concentrations relative to compounds A and $AH^+$. Since the step associated with "$k$" is rate determining, we can set up a rate expression for the reaction in the absence of buffers:

$$v = k_{obsd}[A]_T = k[IH^+](H_2O)^n \tag{1}$$

$$[A]_T \cong [A] + [AH^+] \tag{2}$$

$$k_{obsd} = k[IH^+](H_2O)^n/[A]_T$$
$$= k[IH^+](H_2O)^n/\{[A] + [AH^+]\} \tag{3}$$

$$K_1 = (I)/(A), K_2 = (I)(H^+)/(IH^+),$$
$$K_3 = (A)(H^+)/(AH^+) \tag{4}$$

$$(IH^+) = \gamma_1[IH^+], (A) = \gamma_2[A], (AH^+) = \gamma_3[AH^+] \tag{5}$$

$$[IH^+] = \{(IH^+)/\gamma_1\} = \{K_1(A)(H^+)/\gamma_1 K_2\}$$
$$= K_1[A](H^+)\gamma_2/\gamma_1 K_2 \tag{6}$$

$$k_{obsd} = \frac{kK_1(H^+)(H_2O)^n\gamma_2/\gamma_1}{K_2\left(1 + \dfrac{(H^+)}{K_3}\gamma_2/\gamma_3\right)} \tag{7}$$

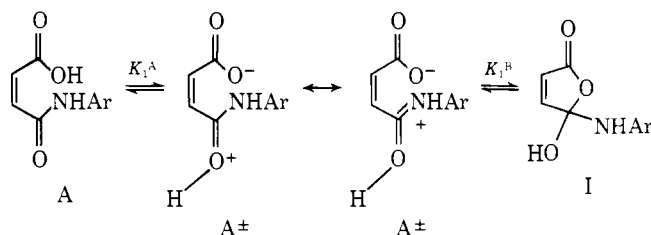When A is not significantly protonated, i.e., $[A] \gg [AH^+]$ and $(H_2O) \cong 1$

$$k_{obsd} = [kK_1/K_2](H^+)\gamma_2/\gamma_1 \tag{8}$$

$$\log k_{obsd} = \log kK_1/K_2 + \log (H^+)\gamma_2/\gamma_1 \tag{9}$$

The term $(H^+)(\gamma_2/\gamma_1)$ has the form of the Hammett acidity function, $H_0$. Since $\gamma_2/\gamma_1$ is part of an equation involving the equilibrium between a protonated amine and an unprotonated amide, it is likely that an acidity function that is a hybrid of $H_0$ and $H_a$[21] would be most appropriate. However, since the functions are linearly related, only slope will be affected. Therefore, a plot of log $k_{obsd}$ vs. $H_0$ should be linear with an intercept at log $k_{obsd} = \log kK_1/K_2$.

The intercepts in Figure 1 on the $H_0 = 0$ axis are related by a Bronsted plot (Figure 2) to the $pK_a$ of the amine from which the maleanilide is derived. The slope of the plot is 0.15, whereas the related plot for results in very dilute acid at 50 °C has a slope of 0.2.[14] The linear relationship in both instances suggests that the formulation is probably correct. This indicates that log $kK_1/K_2$ is linearly and positively related to the amines' $pK_a$'s. Substituent effects on $K_1$ should be relatively small. A quantitative estimate can be made by considering a two-step process[4] involving initial transfer of the proton of the carboxylic acid of A to its amide to form $A^+$ ($K_1^A$), followed by cyclization to give I ($K_1^B$). Effects on $K_1^A$ should be defined by the relative sensitivities of amine and amide basicities to substit-



uents. At eq 16 we show that the slope of the line relating the $pK_a$'s of the conjugate acids (amide as a function of amine) has

a value of about $+0.3$. Effects on $K_1{}^B$ should be analogous to those for addition of nucleophiles to protonated N-aryl imidate esters:
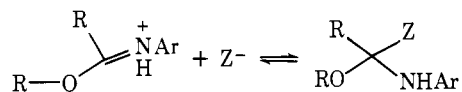


Schmir[22] has presented data for a series of N-aryl imidates which indicate that the rates of addition of water and hydroxide to these compounds when plotted as log rate vs. $pK_a$ have slopes of $-0.6$ and $-0.5$, respectively. We can assume that carboxylate being anionic should be nearer hydroxide in behavior and that the transition state for addition should be close in free energy to the tetrahedral intermediate I.[15] Therefore we expect the slope of the dependence of $\log K_1{}^B$ on $pK_a$ to be about $-0.5$. Therefore, proceeding from A to I should have a dependence on amine $pK_a$ overall of $-0.5 + 0.3 = -0.2$. The term "$-\log K_2$" should correlate with unit positive slope to the $pK_a$ of the conjugate acid of the leaving amine. Following Guthrie's procedure,[15] we estimate the amine of the neutral tetrahedral intermediate should be a weaker base by about 5 pK units than the corresponding unsubstituted aniline. The "$\log k$" term should be related with negative slope to the $pK_a$ of the conjugate acid of the amine, since the more readily the N–H bond of the conjugate acid dissociates, the more reactive the compound should be toward C–N bond breaking. We have shown that in dilute acid the relative order of reactivity is positively correlated with a slope of about 0.2 to the $pK_a$ of the conjugate acid of the departing amine. Therefore, the dependence of $\log k$ on $pK_a$ can be stated by

$$\Delta \log k \simeq -0.6 \Delta pK_a \qquad (10)$$

Since $k$ involves the rate of C–N bond breakage, we have no internally defined upper limit on the value of the slope for (10). Furthermore, for each leaving group we should expect a different reaction–transition state profile since we have a wide range of leaving groups.

In more concentrated acid, where the starting amide is largely protonated, eq 7 reduces to eq 11.

$$k_{obsd} = \frac{kK_1(H^+)(H_2O)^n}{K_2(H^+)/K_3} \frac{\gamma_2 \gamma_3}{\gamma_1 \gamma_2} \qquad (11)$$

$$k_{obsd} = \frac{kK_1K_3(H_2O)^n}{K_2} \frac{\gamma_3}{\gamma_1} \qquad (12)$$

Equation 12 suggests that in stronger acid, as A becomes protonated, the reaction rate will become independent of the acidity of the solution (if $\gamma_3/\gamma_1$ does not change significantly). One would predict that a rate-maximum plateau would be observed. However, in acidic solutions strong enough to protonate A to a large extent, the activity of water is significantly less than unity[20] (unit activity being that in dilute solutions). Thus we can consider eq 13 which is derived from eq 12.

$$\log k_{obsd} = \log kK_1K_3/K_2 + n \log (H_2O) + \log \gamma_3/\gamma_1 \qquad (13)$$

A plot of $\log k_{obsd}$ vs $H_0$ should show a negative curved dependence on $H_0$ since $\log (H_2O)$ will decrease. However, if $\gamma_3/\gamma_1$ remains relatively constant, a plot of $\log k_{obsd}$ vs. $\log (H_2O)$ should be a straight line with slope = $n$. In Figure 3, $n$ has a value of 1 with curvature toward a slope of 2 for the more basic compounds in the most concentrated solutions.

It is difficult to assign specific "break" points due to the conversion of A to AH$^+$ by direct examination of Figure 1. However, the intercepts of Figure 2 and Figure 3 according to eq 13 and 9 differ only by a factor of $\log K_3(\gamma_1/\gamma_3)$. Therefore the difference of intercepts for a particular compound in the two plots is proportional to its $pK_a + \log \gamma_1/\gamma_3$. The difference of any two intercept values will be equal to the difference in

**Table I.** The $pK_a$ of the Conjugate Acid of Substituted Maleanilinic Acids[a]

| Substituent | $pK_a$ (maleanilide) | $pK_a$ (acetanilide) |
|---|---|---|
| 4'-OCH$_3$ | $-0.9$ | $-1.1$ |
| H | $-1.0$ | $-1.4$ |
| 4'-Cl | $-1.3$ | $-1.6$ |
| 3'-NO$_2$ | $-1.7$ | (not reported) |
| 4'-NO$_2$ | $-1.9$ | $-2.2$ |

[a] Calculated from the differences of "intercepts" of Figures 1 and 3, according to eq 9 and 13. For comparison, $pK_a$'s determined by Giffney and O'Connor for the conjugate acids of substituted acetanilides[23] are listed.

$pK_a$'s. If $\gamma_1/\gamma_3$ is near unity, absolute values of the $pK_a$'s should be obtained. If $\gamma_1/\gamma_3$ is relatively independent of the substrate (essentially the Hammett base assumption), then the differences in the calculated "$pK_a$'s" should be identical with the differences in the actual $pK_a$'s. Table I summarizes calculations of $pK_a$ values based on the differences of intercepts in Figures 2 and 3. Literature values for related acetanilides are given for comparison. It is satisfying that the calculated $pK_a$'s do come within reasonable absolute value of the literature values and are in proper relative order.

The slope of Figure 2 implies a "stoichiometry" of one water molecule in the rate-determining process. Water is likely to be fulfilling the role of the general base we have indicated in formulating the nature of the rate-determining step. It is interesting that for the hydrolysis of amides, values of parameters related to $n$ are usually near 3.[21] In those unassisted cases, water adds to the carboxyl group to form an amide addition product in the rate-determining step.

In Figure 4 the intercepts of Figure 3 are plotted as a function of the $pK_a$ of the amine which departs in the rate-determining step. Again, since only differences in $\log k$ are actually being plotted, the activity coefficient ratio will cancel. This figure gives a straight line of slope = $-0.12$. Since the differences of intercepts ($\alpha$) are functions of eq 13, then

$$\alpha = \log k'/k + \log K_1'/K_1 + \log K_3'/K_3$$
$$- \log K_2'/K_2 + \log (\gamma_3'/\gamma_1')(\gamma_1/\gamma_3) \qquad (14)$$

We have said that $(\gamma_3/\gamma_1)$ should be independent of substituents on the aromatic ring so that eq 14 reduces to:

$$\alpha = \log k'/k + \log K_3'/K_3$$
$$- \log K_2'/K_2 + \log K_1'/K_1 \qquad (15)$$

We know from the correlation of intercepts in dilute acid and eq 9 that eq 16 holds.

$$0.15 \simeq \log k'/k - \log K_2'/K_2 + \log K_1'/K_1 \qquad (16)$$

Therefore, since the slope of Figure 4 is $-0.12$, $\log K_3'/K_3 \simeq -0.3$. We find that a plot of $pK_a$ of the conjugate acid of amides[23] derived from acetanilide as a function of the $pK_a$ of the conjugate acid of the corresponding aniline has a slope of about 0.3.

It has been suggested that "concerted" elimination reactions from tetrahedral intermediates occur only when the stepwise process would generate energetically unfavorable intermediates.[15,24] We have shown that the decomposition of intermediates leading to expulsion of amines from maleanilinic acids is most readily explained as involving both proton transfer (from oxygen) and breaking of the C–N bond. This is because a role for the buffer catalyst and C–N bond breaking are reflected in our correlations. The concerted mechanism will account for our observations over the full range of acidity. If this mechanism is correct, then the unfavorable species avoided by
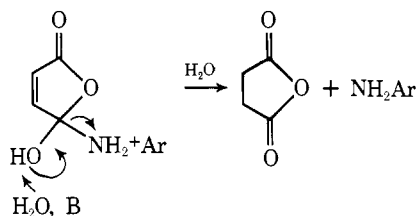
the concerted reaction are the zwitterion, which would result from stepwise decomposition of IH$^+$ by initial loss of a proton from oxygen, and protonated maleic anhydride, which would result from initial loss of the amine from IH$^+$.

Our results would indicate that once a tetrahedral addition product of an amide has been produced, two factors will promote decomposition in the direction of amine expulsion for any compound. These are (1) removal of the hydroxylic proton and (2) protonation of the amine functionality. Other aspects of rate differences probably will be inherent to the substrate and nucleophilic catalyst. The relative sizes of $k_1$ and $k_{-1}$ will

I
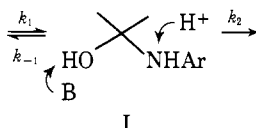
determine the concentration of I, if $k_2 \ll k_{-1}$. Obviously, in the case of formation of an enzyme–substrate derivative, $k_1/k_{-1}$ can be extremely favorable and internal bases can supply the function of B. The rate of protonation of I at the amine will probably be diffusion limited so that this feature of catalysis will not evolve as a kinetic factor for the enzyme. Rather, the apparent basicity of the amine should be increased

without at the same time increasing the strength of the C–N bond. We are currently investigating chemical means through which this may be accomplished.

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# Carbenoids with Neighboring Heteroatoms. V. Nucleophilic Reactions of Lithium Carbenoids of the exo-8-Halo-3,5-dioxabicyclo[5.1.0]octyl System[1]

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**Abstract:** The $\alpha$-haloorganolithium compounds **1b**, **2b**, and **3b** were prepared from the *gem*-dihalocyclopropanes by stereoselective halogen–lithium exchange using methyl- or butyllithium. The nucleophilic properties of these carbenoids were studied by reactions with the electrophiles H$^+$, D$^+$, CH$_3$I, benzophenone, and halogenating agents. The chlorination (CCl$_4$) of **1b** and bromination (BrCCl$_3$) of **3b** provided stereoselective routes to the epimeric bromochlorocyclopropanes **3d** and **6a**. Factors influencing the nucleophilic reactivity of **1b** and **2b** are discussed.

In previous papers in this series[2] we have reported on the stereoselective synthesis of stabilized lithium carbenoids and some of their nucleophilic and electrophilic reactions. In this and the accompanying paper[3] we report, in turn, on nucleophilic and electrophilic reactions of lithium carbenoids in the 3,5-dioxabicyclo[5.1.0]octyl system, a study which ultimately led to the individual preparation of epimeric $\alpha$-chlorocyclopropyllithium reagents, and the first direct observation of the effect on electrophilic reactivity of stereochemical change at a carbenoid carbon.

The requisite crystalline *gem*-dihalocyclopropanes **1a**, **2a**, and **3** were prepared in low to moderate yields by dihalocarbene addition to the corresponding olefins, which, in turn, were

prepared from *cis*-2-butene-1,4-diol by the method of Bannock and Lappin.[4] The acetals, **1a** and **3a**, were relatively stable toward hydrolysis of that function if reasonable work-up precautions were taken with regard to pH and temperature. Ketal **2a**, however, required basic conditions at all times, even to the extent of using K$_2$CO$_3$ (rather than Na$_2$SO$_4$) as drying agent in addition to using it as an additive during purification of **2a** by sublimation.

**Nucleophilic Reactions of Carbenoids 1b and 2b.** Treatment of ethereal **1a** at −78 or −20 °C with methyllithium–lithium bromide gave a suspension of the carbenoid **1b** in high yield as evidenced by the formation of monobromo compound **1c** in 90% yield upon water or methanol quench of the reaction. The