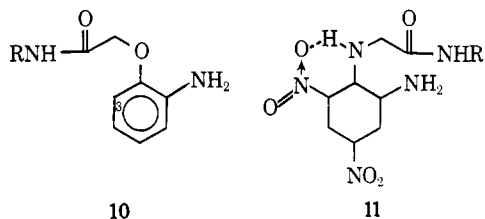conformational restriction on the side chain. In the absence of a sizable ortho substituent (at C-3 in **10**), the nonproductive, planar transoid conformation **10** is the more likely, since it avoids steric interference with the solvated aniline (or anilinium ion). Hydrogen bonding

10   **11**

between the o-nitro group and NH (**11**) would serve to increase the population of molecules in the productive cisoid form. This factor has been found to increase the rate constant for amide hydrolysis in **12** over that in **13** ca. 100-fold.[17b] Furthermore, the introduction of a

bulky substituent (such as nitro in **11**) should also have

12   **13**   **14**
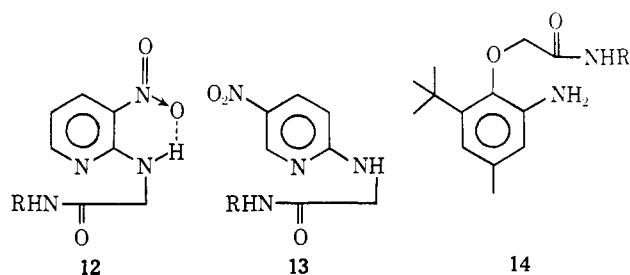
the effect of increasing considerably the population of the productive cisoid conformer. This is, indeed, the case; the rate constant for general acid catalyzed lactamization of **14** has been found to exceed that of **5c** by a factor of ca. 3000.[29] The assumption that the rapid conversion of **2** to **3** is strongly assisted by stereopopulation control is, therefore, entirely reasonable.

(29) To be published separately.

Aminolysis of Acid Anhydrides in Water. I. Rate Acceleration by Hydrophobic Bonding in Reactions between Small Molecules

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Abstract: The aminolyses of phthalic anhydride in water by 14 aliphatic and alicyclic secondary amines were examined. The reactions were first order in both anhydride and amine neutral molecule concentrations when the total amine concentration (cation plus neutral molecule) did not exceed 5×10^{-3} M. At higher amine concentrations the reactions of amines containing six or more carbon atoms became zero order in amine concentration. Product analysis indicated that the amine neutral molecules participated primarily in the aminolysis reactions and did not significantly catalyze the parallel reaction in which the anhydride was being hydrolyzed. Linear correlations were observed between the logarithms of the aminolysis rate constants for amines that were structurally related and the logarithms of the partition coefficients of the amines between cyclohexane and 1.0 M NaOH but not between the logarithms of the rate constants and the acid dissociation constants of the amine cations. These results are suggested to be consistent with mechanisms in which either the reactants are approximated by intermolecular hydrophobic bonds prior to the rate-determining step in which a N–C bond is partially formed or in which the transition states are stabilized by hydrophobic forces.

Several reports have recently appeared about the accelerating effects on chemical reactions that result from approximation of the reactants by intermolecular hydrophobic bond formation. For example, pre-rate-determining step hydrophobic bond formation between reactants has been postulated to occur during the aminolyses of o-acylhydroxyquinolines[1] and of p-nitrophenyl esters[2] by aliphatic amines. In both of these studies the acceleration effects were only significant when molecules with large hydrophobic moieties were allowed to react. The present study was undertaken to ascertain whether similar effects could be observed during the aminolysis of phthalic anhydride by secondary amines with relatively short carbon chains.

Previous mechanistic studies on the aminolysis of anhydrides have been largely confined to the reactions occurring in nonaqueous solvents.[3-8] Under these conditions the reactions are very complex and, in many cases (e.g., ref 3 and 4), probably involve rate-determining rearrangement or decomposition of a tetrahedral intermediate. The presence or absence of intermolecular hydrophobic bonding between reactants would,

(1) T. Maugh and T. C. Bruice, *J. Amer. Chem. Soc.*, **93**, 6584 (1971).
(2) J. R. Knowles and C. A. Parson, *Chem. Commun.*, 755 (1957).

(3) T. Higuchi, I. H. Pitman, and H. L. Fung, *J. Chem. Soc.*, in press.
(4) D. B. Denney and M. A. Greenboum, *J. Amer. Chem. Soc.*, **78**, 877 (1965).
(5) M. H. Loucheux and A. Banderet, *Bull. Soc. Chim. Fr.*, 2242 (1961).
(6) L. M. Livinenko, D. M. Aleksandrova, and A. A. Zhilinskaya, *Ukr. Khim. Zh.*, **26**, 476 (1960); *Chem. Abstr.*, **55**, 10022h (1961).
(7) S. Bruckenstein and A. Saito, *J. Amer. Chem. Soc.*, **87**, 698 (1965).
(8) J. Hipkin and D. P. N. Satchell, *J. Chem. Soc.*, 345 (1966).

consequently, be difficult to determine in these reactions.

On the other hand, it was anticipated that the rate-determining step in the aminolyses of phthalic anhydride in water by strongly basic amines would occur before a tetrahedral intermediate was formed (or it may proceed by a concerted mechanism) and be similar to what has been observed during the aminolysis of other reactive acylating agents in water with strongly basic amines.[9] It was thus anticipated that the rates of these reactions would be sensitive to the hydrophobic properties of the amine if intermolecular hydrophobic bond formation occurred between the reactants.

In addition to providing mechanistic information about the aminolysis of anhydrides in water, the rate constants sought in this study should be useful in predicting the course of reactions in water between 1,2-dicarboxylic acids and amines. This is the case because previous studies[10-12] have shown that these reactions may be the cause of some drug degradations in water and that they are facilitated by reactions between amines and the cyclic acid anhydrides which are always in equilibrium with 1,2-dicarboxylic acids.

Experimental Section

Reagents. Phthalic anhydride was recrystallized from a chloroform-cyclohexane mixture (mp 129–130°). All the amines were refluxed with KOH pellets, fractionally distilled under vacuum (for a sufficient number of times until their boiling point range was no greater than 2°), and stored under nitrogen in closed containers in the refrigerator. Each amine's purity was checked by gas or thin-layer chromatography, and their structures were confirmed by nmr. Concentration of the amine in stock solutions was checked by titration with standard acid. Cyclohexane was distilled over phosphorous pentoxide. Spectrophotometric grade dioxane was used without purification. Double-distilled water stored in Pyrex was used for all solutions. All other reagents were of analytical grade.

Ionization Constants (pK_a Values). The ionization constants at ionic strength 1.0 M (adjusted with NaCl) and 25° were determined potentiometrically[13] in water and in a 10% solution of dioxane in water. Ionization constants in 10% dioxane solution were found to be, on the average, about 0.2 pK_a unit lower than those in water.

Partition Coefficients. Partition coefficients of the amines were calculated from measurements of the concentration of amine in a solution of cyclohexane that had been equilibrated with 1.0 M sodium hydroxide solution at 25°. The amine concentration was determined by a nonaqueous titration method.[14]

Temperature and pH Control. Temperature was maintained at 25.0 ± 0.1° during kinetic runs and ionization constants and partition coefficients were determined by using circulating water baths controlled with Sargent thermistors. pH was maintained constant by the use of appropriate buffers.

Kinetic Studies. Rate constants were calculated from rates of change of ultraviolet absorbance during a reaction. Measurements were made at 302 nm because this is a wavelength where phthalic anhydride absorbs much more strongly than the reaction products, phthalic acid and phthalic acid amides. Cary Models 14A and 15 recording spectrophotometers were used. The instruments were modified by drilling a hole in the cell compartment cover just large enough to accommodate a 15-gauge hypodermic needle. Concentrated solutions of phthalic anhydride in anhydrous dioxane (0.3 ml) were placed in the 1-cm absorption cell and aqueous buffer solutions of amine (2.7 ml) in a hypodermic syringe. The instrument's recorder was turned on after insertion of the hypodermic needle through the cell compartment cover. The solutions were

then mixed and subsequent changes in absorbance measured. Each reaction mixture initially contained a concentration of phthalic anhydride within the range $(3.4-6.7) \times 10^{-4}$ M and had an ionic strength of 1.0 M (adjusted with sodium chloride) and contained 10% dioxane.

Product Ratio at Equilibrium. The ratio of concentrations of phthalic acid and N,N-diethylphthalamic acid following the reaction of phthalic anhydride in an aqueous solution of diethylamine (at pH 5.30, $I = 1.0$ M, 25°, and containing 10% dioxane) was calculated by analyzing the ultraviolet spectrum of the equilibrium mixture and comparing it to that of authentic samples of phthalic acid and N,N-diethylphthalamic acid under identical conditions. The sample of phthalamic acid was synthesized by the method of Maxim[15] (mp 151–152°). The calculated molar absorptivities that were used in the spectral analysis were: for phthalic acid ϵ_{280} 867.5, ϵ_{265} 832.5; and for N,N-diethylphthalamic acid ϵ_{280} 670.0, ϵ_{265} 795.0. The value of the ratio of [acid]:[amide] was calculated to be 4.34 ± 0.11.

Results and Discussion

Aminolysis Rate Constants. When the initial total amine concentration, $[\text{amine}_T]_0$, was at least five times greater than the initial anhydride concentration, $[\text{anhydride}]_0$, the rates of change in ultraviolet absorbance which followed the mixing of the reactants obeyed a first-order rate law. Independent studies also showed that phthalic acid and its amides, which were the products of the hydrolysis and aminolysis of phthalic anhydride, respectively, were stable against further reaction under the experimental conditions. Consequently, the pseudo-first-order rate constants, k_{obsd} values, which were calculated from the absorbance changes, were related to the rate of change in anhydride concentration, v, by the identity

$$v = k_{obsd}[\text{anhydride}] \tag{1}$$

k_{obsd} values were found to have a first-order dependence on $[\text{amine}_T]_0$ for reactions of amines containing less than six carbon atoms but they exhibited both a first-order and a zero-order dependence for reactions of amines containing larger numbers of carbon atoms. The order of dependence in these latter reactions changed from first order at low values of $[\text{amine}_T]_0$ to zero order at high values of $[\text{amine}_T]_0$. Typical plots of k_{obsd} against $[\text{amine}_T]_0$ for reactions of amines containing less than six carbon atoms and six or more carbon atoms are shown in Figures 1 and 2, respectively. The value of the total amine concentration at which the transition from first- to zero-order dependence occurred decreased with increasing numbers of carbon atoms in the amine. Approximate values of some of these critical concentrations are listed in Table I. Although the precise nature of these critical concentrations was not investigated it seems likely that they are

(9) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968).

(10) T. Higuchi and T. Miki, *ibid.*, **83**, 3899 (1961).

(11) T. Higuchi, T. Miki, A. C. Shah, and A. K. Herd, *ibid.*, **85**, 3655 (1963).

(12) T. Higuchi and F. D. Pisano, *J. Pharm. Sci.*, **53**, 644 (1964).

(13) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962.

(14) J. S. Fritz, "Acid Base Titration in Non-Aqueous Solvents," The G. Frederick Smith Co., Columbus, Ohio, 1952.
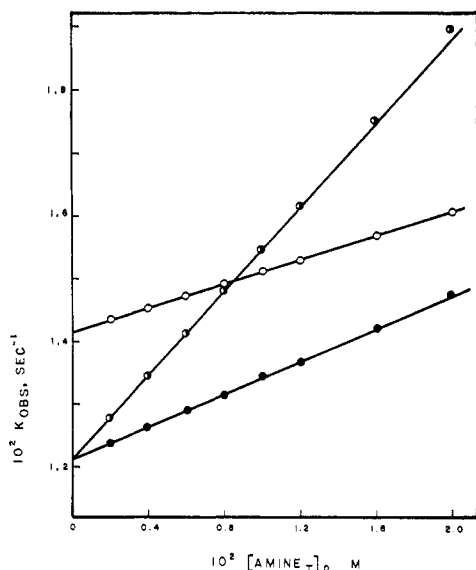
Table I. Approximate Values of $[\text{Amine}_T]_0$ at Which the Dependence of the First-Order Rate Constants for Disappearance of Phthalic Anhydride Changed from First to Zero Order in $[\text{Amine}_T]_0$

Amine	pH	Critical $[\text{amine}_T]_0$, 10^2 M
Dipropylamine	5.03	>2.0
Butylpropylamine	4.67	>1.6
Dibutylamine	4.54	1.2
Amylbutylamine	4.56	0.8
Diamylamine	4.55	0.5

(15) N. Maxim, *Ann. Chim. (Paris)*, **9**, 62 (1928).

Figure 1. Plots against [amine$_T$]$_0$ of the pseudo-first-order rate constants for disappearance of phthalic anhydride in aqueous solutions of (◑) piperidine at pH 4.54, (○) diethylamine at pH 5.37, and of (●) methylpropylamine at pH 4.63.

the critical micelle concentrations (CMC) of the amine cations in solutions of ionic strength 1.0 M. If this assumption is correct it leads to the conclusion that the reactive species of amine in the aminolysis reaction is one that is free and not part of the micelle. Hence, once the CMC of the amine has been exceeded, the addition of extra amine does not significantly increase the thermodynamic activity of free amine and consequently the rate of aminolysis does not increase.

The dependence of the aminolysis rate constants on [amine$_T$]$_0$ and pH was investigated exclusively from rate measurements in experiments where the total amine concentration was well below the CMC for the particular amine. Hence, under these conditions, values of k_{obsd} were related to the total amine concentration by the identity

$$k_{obsd} = k_H + k_C[\text{amine}_T]_0 \qquad (2)$$

Values of k_H that were calculated from plots such as those in Figures 1 and 2 were identical with values of the pseudo-first-order rate constant for hydrolysis of phthalic anhydride under identical conditions except that amine was excluded. These latter values were calculated from separate experiments. Consequently, k_H values were taken to be the non-amine-catalyzed rate constants for hydrolysis of phthalic anhydride.

k_C values which were subsequently used to calculate pH-independent, second-order rate constants were not calculated graphically from k_{obsd} values but were calculated by using eq 2 and substituting into it values of k_{obsd}, k_H, and [amine$_T$]$_0$ from an experiment at a particular pH. This was done because it was difficult to keep the pH constant when the amine concentration was varied widely and k_C values were very susceptible to changes in pH. A typical set of data is shown in Table II.

It was possible that the k_C values included contributions from both the aminolysis rate constant and from a catalytic rate constant for the amine or its cation acting as general base or general acid catalysts for the
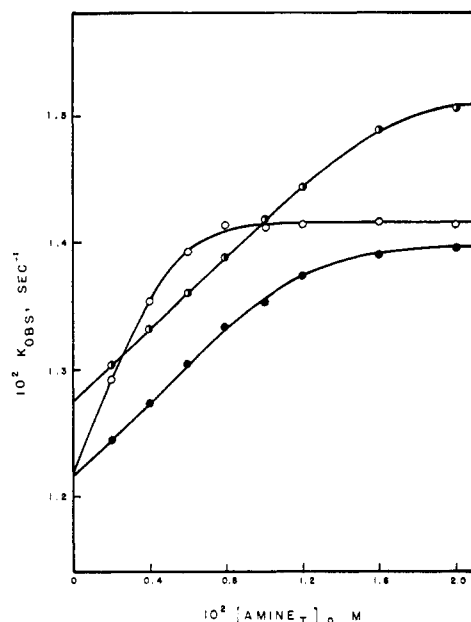

Figure 2. Plots against [amine$_T$]$_0$ of the pseudo-first-order rate constants for disappearance of phthalic anhydride in aqueous solutions of (◑) dipropylamine at pH 5.03, (○) diamylamine at pH 4.55, and of (●) dibutylamine at pH 4.54.

Table II. Kinetic Data for the Aminolysis of Phthalic Anhydride by Diethylamine at 25° in a Solution of 10% Dioxane in Water and $I = 1.0$ M

$10^3[\text{amine}_T]_0$, M	pH	$10^2 k_{obsd}$, sec^{-1}	$10^2 k_C$, M^{-1} sec^{-1}	$10^{-4} k_A$, M^{-1} sec^{-1}
0	5.36	1.41		
2.0	5.36	1.43	7.50	1.88
4.0	5.35	1.44	7.25	1.84
6.0	5.35	1.46	7.50	1.89
8.0	5.37	1.47	7.50	1.81
10.0	5.42	1.51	9.20	1.96
12.0	5.44	1.54	10.50	2.14
16.0	5.47	1.58	10.06	1.91
20.0	5.50	1.61	9.85	1.75

hydrolysis reaction. However, results of an experiment in which the actual ratios of hydrolysis and aminolysis product concentrations were compared to those predicted from the measured rate constants for the parallel reactions suggested that any catalysis of the hydrolysis by the amines was very small compared to their nucleophilic participation in the aminolysis reaction. When diethylamine and phthalic anhydride were allowed to react at pH 5.30, the ratio [phthalic acid]:[N,N-diethyl-phthalamic acid] was determined to be 4.34 ± 0.11. The value of this ratio that would be predicted from the ratio of k_H:k_C[amine] (from eq 2) is 4.10. Because this latter calculation involves the assumption that the amine species are only involved in the aminolysis reaction, the near equality of the values of the determined and calculated ratios suggests that the amines are not significantly catalyzing the hydrolysis reaction. It is assumed that similar assumptions can be made for all the reactions studied.

The pH dependence of k_C values suggested that the amine neutral molecule rather than its cation was the major amine species that participated in the aminolysis reaction. Hence, as can be seen from the example displayed in Figure 3, plots of log k_C against pH increased
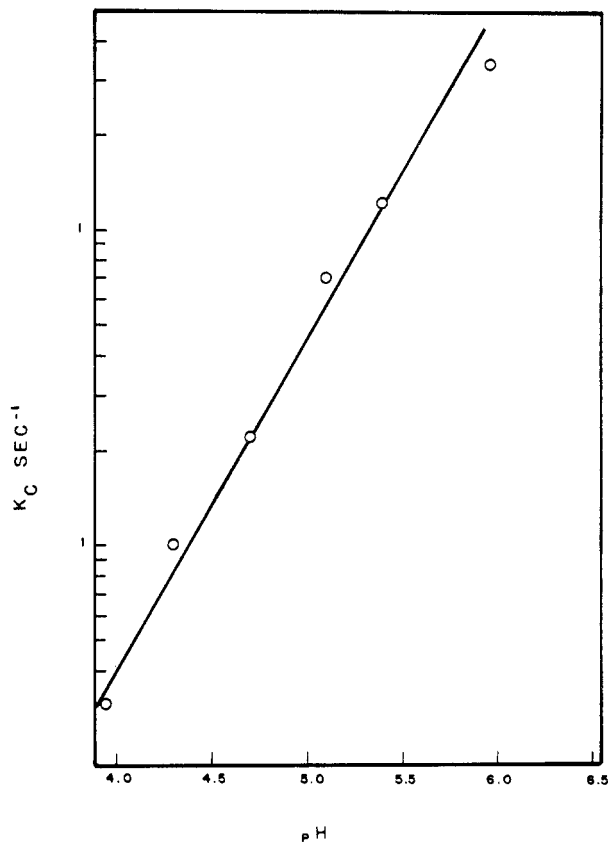
Figure 3. Plot of log k_c against pH for the aminolysis of phthalic anhydride by piperidine at 25° in a 10% solution of dioxane in water and $I = 1.0\ M$. The slope of the drawn line is 1.0.
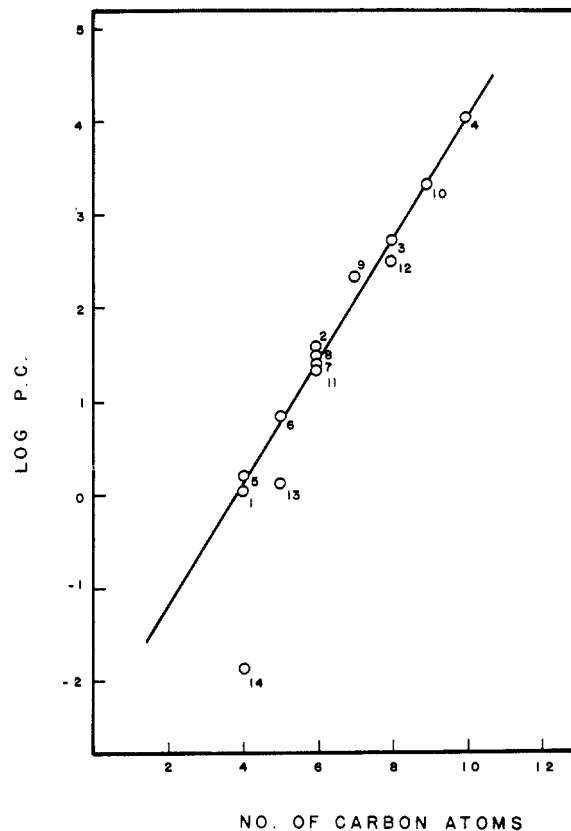

Figure 4. Plot of the logarithms of the partition coefficients of secondary amines between 1.0 M NaOH and cyclohexane against the number of carbon atoms in the amine.

linearly with a slope very close to 1.0. Values of a pH-independent, second-order rate constant for aminolysis (k_A) were subsequently calculated by dividing k_C values by the fraction of the total amine that was present as the neutral molecule at a particular pH. Except in the example displayed in Figure 3, the k_C values used in these calculations were obtained over a pH range of no greater than 1 unit. Values of k_A are listed in Table III.

Table III. Kinetic Data for the Aminolysis of Phthalic Anhydride[a] by 14 Secondary Amines at 25° in Water Containing 10% Dioxane and at $I = 1.0\ M$

Amine	$10^2[\text{amine}_T]_0$ range, M	pH range	$10^5 k_A$, $M^{-1}\ \text{sec}^{-1}$	No. of experiments
Diethyl- (1)	0–2.0	5.4–5.5	0.19	9
Dipropyl- (2)	0–1.2	5.0–5.1	0.61	7
Dibutyl- (3)	0–0.8	4.5	2.80	5
Diamyl- (4)	0–0.6	4.5–4.6	7.29	4
Methylpropyl- (5)	0–1.7	4.6	0.99	9
Methylbutyl- (6)	0–1.2	4.6	1.50	7
Methylamyl- (7)	0–1.8	5.0–5.1	2.18	8
Butylethyl- (8)	0–1.2	4.8	0.92	7
Butylpropyl- (9)	0–1.2	4.7	1.42	6
Butylamyl- (10)	0–0.6	4.5–4.6	4.95	4
Diisopropyl- (11)	0–1.2	5.3–5.4	0.30	7
Diisobutyl- (12)	0–1.2	4.5	1.23	7
Piperidine (13)	0–2.0	4.5–4.6	6.98	9
Morpholine (14)	0–2.0	3.9–4.1	1.63	9

[a] Initial concentration was within the range $(3.4–6.7) \times 10^{-4}\ M$.

Partition Coefficients and Ionization Constants of the Amines. The calculated partition coefficients of

Table IV. Partition Coefficients of Secondary Amines between Water[a] ($I = 1.0\ M$) and Cyclohexane and Ionization Constants of Secondary Amine Cations ($I = 1.0\ M$) at 25°

Amine	Partition coefficient	$pK_{a_{\text{water}}}$	$pK_{a_{10\%\ \text{dioxane}}}$
Diethyl-	1.05	10.98	10.73
Dipropyl-	34.0	10.90	10.71
Dibutyl-	479	10.98	10.84
Diamyl-	(10,000)[b]	11.10	10.90
Methylpropyl-	1.48	10.72	10.51
Methylbutyl-	6.59	10.85	10.61
Methylamyl-	23.9	10.91	10.68
Butylethyl-	33.0	10.94	10.72
Butylpropyl-	239	10.86	10.69
Butylamyl-	1,790	10.92	10.71
Diisopropyl-	19.7	10.94	10.73
Diisobutyl-	(371)[c]	10.78	10.50
Piperidine	1.25	11.14	10.88
Morpholine	0.01	8.76	8.62

[a] Water containing 1.0 M NaOH. [b] Estimated from extrapolation of the line in Figure 2. [c] Estimated as described in the text.

the amines are listed in Table IV and their logarithms are plotted against the number of carbon atoms in the amine in Figure 4. The closeness with which each of the straight chain aliphatic amines fits the linear plot in Figure 4 indicates that each methylene group that is added to the carbon chain makes an approximately equal contribution to the free energy of transfer of the amine between water and cyclohexane. Hence, it suggests that the carbon chains in these amines are independent of each other and that no significant interchain hydrophobic bonding occurs. It was originally thought that some phenomenon of this type might in-
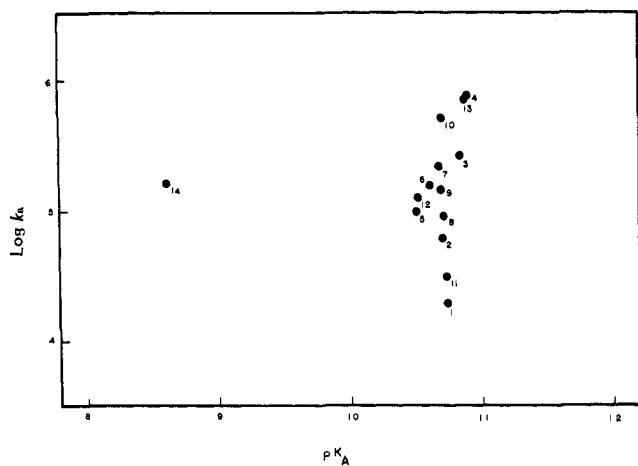
Figure 5. Plot of the log k_A against the pK_a of the amine cation for the aminolyses of phthalic anhydride.

Figure 6. Plots of log k_A for the aminolyses of phthalic anhydride against the logarithms of the partition coefficients of the amines between 1.0 M NaOH and cyclohexane.

fluence the relative reactivity of symmetrical and unsymmetrical aliphatic secondary amines. The slope of the line in Figure 4 indicates that the contribution of each methylene group to the free energy of transfer is 870 cal. Other studies[16] have yielded values of the methylene group contribution between 800 and 900 cal.

Separate studies which have been carried out in our laboratories[17] have led to the conclusion that the free energy of transfer of hydrocarbon functions between water and nonpolar solvents decreases in a linear fashion with increasing surface area of the function. Hence, it is likely that the explanation for the fact that the values in Figure 4 for piperidine and the branched-chain amines fall below the line for the straight-chain amines is because these molecules have a smaller surface area than the isomeric straight-chain amines. The partition coefficient for morpholine, which falls well off the line, would not be expected to be comparable to that of the other amines because it contains an oxygen atom.

The partition coefficient of diisobutylamine was not measured because of experimental difficulties. The value of 371 was estimated by taking the measured value of the partition coefficient for diisopropylamine and assuming that the addition of two methylene groups to yield diisobutylamine would decrease the free energy of transfer by 1740 cal (*i.e.*, 2 × 870).

The fact that the acid dissociation constants of all the amine cations except morpholine fall within the range 10.71 ± 0.21 indicates that the length of or structure of the hydrocarbon chain in dialkylamines has very little influence on the ionization reaction. Consequently, it is expected that these features would have very little influence on the stabilization of positive charge on the nitrogen atom during the aminolysis reaction.

Structure–Reactivity Relationships. The plot of log k_A against pH in Figure 5 suggests that no simple relationship exists between the basicity of these amines toward a proton and their nucleophilicity in the aminolysis reaction. Jencks[9] observed a similar behavior during the aminolysis of very reactive acylating reagents such as 2,4-dinitrophenyl acetates by strongly basic amines and concluded that very little positive charge
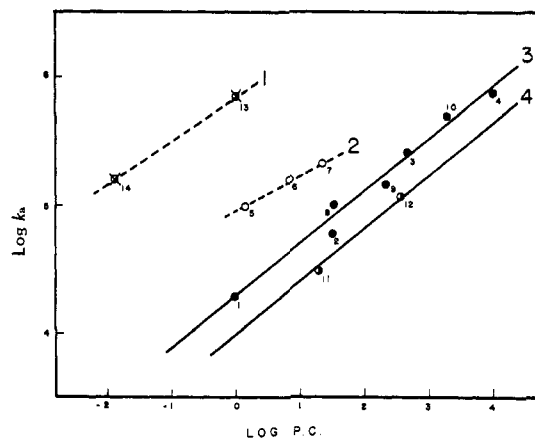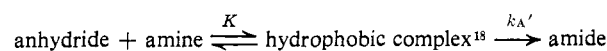
had been generated on the amine nitrogen atom (and consequently very little N–C bond formation had occurred) in the rate-determining transition state for aminolysis. This author suggested that the rate-determining step occurred earlier along the reaction coordinate than the point where a tetrahedral intermediate was formed or a concerted displacement occurred.
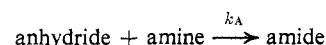
We believe that the present results can be interpreted in a similar fashion but that, in addition, they indicate that the reactants are either approximated prior to the rate-determining step by intermolecular hydrophobic bond formation or that the rate-determining transition state is stabilized by hydrophobic interactions.

These alternative mechanisms can be depicted as follows.

Mechanism 1

$$\text{anhydride} + \text{amine} \underset{K}{\overset{}{\rightleftharpoons}} \text{hydrophobic complex}[18] \xrightarrow{k_A'} \text{amide}$$

Mechanism 2

$$\text{anhydride} + \text{amine} \xrightarrow{k_A} \text{amide}$$

If mechanism 1 is occurring, the value of the calculated second-order rate constant for aminolysis, k_A, would be the product of the formation constant for the hydrophobic complex,[18] K, and the first-order rate constant for aminolysis within the complex k_A'. Hence, values of k_A would be expected to increase as the tendency for intermolecular hydrophobic bonding between reactants increased because this would lead to larger values of K. It is believed that the frequency of the intrahydrophobic complex aminolysis reaction would be greater than that for an intermolecular reaction between nonapproximated molecules.

If mechanism 2 was occurring, the value of k_A would be expected to increase as the strength of hydrophobic bonds within the rate-determining transition state increased. The energy released by formation of these bonds would decrease the free energy of the transition state and facilitate the aminolysis reaction.

These conclusions were reached as a result of relationships which apparently exist between the aminolysis rate

(16) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969.
(17) M. J. Harris, Ph.D. Thesis, University of Kansas, 1971.

(18) The structures of these complexes are not known but it is likely that they are formed by interactions between the hydrophobic portions of both the anhydride and amine reactants.
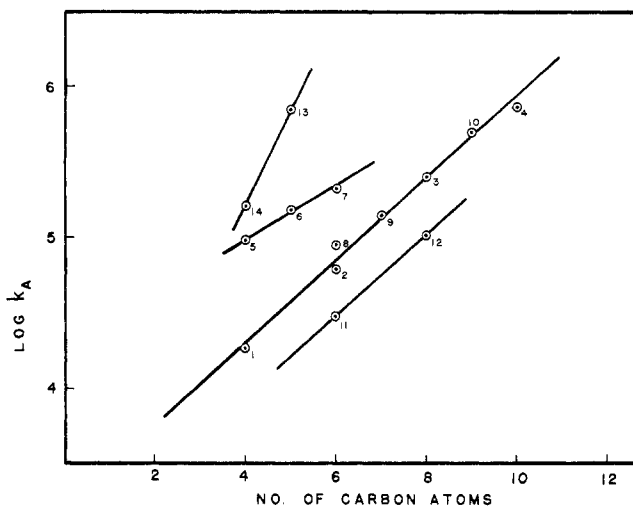
Figure 7.

constants for reactions of structurally similar amines and their hydrophobic character. This behavior can be seen in Figure 6 where the logarithms of the aminolysis rate constants are plotted against the logarithms of the partition coefficients of the amines between cyclohexane and water. The reason for selecting these partition coefficients of the amines as a measure of their hydrophobic character is because this property has frequently been shown to be directly related to such other hydrophobic properties as CMC and vapor pressure above aqueous solutions. In the present context it is believed to be proportional to the tendency that the amine possesses to form intermolecular hydrophobic bonds with phthalic anhydride or within the transition state.

Examination of Figure 6 reveals that the amines studied fall onto one of four straight lines. The secondary amines on line 1 are cyclic amines and those on lines 2, 3, and 4 are, respectively, ones with one methyl substituent and one longer straight-chain aliphatic group, ones with two straight-chain aliphatic groups larger than methyl, and ones with two branched-chain substituents. Within any one of these four classes of amine it appears that the aminolysis rate constant increases with increasing hydrophobic character (or partition coefficient) of the amine in a linear fashion.

When the data on lines 3 and 4 (i.e., for straight-chain aliphatic secondary amines) were plotted against the number of carbon atoms in the amine rather than their partition coefficient they also yielded two parallel straight lines, as shown in Figure 7. This result was expected because, as shown in Figure 4, the logarithms of the partition coefficients are themselves linearly related to the number of carbon atoms. Calculations based on the slope of this line ($\Delta\Delta F^{\pm} = -RT \ln (k_n/k_{n-1})$) indicate that each methylene group lowered the free energy of the reaction by $\simeq 380$ cal. This value is surprisingly close to that predicted[19] for hydrophobic bonding via minimum contact but is less than the contribution each methylene group makes to the free

energy of transfer of the amines from water to cyclohexane. Although all the lines in Figure 6 are not strictly parallel it is believed that the increases in rate constants along each line are also related to increases in hydrophobic bonding potential.

It remains to account for the existence of four nearly parallel straight lines in Figure 6. It is believed that these arise because of differences in the stereochemistry around the nitrogen atom from one class of amines to the other and in the steric consequences of proceeding from the hydrophobically bound reactants into the rate-determining step where a N–C bond is at least partially formed. It is suggested that in proceeding from the cyclic secondary amines (line 1) through the branched-chain secondary amines (line 4) there is an increasing amount of steric crowding around the nitrogen atom. Hence, as a N–C bond begins to form there would be an increasing loss of entropy and corresponding increase in free energy in the rate-determining transition state. A corresponding effect was not observed in the formation of a N–H bond in the ionization reaction where, as pointed out earlier, the free energy change in this reaction was not apparently affected by the length or structure of the aliphatic chains. However, it is likely that the proton is so much smaller than the anhydride molecule (the electrophile in this step of the aminolysis reaction) that only a much smaller loss of entropy was experienced. A similar explanation has been proposed[20] to account for the fact that increasing the bulk of groups attached to the nitrogen atom lowers the equilibrium constant for the formation of trimethyl-boron–amine complexes, whereas, again, it has little effect on ionization constants of the amines.

When Maugh and Bruice[1] were discussing the rate accelerating effects of hydrophobic bonding in the aminolysis of o-acylhydroxyquinolines they pointed out that it was hard to distinguish between pre-rate-determining step complex formation and stabilization of the transition state by hydrophobic bonding because no saturation kinetics were observed. Although the rate constants for aminolysis in the present study did become independent of amine concentrations when these were high, the shapes of plots of log k_{obsd} against $[amine_T]_0$ were not paraboloid but were discontinuous straight lines (see Figure 2). Hence, Michaelis–Menten type saturation kinetics were not observed in this study and similar arguments to those presented by Bruice can be used to support an alternative mechanism (mechanism 2 in this paper) in which the rate-determining step is stablized by hydrophobic bonding rather than one in which pre-rate-determining complexation occurs.

However, the important conclusion is that one or the other of these mechanisms involving hydrophobic bonding appears to be important in the reactions of these relatively simple small molecules.

(19) G. Nemethy and H. Scheraga, *J. Phys. Chem.*, **66**, 1773 (1962).

(20) J. W. Smith in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, London, 1968.