Aminolysis of Acid Anhydrides in Water. II.[1] Nonlinear Structure–Reactivity Relationships in the Aminolyses of Phthalic and Succinic Anhydrides

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Abstract: The reactions in water of 21 primary and secondary amines with phthalic and succinic anhydrides were examined. Each reaction was first order in both anhydride and amine neutral molecule concentrations, and product analysis showed that the amines did not significantly catalyze the hydrolysis reactions of the anhydrides. Plots of the logarithms of the aminolysis rate constants against the pK_a values of the amine cations were not linear and revealed that the reactions with weakly basic amines were considerably more sensitive to the basicity of the amine than were the reactions with the strong bases. The results suggest that a considerable amount of N–C bond formation has occurred in the rate-determining transition state for reactions with the weakly basic amines and that very little rate facilitation is brought about by hydrophobic bonding between reactants or in the transition state. This behavior thus contrasts markedly with the structure–reactivity relationships exhibited by strongly basic amines which were discussed in part I of this series.

In part I[1] of this series, it was shown that the rates of aminolysis of phthalic anhydride by strongly basic secondary amines were relatively insensitive to the basicity of the amine but were significantly influenced by the hydrophobic and steric properties of the amine.

The present study is an extension of this work and was undertaken to ascertain the influence of these factors on the aminolyses of phthalic and succinic anhydrides by weakly basic primary and secondary amines.

Experimental Section

All the experimental details were identical with those reported in part I[1] except for the following additional points.

Reagents. Succinic anhydride was prepared using method B given in Vogel.[2] The solid amines were recrystallized from appropriate solvents until their melting points corresponded to literature values. Technical grade dioxane was purified as described in Vogel.[2] Phthalamic acid was prepared by the method of Anschütz[3] (mp 169°).

Ionization Constants. Ionization constants in water at 25° and $I = 1.0\ M$ (adjusted with sodium chloride) were determined either potentiometrically[4] or spectrophotometrically.[4] The calculated values were accurate to within ±0.05 pK unit and are displayed in Table I. Unfortunately, in contrast to the procedure in part I,[1] 10% dioxane was not present in the solutions in which the pK determinations were made, whereas it was present in the reaction mixtures of the kinetic studies. Consequently, the values of pH-independent rate constants and the structure–reactivity correlations which were calculated by using the measured pK values are probably different from the absolute values. However, because all the pK values used are likely to be in error by a constant amount,[5] it is believed that the relative magnitudes of the rate constants calculated in this study are correct.

Kinetic Studies. The analytical wavelength used in the studies with succinic anhydride was chosen on the basis of optimizing absorbance changes during the reaction. As in part I,[1] all reaction mixtures contained 10% dioxane and were maintained at $I = 1.0\ M$ (with NaCl), constant pH (either self-buffering by amines or with buffers) and 25 ± 0.1°. Where external buffers were used (succinate and acetate 0.1 M), experiments were performed at three different buffer concentrations and the rate constants were calculated at zero buffer concentration. Phosphate buffers were avoided because of their known[6] significant interactions with anhydrides. Reactions with each amine–anhydride system were carried out at at least three pH values and with at least three different amine concentrations. Values of the pH-independent rate constants were reproducible to within ±10%.

Table I. Ionization Constants (±0.05 pK Unit) of Secondary Amine Cations in Water at $I = 1.0\ M$ and 25°

No.	Amine	pK_a	Method[a]
1	*o*-Nitroaniline	−0.29	S
2	2,4-Dichloroaniline	2.05	S
3	*m*-Nitroaniline	2.50	S
4	*o*-Chloroaniline	2.61	P, S
5	Ethyl *p*-aminobenzoate	2.81	P
6	*m*-Chloroaniline	3.34	P
7	*p*-Iodoaniline	3.78	S
8	*p*-Bromoaniline	3.89	P
9	α-Naphthylamine	3.92	P
10	*p*-Chloroaniline	3.99	P
11	*m*-Methoxyaniline	4.20	P
12	*p*-Phenylaniline	4.27	S
13	*o*-Methoxyaniline	4.49	P
14	Aniline	4.57	P, S
15	*N*-Methylaniline	5.06	P
16	*p*-Ethoxyaniline	5.25	P
17	*p*-Methoxyaniline	5.29	S
21	Morpholine	8.70	P
22	Benzylmethylamine	9.83	P
23	Methylbutylamine	10.65	P
24	Dipropylamine	10.84	P
25	Diethylamine	10.93	P
27	Piperidine	11.22	P

[a] S and P signify that the spectroscopic or potentiometric methods in ref 4 were used.

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(1) Part I: I. H. Pitman, K. Uekama, T. Higuchi, and W. E. Hall, *J. Amer. Chem. Soc.*, **94**, 8147 (1972).

(2) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Wiley, New York, N.Y., 1962.

(3) R. Anschütz, *Ber.*, **20**, 3215 (1887).

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

(5) As reported in part I,[1] the pK_a values of the cations of 14 aliphatic and alicyclic amines were, on the average, 0.2 pK unit lower in water containing 10% dioxane than in water alone.

(6) T. Higuchi, G. L. Flynn, and A. C. Shah, *J. Amer. Chem. Soc.*, **89**, 616 (1967).

Results and Discussion

Aminolysis Rate Constants. The kinetic characteristics of all the reactions studied were essentially the same as those described in part I[1] and the same methods were used to calculate the aminolysis rate constants. The only significant difference between this study and the previous one was that none of the reactions became zero order in amine concentration even when the initial total amine concentration ($[\text{amine}_T]_0$) exceeded 10^{-2} *M*. This observation was consistent with the previously given explanation which suggested that zero-order kinetics only arose when the $[\text{amine}_T]_0$ was higher than the CMC (critical micelle concentration) of the amine cation. The cations of aromatic amines are known[7] to have very much higher CMC's than aliphatic amines containing the same number of carbon atoms because a benzene ring only appears to be equivalent in lipophilic character to about 3.5 carbon atoms of a straight hydrocarbon chain.

To ascertain whether the second-order rate constants in these reactions contained a term for general acid or general base catalysis of the hydrolysis reaction, a product analysis similar to that described in part I[1] was carried out on one reaction system. The system studied was the reaction of phthalic anhydride with aniline at pH 5.30. From the previously determined values of the molar extinction coefficients of substances present in the final reaction mixture (aniline $\epsilon_{257.5}$ 3176, ϵ_{260} 398, $\epsilon_{262.5}$ 414; phthalic acid $\epsilon_{257.5}$ 1050, ϵ_{260} 890, $\epsilon_{262.5}$ 812.5; phthalamic acid $\epsilon_{257.5}$ 8750, ϵ_{260} 8175, $\epsilon_{262.5}$ 7600) it was calculated that the value of the ratio [phthalic acid]:[phthalamic acid] was 5.8×10^{-4}. Because this value compared so favorably with the value of 6.4×10^{-4} which was predicted from the rate constants on the assumption that the amine species were not catalyzing the hydrolysis, it was concluded that k_C values were the pH-dependent aminolysis rate constants for this system. It was also assumed that a similar situation pertained in all of the systems.

In contrast to the aminolyses of esters such as 2,4-dinitrophenyl acetate,[8] no second-order dependence on amine concentration was observed for the reactions of weakly or strongly basic amines with either anhydride. This observation may only apply under the reaction conditions (especially pH range) employed in this study but it could be generally true and arise because of the greater intrinsic electrophilicity and reactivity of the anhydrides compared to the esters. Hence, whereas a second amine molecule in the rate-determining transition state for aminolysis of phenyl esters can be visualized[9] as activating the acyl molecules by a hydrogen-bonding mechanism, it could be that anhydrides have sufficient intrinsic reactivity without this activation step.

The pH dependence of the reactions with the weakly basic amines was identical with that found[1] for the stronger bases and was consistent with the neutral amine molecule being the major amine species that participated in the reaction. The pH-independent aminolysis rate constants, k_A values, were again calculated from the pH-dependent values (k_C) by dividing them by the fraction of the total amine species that was present as a neutral molecule. The values recorded in Table II and III are the mean of at least five values and are believed to be accurate to within ±10%.

Table II. Rate Constants for the Aminolysis of Phthalic Anhydride in Water Containing 10% Dioxane and Sodium Chloride to $I = 1.0$ *M* by 21 Primary and Secondary Amines[a,b]

Amine	$10^3[\text{amine}_T]_0$ range, *M*	k_A, M^{-1} sec^{-1}
m-Nitroaniline	0–2	5.77
o-Chloroaniline	0–4	2.65
Ethyl *p*-aminobenzoate	0–2	6.90
m-Chloroaniline	0–0.3	41.0
p-Iodoaniline	0–0.1	87.0
p-Bromoaniline	0–0.1	107
α-Naphthylamine	0–0.3	35
p-Chloroaniline	0–0.06	170
m-Methoxyaniline	0–0.06	228
p-Phenylaniline	0–0.1	116
o-Methoxyaniline	0–0.04	379
Aniline	0–0.04	396
N-Methylaniline	0–0.1	241
p-Ethoxyaniline	0–0.04	2,190
p-Methoxyaniline	0–0.01	3,070
Morpholine	0–20	210,000
Benzylmethylamine	0–20	162,000
Methylbutylamine	0–20	131,000
Dipropylamine	0–20	19,100
Diethylamine	0–20	18,100
Piperidine	0–20	795,000

[a] Measurements were made in the pH range 4 ± 2 pH units.
[b] Each k_A value represents the mean of at least five determinations.

Table III. Rate Constants for the Aminolysis of Succinic Anhydride in Water Containing 10% Dioxane and Sodium Chloride to $I = 1.0$ *M* by 20 Primary and Secondary Amines[a,b]

Amine	$10^3[\text{amine}_T]_0$ range, *M*	k_A, M^{-1} sec^{-1}
m-Nitroaniline	0–7	0.53
Ethyl *p*-aminobenzoate	0–8	0.46
m-Chloroaniline	0–3	1.53
p-Iodoaniline	0–2	2.72
p-Bromoaniline	0–1	3.61
α-Naphthylamine	0–1	1.02
p-Chloroaniline	0–0.8	4.57
m-Methoxyaniline	0–0.8	5.78
p-Phenylaniline	0–0.8	6.45
o-Methoxyaniline	0–0.3	7.83
Aniline	0.0.8	18.0
N-Methylaniline	0–0.3	8.85
p-Ethoxyaniline	0–0.3	67.0
p-Methoxyaniline	0–0.3	68.0
Morpholine	0–20	13,000
Benzylmethylamine	0–20	14,800
Methylbutylamine	0–20	3,800
Dipropylamine	0–20	2,300
Diethylamine	0–20	1,215
Piperidine	0–20	34,900

[a] Measurements were made in the pH range 4 ± 2 pH units.
[b] Each k_A value represents the mean of at least five determinations.

Structure–Reactivity Relationships. The sensitivity of the aminolysis rate constants to the pK_a value of the amine cation decreased as the amines became more basic in a manner that is apparently similar to that observed[8] in the aminolyses of reactive phenyl acetates. This behavior is shown in Figure 1 where the logarithms of the aminolysis rate constants are plotted against the pK_a values of the amine cations.

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(7) R. G. Pagnette, E. C. Lingafelter, and H. V. Tartar, *J. Amer. Chem. Soc.*, **65**, 686 (1943).
(8) W. P. Jencks and M. Gilchrist, *ibid.*, **90**, 2622 (1968).
(9) T. C. Bruice, A. F. Hegarty, S. M. Felton, A. Dowgel, and N. Y. Kundu, *ibid.*, **92**, 1370 (1970).

The apparent independence of the aminolysis rate constants for reactions with the strongly basic amines from the basicity of the amine was discussed in part I[1] and it was suggested that very little N–C bond formation had taken place in the transition state and that either the reactants were approximated, or the transition state was stabilized, by hydrophobic forces.

The reactions with the weakly basic amines appear to be quite different and the fact that the slopes of the plots in Figure 1 approach 1.0 suggests that a considerable amount of positive charge has been generated on the amine nitrogen atom and a considerable amount of N–C bond formation has occurred by the time the rate-determining transition state is reached. The values of the slopes of these lines, or the β values for the reactions, are 0.78 ± 0.07 for reactions with succinic anhydride and 0.78 ± 0.06 for reactions with phthalic anhydride. These values are thus very similar to the β value of 0.8 that was reported[8] for aminolysis of 2,4-dinitrophenyl acetate with weakly basic amines and are consistent with the proposition that all the reactions proceed by similar mechanisms.

In contrast to the reactions with the strongly basic amines, these reactions with the weaker bases do not appear to be very sensitive to the hydrophobic properties of the amine. For example, based on data reported by Hansch,[10] it would be anticipated that a chloro substituent in the meta or para position of an aniline molecule would increase its partition coefficient (and consequently its hydrophobic nature) between water and octanol by about the same amount as would two methyl substituents. A bromo or iodo substituent would be expected to increase it even more. However, the rate constants for these compounds and all the weakly basic amines appear from Figure 1 to be related by their basicities and relatively insensitive to their hydrophobic properties.

Hence, this observation tends to indicate that, in contrast to the reactions with strongly basic amines, the reactants in reactions with weakly basic amines are not significantly approximated by hydrophobic forces or the rate-determining transition states are not stabilized by hydrophobic bonds. A possible explanation for these differences may be found by considering the effects of the different amounts of charge present on the nitrogen atom in these two different types of transition states. In the reactions with weak bases it appears that about 0.8 unit of positive charge has been built up on the nitrogen atom. This charge on the nitrogen atom would in turn polarize the benzene ring attached to it (a measure of the extent to which this polarization occurs is obtained by considering that a m-N^+H_3 substituent has a Hammett σ value of 0.634[11]). This polarized hydrocarbon group would consequently not be expected to strongly interact through hydrophobic forces with other hydrocarbon groups such as those on the anhydride to stabilize the transition state. Approximation of the reactants may occur when they are in their ground states but as positive charge was built up on the nitrogen atom the hydrophobic forces would break down and little acceleration would result. On the other hand, it appears that little positive charge is developed on the nitrogen atom in the reactions of the strongly basic amines and any hydrophobic bonding that occurred in the ground state would persist through the transition state.

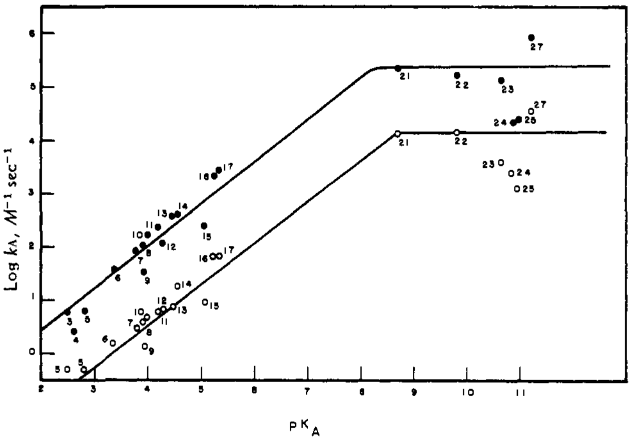

Figure 1. Plot against pK_a of the amine cations of the logarithms of the aminolysis rate constants for primary and secondary amines with (●) phthalic and (○) succinic anhydrides. The numbers refer to the amines listed in Table I.

The rates of reaction with the weakly basic amines did appear to share a common sensitivity to steric crowding around the amine nitrogen atom with those of the strongly basic amines. Hence, examination of the data in Figure 1 indicates that the points for ortho- or N-substituted anilines fall well below the line for those of the meta- or para-substituted compounds.

Finally, it remains to discuss the fact that the differences in reactivity of each anhydride with either strongly or weakly basic amines were approximately the same. The Δ log k_A values are in Table IV. This result is perhaps surprising in the light of the fact that the mechanism of reactions with strongly and weakly basic amines appeared to be different. However, it would be consistent with a postulate that some C–O bond breaking has occurred in each type of transition state. The β values for the leaving groups in these reactions cannot

Table IV. Δ Log k_A Values (Log $k_{A,\text{phthalic anhydride}}$ – Log $k_{A,\text{succinic anhydride}}$)

Amine	Δ Log k_A
m-Nitroaniline	1.0
Ethyl *p*-aminobenzoate	1.2
m-Chloroaniline	1.4
p-Iodoaniline	1.5
p-Bromoaniline	1.4
α-Naphthylamine	1.5
p-Chloroaniline	1.5
m-Methoxyaniline	1.6
p-Phenylaniline	1.3
o-Methoxyaniline	1.7
Aniline	1.3
N-Methylaniline	1.4
p-Ethoxyaniline	1.5
p-Methoxyaniline	1.7
Morpholine	1.2
Benzylmethylamine	1.0
Methylbutylamine	1.5
Dipropylamine	0.9
Diethylamine	1.2
Piperidine	1.4

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(10) From the data in A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971), it appears that the Δ logPC (log$PC_{\text{derivative}}$ – log PC_{aniline}) values are $\simeq$0.44 for a m-Me and 0.81 for a m-Cl substituent.

(11) H. H. Jaffe, *ibid.*, **53**, 191 (1953).

be discussed in a meaningful way, but, because phthalamic acid (the leaving group in a hypothetical phthalic anhydride reaction with ammonia) is a stronger acid ($pK_a = 3.75$)[12] than succinamic acid (the leaving group in a hypothetical reaction of succinic anhydride with ammonia) ($pK_a = 4.54$)[12] it seems likely that the leaving process would always be more favorable from the phthalic anhydride reactions. This conclusion would lead to the postulate that all the reactions proceed *via* a concerted mechanism and that a tetrahedral intermediate is not formed.[13]

Acknowledgment. This work was supported in part by grants from the Institute of Pharmaceutical Chemistry, Alza Corporation, and the National Institutes of Health (GM 05830-09).

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[12] G. Kortüm, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution," Butterworths, London, 1961.

[13] A referee suggested that an alternative explanation would be that the benzene ring in phthalic anhydride simply exerted an inductive effect ($-I$) on the carbonyl groups and thereby increased the rate of tetrahedral intermediate formation or of a concerted mechanism. This explanation is certainly possible and cannot be distinguished from the above explanation on the basis of the available data.

Reactions of *N*-Arylphthalamic Acids with Acetic Anhydride[1]

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Abstract: The reactions of para-substituted *N*-phenylphthalamic acids with acetic anhydride have been investigated. *N*-Arylphthalisoimides have been shown to be kinetic products of the dehydration in the presence of sodium acetate. The *N*-arylphthalimides formed as major products of these reactions are produced by the dehydration process and by the rearrangement of isoimides to imides. The yields of the transacylation products, phthalic anhydride and acetanilides, are increased in the presence of acetic acid or high amic acid concentration and are decreased by the presence of sodium acetate. The rate of the reactions of the *N*-arylphthalamic acids increases with increasing acetic acid concentration except for *N*-*p*-nitrophthalamic acid which reacts more slowly with increasing acetic acid concentration. The reactions of *N*-*p*-anisyl- and *N*-phenylphthalamic acids were found to obey the equation $k_{\mathrm{obsd}} = k_s' + k_A[\mathrm{HOAc}] + k_B([\mathrm{OAc^-}]/[\mathrm{HOAc}])$. The order of reactivity observed for k_A was $CH_3O > H > Cl$ while k_B for *N*-*p*-anisylphthalamic acid was slightly less than k_B for *N*-phenylphthalamic acid. The results have been interpreted in terms of rate-determining formation of the phthalanilic acid–acetic acid mixed anhydride followed by rapid ring closure steps.

Amide groups are known to participate as neighboring nucleophiles in a variety of ester or amide hydrolysis[3] and acid dehydration reactions.[4] In most of the basic hydrolysis reactions which have been investigated, the amide group appears to undergo a preliminary ionization to the anion which then participates at the nitrogen[5] although this tendency can be thwarted by steric problems in systems where only the oxygen of the amide can extend to the reaction site.[6] Under neutral or acidic conditions, the amide groups would be expected to have considerable electron density located on the oxygen.[7] Ernst and Schmir have suggested that cyclic isoimides formed by O participation might be intermediates in certain hydrolysis reactions.[8] This hypothesis gains support from the differential behavior of amides in S_N2 reactions under acidic or basic conditions,[9] as well as from the production of isoimides *via* O participation in a variety of dehydrations of amic acids.[4]

Earlier we had suggested that isoimides might be the kinetic products of the reactions of maleamic acids with acetic anhydride and that the imides were formed by rearrangement of the intermediate isoimides.[4a] Subsequently we were able to demonstrate that this hypothesis was partially correct[10] and Pyriadi and Harwood obtained similar results with acetic anhydride–triethylamine dehydrations of *N*-*n*-butylmaleamic acids.[11] Moreover, Boyd has recently shown that acetic anhydride–perchloric acid reagent dehydrates amic acids with oxygen participation of the amide

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[1] A portion of this paper was presented at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971.

[2] (a) American Chemical Society Petroleum Research Fund Undergraduate Scholar, 1970. (b) Undergraduate Scholar, Research Corporation, 1970.

[3] (a) T. Cohen and J. Lipowitz, *J. Amer. Chem. Soc.*, **86**, 5611 (1964); (b) E. Sondheimer and R. W. Holley, *ibid.*, **79**, 3767 (1957); **76**, 2467 (1954); (c) A. R. Battersby and J. C. Robinson, *J. Chem. Soc.*, 259 (1955); (d) S. A. Bernhard, A. Berger, J. H. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *J. Amer. Chem. Soc.*, **84**, 2421 (1962).

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[5] (a) J. A. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1899 (1963); (b) M. T. Behme and E. H. Cordes, *ibid.*, **29**, 1255 (1964); (c) R. M. Topping and D. E. Tutt, *Chem. Commun.*, 698 (1966).

[6] S. Hanissian, *J. Org. Chem.*, **32**, 163 (1967).

[7] (a) M. B. Robin, F. A. Bovey, and H. Basch in "The Chemistry of Amides," J. Zabicky, Ed., Interscience, New York, N. Y., 1970, p 46; (b) see R. B. Homer and C. D. Johnson, ref 7a, p 220.

[8] M. L. Ernst and G. L. Schmir, *J. Amer. Chem. Soc.*, **88**, 5001 (1966).

[9] (a) S. Winstein and R. Boschan, *ibid.*, **72**, 4669 (1950); (b) C. J. M. Stirling, *J. Chem. Soc.*, 255 (1960).

[10] C. K. Sauers, *J. Org. Chem.*, **34**, 2275 (1969).

[11] T. M. Pyriadi and H. J. Harwood, *ibid.*, **36**, 821 (1971).