direction the ground-state energy of the \( m_{\text{SoA}} \) is displaced by the dielectric changes brought about by the exciton.

Acknowledgment. We are grateful to the National Science Foundation (Grants CHE-8121140 and CHE-8135303) for support of this work. We also thank Mrs. Marjorie Richter for her technical assistance and patience in preparing films and supported multilayers.


Aminolysis of Maleic Anhydride. Kinetics and Thermodynamics of Amide Formation

Ronald Kluger* and John C. Hunt

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Abstract: The rates of reaction of maleic anhydride with a series of a primary straight-chain amines were measured for solutions at pH 4, 25 and 15 °C. The series was selected to minimize complications due to steric and hydrophobic effects. The second-order rate constants for production of N-alkylmaleamic acids at 25 °C range from 3 \times 10^2 to 1 \times 10^3 M^{-1}s^{-1}. The rate constants follow a nonlinear Bronsted relationship (\log k vs. pK_a of the conjugate acid of the nucleophile) and conform to the expression \( k = 10^{0.6pK_a - 3.0} + 10^{0.2pK_a - 5.2} \). The data fit the rate law for a process in which a change in rate-determining step in a single mechanism occurs, a change in slope from 0.95 to 0.23, with equal rates for the two steps for the case of an amine with a conjugate acid of pK_a = 7.7. The results are interpreted in terms of a mechanism in which proton transfer in the zwitterionic tetrahedral intermediate is the rate-determining step for amines whose conjugate acids have pK_a values less than 7.7. The reactions of more basic amines involve rate-determining formation of the tetrahedral intermediate. These results contrast with those for aminolysis reactions in which acyllammonium compounds are produced and which do not involve proton-transfer steps. The equilibrium constants for formation of amides from maleic anhydride and the amines at 50 °C were determined by combining these data with the rates of the reverse reaction. The equilibrium fits the expression log \( K = 0.44pK_a + 4.7 \). The free energies of hydrolysis of the maleamic acids are estimated to range from 7.6 to 11 kcal/mol.

The detailed mechanism of addition of nucleophiles to reactive carbonyl compounds is a problem of continuing interest. The reaction of primary amines with anhydrides is a common and practical approach to the formation of amides. There have been very few studies in this system, and the most complete have been complicated by steric effects.2 The addition of pyridines to acetic anhydride has been studied, but in that case, since the nucleophile lead to stable neutral amides since proton loss occurs.

Detailed mechanistic analysis of a reaction is assisted by information from studies of the reverse reaction. Acylation of amides, the reverse of the aminolysis reaction, is observed for aqueous solutions only in the case of intramolecular reactions. The intramolecular carboxyl-assisted hydrolysis of amides proceeds via intermediary formation of an anhydride along with expulsion of the amine.4 This class of reaction has been studied in detail and is the reverse of the aminolysis of a cyclic anhydride.5 We have now examined the aminolysis of maleic anhydride, a reaction whose reverse has earlier been subject to kinetic analysis. The kinetic results enhance the mechanistic analysis and provide information about aminolysis reactions in general.

Experimental Section

Materials. All amines except 2,2,2-trifluoroethylamine were purchased from the Aldrich Chemical Co. All liquid amines were distilled prior to use. Hydrochloride salts were purified as reported by Kertes. Maleic anhydride and spectrophotometric grade acetonitrile were purchased from the Aldrich Chemical Co. and were used without further purification. Reagent grade inorganic materials and organic reagents were obtained from Fisher Scientific.

Registry No. p-Bu,C,H,CHO; 1200-14-2; Sano, 77824-98-7; Sano, 77814-49-4; Sano, 74392-06-6; Sano, 91202-35-6; Sano, 91202-36-7; TKAE, 91202-39-0; TKAE, 91202-40-2; TKAE, 85554-56-9; BrTKAE, 91202-41-4; BrTKAE, 91202-43-6; BrTKAE, 91202-42-5; SKAE, 91202-44-7; SKAE, 91202-46-9; SKAE, 91202-45-8; SKAE, 91202-47-0; SKAE, 91202-49-2; SKAE, 91202-48-1; SKAE, 103-30-0; cyclohexane, 108-94-1; 1-(1-cyclohexen-1-yl)-4-methylbenzene, 182-23-4; 1-(4-methylphenyl)cyclooctene, 91202-37-8; 1-(4-methylphenyl)cyclooctene, 91202-38-9.

Supplementary Material Available: Method and calculations of exciton band shifts of \( m_{\text{SoA}} \) assembly systems (6 pages). Ordering information is given on any current masthead page.

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Table 1. Second-Order Rate Constants for the Aminolysis of Maleic Anhydride according to Eq 2

| amine             | pK' (25 °C) | k (25 °C) | pK'' (15 °C) | E acidity
<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>propyl</td>
<td>10.58</td>
<td>9.7 × 10^4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-hydroxypropyl</td>
<td>10.37</td>
<td>8.6 × 10^4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-methoxyethyl</td>
<td>9.68</td>
<td>5.8 × 10^4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-fluoroethyl</td>
<td>9.19</td>
<td>3.2 × 10^4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-ethylacetyl</td>
<td>8.01</td>
<td>1.6 × 10^4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,2-difluoroethyl</td>
<td>7.45</td>
<td>5.3 × 10^4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,2,2-trifluoroethyl</td>
<td>5.40</td>
<td>1.5 × 10^4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Units of rate constants are M⁻¹ s⁻¹. ²pK' values are for the conjugate acids of the listed bases. The values were determined by titration of solutions maintained under the conditions of the aminolysis reactions. ³Corrected for 15 °C. ⁴kcal/mol.

The variation of pK₆ for the conjugate acids of the amines were determined by titration, and in some cases at 15 °C. These data were used to obtain activation parameters. The variation of k₃ for each amine is eq 3.

\[ k = k_1 / (k_1 + k_2) \]  

(3)

Under conditions where the step corresponding to \( k_1 \) is clearly rate determining (\( k_2 \gg k_1 \)), eq 3 reduces to eq 4.

\[ k' = k_1 \]  

(4)

For situations in which the second step is clearly rate determining (\( k_2 \gg k_1 \)), the rate law is given by eq 5.

\[ k'' = (k_1 / k_2) \]  

(5)

We assume a linear relationship between the logarithms of the limiting rate constants (\( k' \) and \( k'' \)) and the \( pK_6 \) values of the conjugate acids of the amines (eq 6 and 7). Since a nucleophilic reaction is involved, this is not formally a Bronsted plot and the \( b \) values would not relate to general base catalysis. Jencks has used the expression \( \beta_{nuc} \) for this parameter. In our analysis, \( b'' \) terms are the same as \( \beta_{nuc} \).

We invert eq 3 and substitute, using eq 4–7.

\[ 1/k = 10^{pK_6} / (10^{pK_6} + 10^{pK''}) \]  

(8)

Finally, we obtain an expression for \( k \) by inverting eq 8.

\[ k = 1 / (10^{pK_6} + 10^{pK''}) \]  

(9)

The parameters to be determined from our experimental results are \( b', b'', c', \) and \( c'' \). These were found by fitting the limiting slopes of the data in Figure 1 to obtain \( b \) and \( b' \) while \( c' \) and \( c'' \) were adjusted to get a good fit to the data using eq 9. The curve in Figure 1 is plotted by using eq 9 and values for parameters as follows: \( b'' = 0.23, c' = -3.03 \) (log of M⁻¹ s⁻¹), and \( c'' = 2.52 \) (log of M⁻¹ s⁻¹). The terms \( b' \) and \( c' \) refer to the linear portion in the higher \( pK_6 \) range and the \( b'' \) and \( c'' \) to the lower \( pK_6 \) region. Since the \( c'' \) terms are intercepts, they are equal to the hypothetical rate constants for addition of amines whose


We have obtained the same result with the similarly basic propyl
mation of maleamic acid from T2 is lower than the barrier to
acid.5 Addition of water of isomaleimides rapidly produces in-
conclusion. intermediate T', the same intermediate as in Scheme
conversion of T' to maleamic acids
is directly affected. For the case of the aminolysis of maleic anhydride under
paper on the hydrolysis reaction6 since the current results are not
basic. Proton transfer within the tetrahedral intermediate is rate
in Scheme II, we conclude that the
steps which are subject to acid catalysis is the inter-
transfer in the thermodynamically favorable direction,11 we expect a
Bransted slope of 0 for the rate-limiting step, kr. The pKb
dependence of log k' then gives the pKb dependence of log (k'/kkr),
which is 0.95.
Our results permit the determination of equilibrium constants for
formation of tetrahedral intermediates from amines and an-
hydrides. Since the rate constants for the proton switch process are known from studies of the reverse reaction, the rate constant
for expulsion of the amines from the tetrahedral intermediate can be
calculated. At pKb = 7.7, the rate constant for expulsion of the amine (k-)
is equal to the rate constant for the proton switch, k'. The rate constant for the proton switch has been determined.6
At the temperature of the current study it should be approximately
1 X 104 s-1 and independent of the basicity of the amine.10 The
rate constant k-1 for the other amines can be obtained from eq
10 since k1 is determined independently (see Table II).

\[ k_{-1} = k_{1} \frac{k_{r}}{k'_{r}} \]  

(10)
The pKb dependence of both k1 and k-1 are known since we have demonstrated that the slope for k1 is 0.95.

\[ d(log k_{1})/dpK_{b} = 0.23 \]  

(11)
\[ d(log k_{-1})/dpK_{b} = -0.72 \]  

(12)
The limiting slopes in Figure 1 are similar to those that have
been determined for other reactions of carboxyl compounds with
nucleophiles in water. Ritchie has suggested that for cases where
addition is rate limiting, the resulting correlation slope should be
near 0.45, based on adjustment of the Bornsted treatment we have used to the "N+" basis.13 The predicted value is twice our observed
result of 0.23. For comparison, in most cases where the Bornsted slope has been measured accurately for the addition of nucleophiles
to carboxyl compounds (in which addition is rate limiting), the slope of log k vs. pKb has been observed to be between 0.20 and 0.25. This disagrees with Ritchie's prediction of 0.45 for the slope. Palling and Jencks have commented on this point at length in a recent paper on the addition of nucleophiles to acetyl chloride, concluding that the N+ scale is not appropriate for use in analysis of the addition of nucleophiles to carboxyl compounds.13 Our results support this conclusion.

The central point of curvature in a biphasic Bornsted plot is designated pKb by Moodie and Castro.14 Their kinetic analysis

corresponding to the value b in eq 6), for the limit of the most basic amines, and 0.95 (corresponding to the value b in the eq 7), for
the limit of the least basic amines. As we have noted, for the less
basic amines, the reaction involves rate-determining switch of a
proton between nitrogen and oxygen. Since this process involves
transfer in the thermodynamically favorable direction,\(^11\) we expect a
Bransted slope of 0 for the rate-limiting step, kr. The pKb
dependence of log k' then gives the pKb dependence of log (k'/kkr),
which is 0.95.

The pKb dependence of both k1 and k-1 are known since we have demonstrated that the slope for k1 is 0.95.

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The central point of curvature in a biphasic Bornsted plot is designated pKb by Moodie and Castro.14 Their kinetic analysis

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uses this quantity as an adjustable parameter. $pK^a$ corresponds to the case where $K_1$ and $k_1$ in eq 3 are equal. In the addition of tertiary amines to reactive acyl compounds, where proton transfer cannot occur in the tetrahedral intermediate, $pK^a$ defines the basicity at which the barrier to expulsion of the adding and leaving groups is the same from a common intermediate. However, since the products are different for the two processes the transition states also will partly reflect the differences in product stabilities. For the addition of pyridines to chlorocarbonates or anhydrides, the product will be an acylpyridinium compound which is relatively unstable. Therefore the $pK^a$ will reflect this instability, and the chloride ion or acyl group will appear to be poorer leaving groups than the pyridine of comparable basicity. Often, $pK^a$ does not coincide with the point where the $pK_a$ of the attacking species is the same as that of the leaving group. In the case we report here, the $pK^a$ point results from a different balancing of effects. The curve in the Bronsted plot is the result of a change in rate-determining step from amine attack to proton switch prior to breakdown of the uncharged intermediate. Therefore the $pK^a$ of 7.7 does not indicate that the maleic acid group is equivalent in leaving ability to an amine whose conjugate acid has a $pK_a$ of 7.7. The acid should be a considerably better leaving group than an amine of the same $pK_a$ since the more stable product is formed when the acid is expelled.

**Equilibrium Constants for Amide Formation.** The equilibrium constant for formation of an amide from an amine and a carboxyl compound is a quantity of considerable interest. Ideally, rate constants for the forward and reverse processes need to be known for reactions under the same conditions in order to determine accurate equilibrium constants. In most cases, the formation of an amide is so unfavorable under conditions that lead to hydrolysis that this approach has not been used. Other methods have been employed, and only a limited amount of information is available. However, our results permit the determination of equilibrium constants since the rate constants for the hydrolysis reaction in the same series are known; only a temperature correction needs to be made. The equilibrium constants $(K_e)$ are presented in Table II. They measure the equilibrium at 50 °C for amide formation from maleic anhydride:

\[
RNH_2 + \text{maleic anhydride} \rightleftharpoons \frac{K_e}{50} \text{maleamic acid}
\]

The basicity dependence of the equilibrium is plotted in Figure 2. Equation 13 fits the data with a correlation coefficient of 0.996, giving the line in Figure 2.

\[
\log K_e = 0.44pK_a + \log(5.0 \times 10^4 \text{ M}) \tag{13}
\]

The slope of the line is an indication of the extent of positive charge on the nitrogen atom of the amide. For comparison, Jencks and co-workers have reported the dependence of the equilibrium constant for formation of acylazolides on the $pK_a$ of a series of substituted anilines. The slope in that study is 0.61. Fersht and Requena found a slope of 0.51 for formation of formamidines. The lower extent of positive charge on the maleamide nitrogen atoms (0.44) may reflect differences in the interactions of vinyl and alkyl substituents with the amide.

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