direction the ground-state energy of the $_mS_{nA}$ is displaced by the dielectric changes brought about by the exciton.

(63) Brocklehurst, B.; Bull, D. C.; Evans, M.; Scott, P. M.; Stanney, G. *J. Am. Chem. Soc.* **1975**, *97*, 2977–2978.
(64) (a) Stevens, B. *Adv. Photochem.* **1971**, *8*, 161–226. (b) Cohen, M. D.; Yakhot, V.; Ludmer, Z. *Ibid.* **1979**, *11*, 489–523.

Aminolysis of Maleic Anhydride. Kinetics and Thermodynamics of Amide Formation

Ronald Kluger* and John C. Hunt

Contribution from the Lash Miller Laboratories, Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 1A1. Received November 22, 1983

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 3×10^2 to 1×10^5 M^{-1} s^{-1}. The rate constants follow a nonlinear Brønsted relationship (log k vs. pK_a of the conjugate acid of the nucleophile) and conform to the expression $1/k = 10^{-0.95pK_a+3.03} + 10^{-0.23pK_a-2.52}$. The data fit the rate law for a process in which a change in rate-determining step in a single mechanism causes 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 acylammonium 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 equilibria fit 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.[1,2] The addition of pyridines to acetic anhydride has been studied, but in that case, since the nucleophile is a tertiary amine, the product is an unstable acylpyridinium salt.[3] The reactions of primary and secondary amines with anhydrides 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. Acylolysis 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.[5,6] 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-difluoroethylamine were purchased from the Aldrich Chemical Co. All liquid amines were distilled prior to use. Hydrochloride salts were purified as reported by Kertes.[7] 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.

N-(2,2,2-Trifluoroethyl)maleisoimide. Dicyclohexylcarbodiimide (DCC, 45 mmol in 50 mL of dichloromethane) was added over 10 min to 45 mmol of *N*-(2,2,2-trifluoroethyl)maleamic acid in 50 mL of dichloromethane. *N,N'*-Dicyclohexylurea began to precipitate before the addition of DCC was complete. The solution was refluxed for 1 h. The urea derivative was removed by filtration and the solvent evaporated from the filtrate. The product was distilled under high vacuum. The maleisoimide is an oil at room temperature. Proton NMR (chloroform-*d*, in ppm from internal tetramethylsilane reference, Varian T-60 spectrometer): 6.90 (d, *J* = 7 Hz), 6.20 (d, *J* = 7 Hz), 3.66 (q, *J* = 9 Hz).

Kinetics. Rate data were obtained with a Varian Cary 210 spectrophotometer to measure the change of absorbance at 255 nm. Data were collected through a microprocessor-controlled interface (built by Comspec Ltd., Downsview, Ontario, Canada). The data were stored in a

(1) Pitman, I. H.; Uekama, K.; Higuchi, T.; Hall, W. E. *J. Am. Chem. Soc.* **1972**, *94*, 8147.
(2) Hall, W. E.; Higuchi, T.; Pitman, I. H.; Uekama, K. *J. Am. Chem. Soc.* **1972**, *94*, 8153.
(3) Castro, C.; Castro, E. A. *J. Org. Chem.* **1981**, *46*, 2939.
(4) Bender, M. L. *J. Am. Chem. Soc.* **1957**, *79*, 1278.
(5) Kirby, A. J.; Lancaster, P. W. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1206.
(6) Kluger, R.; Chin, J. *J. Am. Chem. Soc.* **1982**, *104*, 2891.

(7) Kertes, A. S. *J. Inorg. Nucl. Chem.* **1965**, *27*, 209.

Table I. Second-Order Rate Constants for the Aminolysis of Maleic Anhydride according to Eq 2[a]

amine	pK_a'[b]	k (25 °C)	pK_a''[c]	k (15 °C)	E_{act}[d]
propyl	10.58	9.7×10^4			
3-hydroxypropyl	10.37	8.6×10^4			
2-methoxyethyl	9.68	5.8×10^4			
2-fluoroethyl	9.19	3.2×10^4	9.39	1.7×10^4	11.2
2-ethylacetyl	8.01	1.6×10^4			
2,2-difluoroethyl	7.45	5.3×10^3	7.53	2.6×10^3	12.0
2,2,2-trifluoroethyl	5.40	1.5×10^2			

[a] Units of rate constants are M^{-1} s^{-1}. [b] pK_a' 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. [c] Corrected for 15 °C. [d] kcal/mol.

Commodore 2001 computer during acquisition and then transferred to diskettes using a program we developed called "CARYDISK". The sample compartment was thermostated within 0.1 °C by a Neslab EX-1000 circulator at 15 or 25 °C. The temperature inside the cell compartment was monitored with a Fisher 119 combination meter with a YSI 700 series thermistor probe. The ionic strength of the reaction media was maintained at 1.0 with potassium chloride. Typically, 2.5–3.0 mL of acetate buffer containing the amine was added to a quartz cell and thermally equilibrated in the cell compartment. Reactions were initiated by injection of 20–25 μL of a stock solution of maleic anhydride in acetonitrile. The total concentration of the maleic anhydride in the reaction solution was 10^{-5} M. Each solution was mixed by twice inverting the cell. The cell was then inserted into the sample compartment. Data were collected at a rate of one point per 0.5 or 1 s into the computer.

Rate constants were calculated by fitting the experimental data stored on diskettes to the integrated first-order rate expression using a linear least-squares program. Correlation coefficients were at least 0.997. Twenty to thirty data points were used to determine each first-order rate constant. Plots of the first-order rate constant vs. concentration of unprotonated amine (calculated from the pK_a determined by titration under reaction conditions) gave the second-order rate constants with correlation coefficients of at least 0.995 in a least-squares fit. At least four different amine concentrations were used in each determination. The second-order rate constant was reproducible to within 5%. The total amine concentration was at least 10^{-4} M, which is at least 10 times the concentration of maleic anhydride. We found no buffer catalysis or autocatalysis for the reactions with maleic anhydride of three amines spanning the full range of basicity of our study.

N-(2,2,2-Trifluoroethyl)maleisoimide was hydrolyzed under the conditions of the aminolysis reactions. The UV spectrum of each product was recorded under reaction conditions. The initial spectrum of *N*-(2,2,2-trifluoroethyl)maleisoimide was measured for a solution in acetonitrile, since the compound reacts rapidly with water. Product development was monitored at three wavelengths (250, 255, and 260 nm). This permitted independent determination of concentrations of starting materials and the possible products, using three simultaneous equations, since the individual extinction coefficients were known from separate determinations.

Results and Discussion

Rate constants for the addition of amines to maleic anhydride were obtained by observing the reaction by UV spectroscopy under pseudo-first-order conditions. The observed rate constant (k_{obsd}) was then divided by the concentration of unprotonated amine to give the second-order rate constant, k, according to eq 1 and 2, where S is maleic anhydride.

$$k_{obsd}[S] = k[RNH_2][S] \qquad (1)$$

$$k = k_{obsd}/[(RNH_2)] \qquad (2)$$

Since reported pK_a values had been determined under conditions which were not the same as the conditions of our study, the pK_a' values (pH for half-neutralization under the reaction conditions) for the conjugate acids of the amines were determined by titration. Table I summarizes the pK_a' values and rate constants measured for the addition of primary straight-chain amines to maleic anhydride at 25 °C and in some cases at 15 °C. These data were used to obtain activation parameters.

The variation of k with the pK_a of the conjugate acids of the amines used in the study is presented in Figure 1. If all the amines react by a common mechanism with a common rate-determining step, we would expect a linear relationship between log k and pK_a.
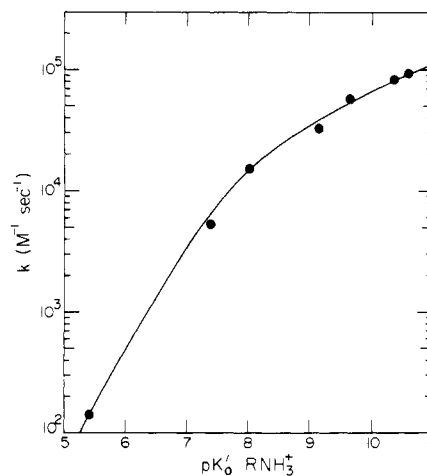
Figure 1. Dependence of observed second-order rate constant for aminolysis of maleic anhydride by primary amines as presented in Table I.

However, the relationship is clearly curved. Since the curve is concave downward, the nonlinearity is consistent with a change in rate-determining step with variation in basicity of the nucleophile.[8,9] The simplest kinetic scheme that will give this behavior is a two-step process involving an intermediate present at low steady-state concentrations, as in Scheme I.

Scheme I

$$RNH_2 + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} I \overset{k_2}{\longrightarrow} P$$
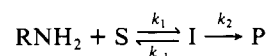
The general expression for k for each amine is eq 3.

$$k = k_1 k_2/(k_{-1} + k_2) \qquad (3)$$

Under conditions where the step corresponding to k_1 is clearly rate determining ($k_2 \gg k_{-1}$), eq 3 reduces to eq 4.

$$k' = k_1 \qquad (4)$$

For situations in which the second step is clearly rate determining ($k_{-1} \gg k_2$), the rate law is given by eq 5.

$$k'' = (k_1/k_{-1})k_2 \qquad (5)$$

We assume a linear relationship between the logarithms of the limiting rate constants (k' and k'') and the pK_a values of the conjugate acids of the amines (eq 6 and 7). Since a nucleophilic

$$\log k' = b'(pK_a) + c' \qquad (6)$$

$$\log k'' = b''(pK_a) + c'' \qquad (7)$$

reaction is involved, this is not formally a Brønsted plot and the b values would not relate to general base catalysis. Jencks has used the expression "β_{nuc}" for this parameter.[10] In our analysis, "b" terms are the same as "β_{nuc}".

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

$$1/k = 10^{-b'(pK_a+c')} + 10^{-b''(pK_a+c'')} \qquad (8)$$

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

$$k = 1/(10^{-b'(pK_a+c')} + 10^{-b''(pK_a+c'')}) \qquad (9)$$

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: $b'' = 0.95$, $b' = 0.23$, $c'' = -3.03$ (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_a range and the b'' and c'' to the lower pK_a region. Since the "c" terms are intercepts, they are equal to the hypothetical rate constants for addition of amines whose

(8) Leffler, J. E.; Grunwald, E. "Rates and Equilibria of Organic Reactions"; Wiley: New York, 1963; pp 187–192.

(9) Chin, J. *J. Chem. Soc., Chem. Commun.* **1980**, 1269.

(10) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963.

Table II. Rate and Equilibrium Constants

| amine	k_1, s^{-1}	k_2/k_{-1}	K_1, M^{-1}	K_e, M^{-1}
propyl	8.9×10^4	123	1.1×10^0	5.1×10^9
3-hydroxypropyl	7.9×10^4	83	6.7×10^{-1}	4.3×10^9
2-methoxyethyl	5.5×10^4	27	1.5×10^{-1}	1.8×10^9
2-fluoroethyl	4.3×10^4	12	5.0×10^{-2}	9.3×10^8
2-ethylacetyl	2.3×10^4	1.6	3.8×10^{-3}	4.5×10^8
2,2-difluoroethyl	1.7×10^4	0.67	1.1×10^{-3}	1.7×10^8
2,2,2-trifluoroethyl	5.7×10^3	0.023	1.3×10^{-5}	2.6×10^7

Scheme II
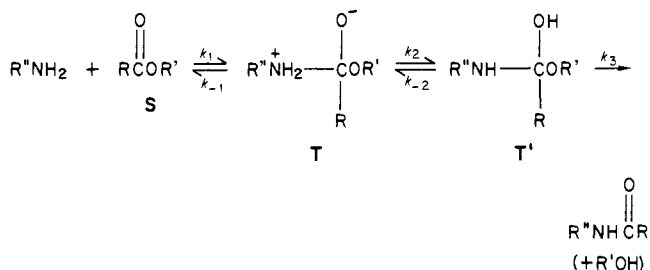
conjugate acid has a pK_a of 0.0 under the conditions where k_1 and k_2 are the respective rate-determining steps. These terms then were used to obtain values of k_1 (the same as k') and k_2/k_{-1} (from k''/k') for the reaction of each amine with maleic anhydride (see Table II).

Identification of the steps responsible for the curvature in Figure 1 permits analysis of the data. The reverse reaction, formation of maleic anhydride and amines from maleamic acids, has been shown to be subject to acid catalysis under the same reaction conditions for cases in which the amine leaving group is weakly basic. The step which is subject to acid catalysis is the interconversion of the uncharged and zwitterionic forms of the intramolecular addition complex (tetrahedral intermediate). With increasing acidity, this ceases to be rate limiting, and the breakdown of the zwitterion becomes rate determining. Using the principle of microscopic reversibility, we conclude that the limiting slopes in Figure 1 must result from the same rate-limiting steps as in the reverse direction. For the most basic amines, formation of the intermediate is rate determining, and for the least basic, proton transfer within the tetrahedral intermediate is rate determining. A mechanism incorporating these steps is presented in Scheme II. The zwitterionic adduct of amine and anhydride is T. This intermediate tautomerizes to the uncharged intermediate T', which then proceeds to the maleamic acid. We have omitted consideration of encounter complexes discussed in the paper on the hydrolysis reaction[6] since the current results are not directly affected.

Evidence has been obtained from studies of the hydrolysis of maleamic acids that conversion of the maleamic acid to the neutral tetrahedral intermediate (T') occurs prior to the rate-determining step.[5] For the case of the aminolysis of maleic anhydride under the conditions of our study, this is equivalent to assuming that conversion of T' to maleamic acids (k_3) is never rate limiting.

The hydrolysis of isomaleimides can be used to confirm this conclusion. Kirby has shown that in acidic solutions, *N*-methylisomaleimide is hydrolyzed exclusively to *N*-propylmaleamic acid.[5] Addition of water of isomaleimides rapidly produces intermediate T', the same intermediate as in Scheme II.
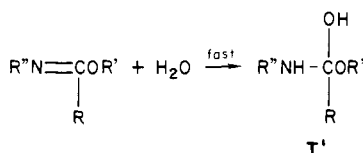
Therefore, Kirby's results show that the barrier toward formation of maleamic acid from T' is lower than the barrier to formation of anhydride if the amide is derived from methylamine. We have obtained the same result with the similarly basic propyl

derivative. In addition, for the isomaleimide derived from the least basic amine in our study, 2,2,2-trifluoroethylamine, we also find that only the maleamic acid is produced as the initial reaction product (analyzed as described in the Experimental Section). This confirms our earlier assumption that the rate-determining step at pH 4 is not conversion of the neutral intermediate T' to the maleamic acid (k_3) but is one of the prior steps.

We can use the steady-state assumption to derive a rate equation for the mechanism in Scheme II. On the basis of the preceding remarks, eq 3 will give the observed rate constant for all amines in our study. For the limit of the most basic amines, formation of T is rate determining. Therefore, eq 4 is valid at that limit and k' will measure k_1 (see Scheme II) for each amine. The values for the less basic amines are obtained from eq 6 since k' is not directly observed. The results are summarized in Table II. For the limit of the less basic amines, tautomerization (k_2) is rate determining. Therefore, we have an equilibrium between the reactants and the zwitterion T, k_1/k_{-1} (eq 5). Values for k'' obtained from eq 7 give $K_1 k_2$ for each amine. These are presented in Table II.

The two *b* values that best fit the data to eq 9 are 0.23 (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 Brønsted slope of 0 for the rate-determining step, k_2. The pK_a dependence of log k' then gives the pK_a dependence of log (k_1/k_{-1}), which is 0.95.

Our results permit the determination of equilibrium constants for formation of tetrahedral intermediates from amines and anhydrides. 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 $pK_a = 7.7$, the rate constant for expulsion of the amine (k_{-1}) is equal to the rate constant for the proton switch, k_2. The rate constant for the proton switch has been determined.[6] At the temperature of the current study it should be approximately 1×10^7 s^{-1} and be independent of the basicity of the amine.[10] The rate constant k_{-1} for the other amines can be obtained from eq 10 since k_1 is determined independently (see Table II).

$$k_{-1} = k_2(k_1/k - 1) \tag{10}$$

The pK_a dependence of both k_1 and k_{-1} are known since we have demonstrated that the slope for K_1 is 0.95.

$$d(\log k_1)/dpK_a = 0.23 \tag{11}$$

$$d(\log k_{-1})/dpK_a = -0.72 \tag{12}$$

The limiting slopes in Figure 1 are similar to those that have been determined for other reactions of carbonyl 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 Brønsted treatment we have used to the "N_+" basis.[12] The predicted value is twice our observed result of 0.23. For comparison, in most cases where the Brønsted slope has been measured accurately for the addition of nucleophiles to carbonyl compounds (in which addition is rate limiting), the slope of log k vs. pK_a 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 carbonyl compounds.[13] Our results support this conclusion.

The central point of curvature in a biphasic Brønsted plot is designated pK^o by Moodie and Castro.[14] Their kinetic analysis

(11) Bernasconi, C. F.; Hibdon, S. A.; McMurry, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 3459.

(12) Ritchie, C. D. *J. Am. Chem. Soc.* **1975**, *97*, 1170.

(13) Palling, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 4869.

uses this quantity as an adjustable parameter. pK^o corresponds to the case where k_{-1} and k_2 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^o 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^o 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^o 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^o point results from a different balancing of effects. The curvature in the Brønsted 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^o 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.[15,16] 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:

$$RNH_2 + \text{maleic anhydride} \overset{K_e}{\rightleftharpoons} \text{maleamic acid}$$
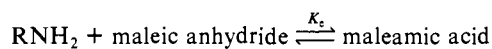
The basicity dependence of the equilibrium is plotted in Figure 2. Equation 13 fits the data with a correlation coefficient of 0.996, giving the line in Figure 2.

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

The slope of the line (b) is an indication of the extent of positive charge on the nitrogen atom of the amide.[15] For comparison, Jencks and co-workers have reported the dependence of the equilibrium constant for formation of acetanilides on the pK_a of a series of substituted anilines.[16] The slope in that study is 0.61. Fersht and Requena found a slope of 0.51 for formation of formamides.[15] 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.

Figure 2. Equilibrium constants (50 °C) for reaction of maleic anhydride with primary alkylamines.

The data also provide accurate absolute equilibrium constants measured at pH 4, 50 °C. These values can be used to determine the complete equilibrium between the carboxylic acid and amine since the dimensionless equilibrium constant for formation of maleic anhydride and water (at unit activity, 60 °C) from maleic anhydride has been estimated by Eberson and Welinder[17] to be 0.01. Multiplication of K_e by 0.01 gives K_e' through a thermodynamic cycle.

$$RNH_2 + \text{maleic acid} \overset{K_e'}{\rightleftharpoons} \text{maleamic acid} + H_2O$$
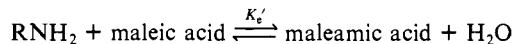
The resulting calculated equilibrium constants ($K_e' = 0.01 K_e$) correspond to free energies of hydrolysis from +7.6 kcal/mol for the trifluoro derivative to +11 kcal/mol for the n-propyl compound. The uncertainty in the equilibrium constant for formation of maleic acid from maleic anhydride is the major source of possible error. For comparison, Jencks has estimated the free energy of hydrolysis of p-methoxyacetanilide to be +3.7 kcal/mol at 25 °C.[16] The amine in this case is about as basic as that in our trifluoro derivative. The difference of 4 kcal/mol may reflect destabilization due to sharing of electron density on nitrogen in the acetanilide between the amide bond and its benzene ring.

(14) Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1974**, 658.

(15) Fersht, A. R.; Requena, Y. *J. Am. Chem. Soc.* **1971**, *93*, 3499.

(16) Jencks, W. P.; Schaffhausen, B.; Tornheim, K.; White, H. *J. Am. Chem. Soc.* **1971**, *93*, 3917.
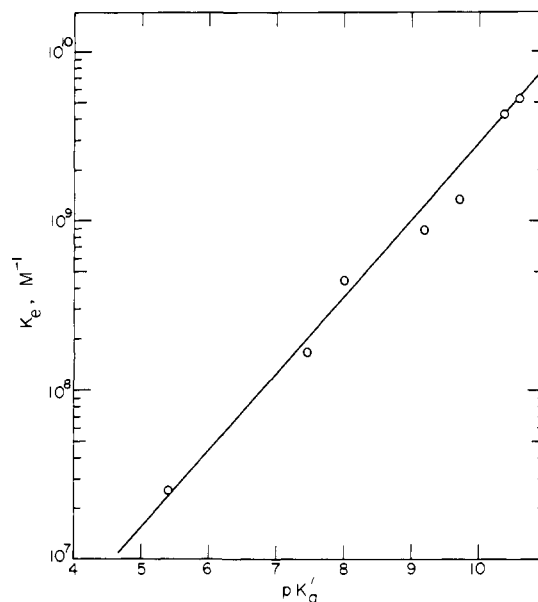
(17) Eberson, L.; Welinder, H. *J. Am. Chem. Soc.* **1971**, *93*, 5821.