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]

(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 $k_{obsd} = k_s' + k_A[HOAc] + k_B([OAc^-]/[HOAc])$. 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.

A mide 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

(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.

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(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).

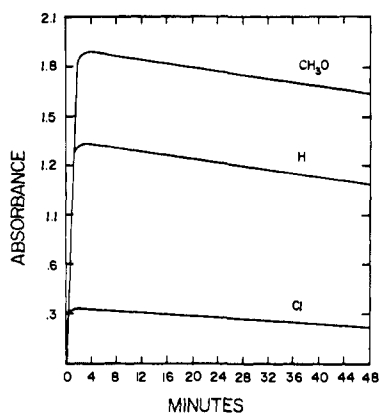(11) T. M. Pyriadi and H. J. Harwood, *ibid.*, 36, 821 (1971).

Figure 1. Absorbance vs. time at 340 nm for the reaction of para-substituted N-arylphthalamic acids with acetic anhydride containing acetic acid and sodium acetate at 60.6°.

group leading exclusively to isoimmonium salts as products.[12] In contrast to this, previous work on the dehydration of N-p-chlorophenylphthalamic acid to the corresponding imide produced evidence that isoimides were not important intermediates in this reaction with acetic anhydride.[13] One of the difficulties in interpreting these results was the subsequent discovery[14] that a transacylation reaction to produce cyclic anhydrides and the appropriate acetanilides was competing with the dehydration process. These two processes are illustrated in Scheme I below.

Scheme I

1a, X = CH₃O
b, X = CH₃
c, X = H
d, X = Cl
e, X = NO₂
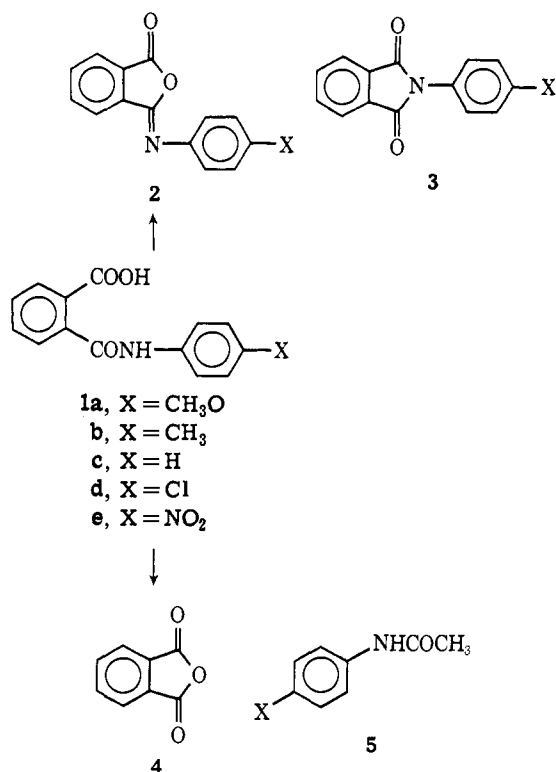
We initiated the present study of the dehydration of N-arylphthalamic acids **1** in order to determine the factors which affect the product distributions as well as

(12) G. V. Boyd, *Chem. Commun.*, 1147 (1969).
(13) W. R. Roderick, *J. Org. Chem.*, **29**, 745 (1964).
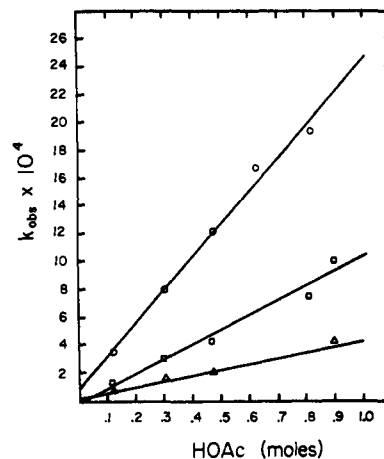(14) C. K. Sauers, C. L. Gould, and E. S. Ioannou, *ibid.*, **36**, 1941 (1971).

Figure 2. Observed rate constants for the reactions of N-arylphthalamic acids with acetic anhydride containing variable amounts of acetic acid at 40.0°: (O) N-p-methoxyphenylphthalamic acid; (□) N-phenylphthalamic acid; (△) N-p-chlorophenylphthalamic acid.

the kinetics of the dehydration process so that the mechanism of these complex reactions might be further understood.

Results

Kinetic Studies. Reactions of the phthalamic acids **1a, 1c,** and **1d** with acetic anhydride containing 0.0175 M sodium acetate and 1.03 M acetic acid were followed at 340 nm. At this wavelength, only the isoimides among the products absorb appreciably. Figure 1 shows the observed initial rapid increase in the absorbance followed by a slower decay. The rate of dehydration is faster than the rate of rearrangement by a factor of several hundred. The rate of the decay was the same within experimental error as the rate of decay of the isoimides **2a, 2c,** and **2d**. These data are summarized in Table I.

Table I. Pseudo-First-Order Rate Constants for the Rearrangement of N-Arylphthalisoimides to N-Arylphthalimides at 60.6° [a]

Compd	Para substituent	Concn,[b] $10^4 M$	$10^5 k_{obsd}$, sec^{-1}
1a	CH₃O	1.67	5.50
2a	CH₃O	0.74	5.69
1c	H	1.63	8.24
2c	H	1.16	8.71
1d	Cl	1.20	16.9
2d	Cl	0.63	17.2

[a] All reactions were run in 0.0175 M sodium acetate and 1.03 M acetic acid in acetic anhydride and were monitored at 340 nm. [b] Initial concentration of the amic acid or isoimide.

The initial dehydration step was studied at 40.0° where conventional kinetic techniques could be used. At that temperature no rearrangement of the isoimide to imide in acetic anhydride containing only acetic acid was observed. It was found that for compounds **1a, 1c,** and **1d** the observed rate increased with increasing acetic acid concentration as shown in Figure 2. The data fit the rate equation

$$k_{obsd} = k_s + k_A[HOAc]$$

Table II. Effect of Acetic Acid on the Rates of the Reactions of N-Arylphthalamic Acids with Acetic Anhydride at 40.0°

Substituent	[Amic acid], 10^4 M	[HOAc], M	$10^4 k_{obsd}$, sec^{-1}	$10^4 k_s$, sec^{-1}	$10^4 k_A$, M^{-1} sec^{-1}
CH$_3$O^a	1.51	0.21	2.20		
CH$_3$O^a	1.51	0.32	3.57		
CH$_3$O^a	1.51	0.46	4.08	1.0	6.85
CH$_3$O^a	1.51	0.79	5.80		
CH$_3$O^a	1.51	0.93	7.74		
CH$_3$O	1.32	0.12	3.65		
CH$_3$O	1.40–1.43	0.30	8.01		
CH$_3$O	1.43–1.87	0.47	12.2	1	24
CH$_3$O	1.50	0.62	16.8		
CH$_3$O	1.79	0.81	19.5		
H	1.90	0.12	1.36		
H	1.21–1.66	0.30	3.09		
H	1.21–1.84	0.47	4.30	0	11
H	1.90	0.81	7.50		
H	1.21–1.90	0.89	10.6		
Cl	1.22	0.12	0.938		
Cl	1.22–1.91	0.30	1.59	0.3	4.5
Cl	1.22–1.61	0.47	2.12		
Cl	1.22–1.71	0.89	4.37		
NO$_2$	2.04	0.10	19.6		
NO$_2$	2.04	0.12	19.9		
NO$_2$	2.04	0.16	18.2		
NO$_2$	2.04	0.21	15.4		
NO$_2$	2.04	0.32	10.5		
NO$_2$	2.04	0.46	7.15		
NO$_2$	2.04	0.79	5.13		
NO$_2$	2.04	0.93	3.73		

^{a} These runs were made at 30°.

Figure 3. Dependence of the rate constants for N-p-methoxyphenyl-phthalamic acid upon the acetate–acetic acid ratio.
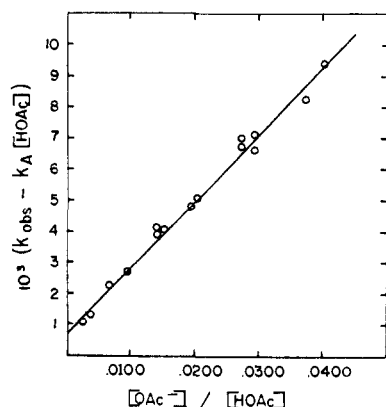

Figure 4. Dependence of the rate constants for N-phenylphthalamic acid upon the acetate–acetic acid ratio.

In contrast to the above results, the rate constants for the reaction of N-p-nitrophenylphthalamic acid (**1e**) with acetic anhydride decreased with added acetic acid in the range of 0.1–1.0 M acetic acid. The data from all of these experiments are summarized in Table II.

A thorough study of the effect of adding sodium acetate to these solutions was made for N-p-methoxyphenylphthalamic acid (**1a**) and N-phenylphthalamic acid (**1c**). The appropriate value for k_A[HOAc] was subtracted from each observed rate constant; the remaining portion of the observed rate constant was found to be proportional to [OAc$^-$]/[HOAc]. Thus, k_{obsd} is given by

$$k_{obsd} = k_s' + k_A[\text{HOAc}] + k_B([\text{OAc}^-]/[\text{HOAc}])$$

The fit to this equation was very good for the methoxy compound **1a** (see Figure 3); however, N-phenylphthalamic acid exhibits some deviations from this expression at high values of [OAc$^-$]/[HOAc] (see Figure 4). The value for k_B given in Table III was calculated

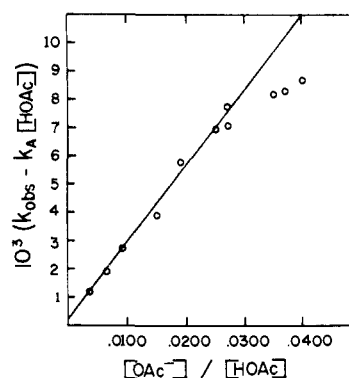from the kinetic data with the omission of the last three points.

The change in absorbance with time for the reaction in the presence of sodium acetate was also studied for N-p-nitrophenylphthalamic acid (**1e**) and N-p-chlorophenylphthalamic acid (**1d**). Neither of these compounds exhibited clean first-order kinetics. At least in part this was because the isoimide–imide rearrangement was sufficiently fast to interfere with infinity absorbance measurements for the dehydration process. Both compounds reacted faster than the methoxy-substituted and unsubstituted N-phenylphthalamic acid. Several runs were made with the chloro compound and qualitatively this acid may be estimated to react about twice as fast as **1a** and **1c** in comparable reaction media.

Product Studies. As we have previously reported, the N-arylphthalamic acids undergo a transacylation reaction to produce phthalic anhydride and acetanilides along with the dehydration products.[14] The amount of

Table III. Rate Constants for the Reactions of N-Arylphthalamic Acids[a] with Acetic Anhydride Containing Acetic Acid and Sodium Acetate at 40.0°

Substituent	[HOAc], M	[OAc⁻], M	$10^3 k_{obsd}$	$10^3(k_{obsd} - k_A[HOAc])$	$[OAc^-]/[HOAc]$	k_s', sec⁻¹	k_B, sec⁻¹
CH₃O	0.92	0.00218	3.23	1.06	0.0024		
CH₃O	0.90	0.00327	3.45	1.32	0.0037		
CH₃O	0.84	0.00545	4.25	2.24	0.0065		
CH₃O	0.83	0.00763	4.65	2.68	0.0092		
CH₃O	0.75	0.0109	5.72	3.94	0.014		
CH₃O	0.83	0.0119	6.09	4.12	0.014		
CH₃O	0.45	0.00634	5.13	4.07	0.015		
CH₃O	0.29	0.00544	5.49	4.80	0.019	0.7×10^{-3}	0.22
CH₃O	0.67	0.0131	6.61	5.07	0.020		
CH₃O	0.61	0.0163	8.21	6.76	0.027		
CH₃O	0.50	0.0136	8.22	7.03	0.027		
CH₃O	0.94	0.0272	9.41	7.17	0.029		
CH₃O	0.76	0.0218	8.46	6.66	0.029		
CH₃O	0.62	0.0226	9.73	8.27	0.037		
CH₃O	0.92	0.0368	11.6	9.42	0.040		
H	0.90	0.00327	2.15	1.20	0.0037		
H	0.84	0.00545	2.89	1.91	0.0065		
H	0.83	0.00763	3.59	2.71	0.0092		
H	0.75	0.0109	4.68	3.88	0.015		
H	0.29	0.00544	6.09	5.78	0.019		
H	0.44	0.0109	7.41	6.94	0.025	2×10^{-4}	0.27
H	0.61	0.0163	7.72	7.08	0.027		
H	0.50	0.0136	8.31	7.78	0.027		
H	0.48	0.0169	8.67	8.16	0.035		
H	0.62	0.0226	8.92	8.27	0.037		
H	0.92	0.0368	9.71	8.73	0.040		

[a] Range of concentrations for the phthalamic acids, 0.9–2.0 × 10⁻⁴ M.

phthalic anhydride produced in reactions that were run on a 0.007–0.17 M phthalamic acid scale was measured by quantitative gas phase chromatography. These experiments are summarized in Table IV along with parallel experiments in which the phthalisoimide yields were determined from the infinity uv readings in the kinetic runs.

It is apparent that the concentrations of the N-arylphthalamic acids 1 have some effect on the product distributions. Comparison of experiments 1 and 6 shows that some phthalic anhydride is produced when the concentration of 1a is 0.17 M but that very little if any phthalic anhydride can be produced when the concentration of 1a is 1.32 × 10⁻⁴. Similar conclusions must be reached from comparisons of experiments 12–15 with experiments 16–19. This effect was measured directly in experiments 20 and 21 which show that phthalic anhydride yields diminish as the starting concentration of 1a is decreased.

The presence of large amounts of the phthalamic acids constitutes a change in the reaction medium similar to that of adding increments of acetic acid. The yields of phthalic anhydride are increased as the concentration of acetic acid is increased (experiments 12–15) and the isoimide yield decreases with increasing acetic acid (experiments 16–19).

The addition of sodium acetate decreases the phthalic anhydride yields. Comparisons of experiments 22–25 with experiments 1–4 demonstrate this effect. It must be noted that the concentration of acetic acid also changes between these two groups of experiments. A comparison of experiment 22 with experiments 14 and 15 illustrates the effect of sodium acetate on the yield of phthalic anhydride in cases where the acetic acid concentrations are more nearly the same.

The presence of added sodium acetate also has an adverse effect on the yields of the phthalisoimide (2).

Substantially more isoimide is produced in the absence of acetate (experiments 6–9) than when it is present (experiments 26–29). A comparison of experiment 26 with experiments 18 and 19 (where the acetic acid concentrations are comparable) clearly demonstrates the drop in isoimide formation with added sodium acetate. Experiments 30–32 summarize the isoimide yields for the remainder of the kinetic runs made in the presence of sodium acetate and illustrate the decreasing yields of isoimide with increasing sodium acetate concentrations. The effect of sodium acetate on the yields of phthalic anhydride and the phthalisoimides is similar to that previously observed in the reactions of N-arylmaleamic acids with acetic anhydride.[10]

Substituent effects also parallel those previously observed.[10] Thus experiments 1–5 show a slight decrease in phthalic anhydride yields as the para substituent is changed from methoxyl to nitro. The isoimide yields also drop with this same variation in substituents. (See experiments 6–9 and experiments 26–29.)

The phthalimides can readily be isolated from the larger scale runs which contain sodium acetate and the yield is considerably improved when the final mixtures are heated until the isoimide–imide rearrangement has gone to completion. Analysis of the kinetic runs by uv for imides was hampered by the fact that in the region of greatest imide absorption (ca. 300 nm) both the isoimides and phthalic anhydride absorb to a larger extent and tail absorption from the media further complicates the problem. The alternative of working up the larger scale reaction mixtures in sodium bicarbonate solution followed by spectral analysis of the isolated products has been tried previously.[13] However, subsequent work has shown that the isoimide–imide rearrangement proceeds rapidly in aqueous buffers;[8] these findings cast some doubt upon this method of analysis.

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Table IV. Product Distribution Studies for the Reactions of N-Arylphthalamic Acids in Acetic Anhydride at 40°

Expt no.	Substituent	[HOAc], M	[NaOAc], M	[Amic acid], M	% phthalic[a] anhydride	% isoimide[b]
1	CH₃O	0.10	0	0.17	20	
2	CH₃	0.10	0	0.17	19	
3	H	0.10	0	0.17	15	
4	Cl	0.10	0	0.17	12	
5	NO₂	0.10	0	0.17	15	
6	CH₃O	0.10	0	1.32×10^{-4}		100
7	H	0.10	0	1.90×10^{-4}		83
8	Cl	0.10	0	1.22×10^{-4}		67
9[c]	NO₂	0.10–1.0	0	2.04×10^{-4}		<5
10[c]	NO₂	0.10–1.0	0	0.17	10–15	
11	NO₂	0.9	0	7.2×10^{-3}	11	
12	CH₃O	0.1	0	0.17	23	
13	CH₃O	0.3	0	0.17	31	
14	CH₃O	0.5	0	0.17	56	
15	CH₃O	0.9	0	0.17	65	
16	CH₃O	0.1	0	1.32×10^{-4}		100
17	CH₃O	0.3	0	1.43×10^{-4}		86
18	CH₃O	0.5	0	1.87×10^{-4}		67
19	CH₃O	0.9	0	1.43×10^{-4}		50
20	CH₃O	1.0	0	0.017	73	
21	CH₃O	1.0	0	0.009	64	
22[d]	CH₃O	0.6	0.018	0.17	15	
23[d]	CH₃	0.6	0.018	0.17	11	
24[d]	H	0.6	0.018	0.17	10	
25[d]	Cl	0.6	0.018	0.17	4	
26	CH₃O	0.6	0.018	1.69×10^{-4}		29
27	H	0.6	0.018	1.56×10^{-4}		26
28	Cl	0.6	0.018	1.71×10^{-4}		10
29	NO₂	1.0	0.018	2.0×10^{-4}		1–2
30[c]	CH₃O	0.9–0.3	0.002–0.04	$1–2 \times 10^{-4}$		47–29
31[c]	H	0.9–0.3	0.003–0.04	$1–2 \times 10^{-4}$		43–24
32[c]	Cl	0.9–0.3	0.002–0.04	$1–2 \times 10^{-4}$		15–10

[a] Analyses for phthalic anhydride were carried out by quantitative gas phase chromatography of the reaction solutions followed by comparison of peak areas of solutions of known phthalic anhydride content. Averages of duplicate or triplicate runs are reported and the average deviations were less than ±3%. [b] Measurements of the infinity absorbance readings in the uv regions where the other products are transparent were used to determine isoimide yields. Averages of duplicate or triplicate runs are reported and the average deviations were less than ±2%. [c] A group of experiments is summarized and ranges of concentrations and yields are reported. [d] The imides from these runs were isolated and identified.

It seems reasonably certain, however, that N-aryl-phthalimides are kinetic products as well as thermodynamic products of the dehydrations run in the presence of sodium acetate.

Discussion

Acetic Acid Catalysis. The dehydration of phthalamic acids with acetic anhydride has been postulated to occur by way of the mixed anhydride 6 followed by ring closure to 2 and 3.[4a,b,10,11] There seems no reason to suppose that this is not the major pathway in the present case although a small amount of imide has been observed to form when succinanilic acids and phthalamic acids are dissolved in water.[15,16]

Formation of the mixed anhydride would be expected to be rate determining because ring closure to the imide or isoimide would be enhanced by proximity effects.[17] Furthermore, it is apparent that attack of carboxylic acids on anhydride is not an extremely rapid process except in the presence of strong acids.[18] The observed catalysis by acetic acid and the order of reactivity CH₃O > H > Cl are consistent with the pathway shown in Scheme II.
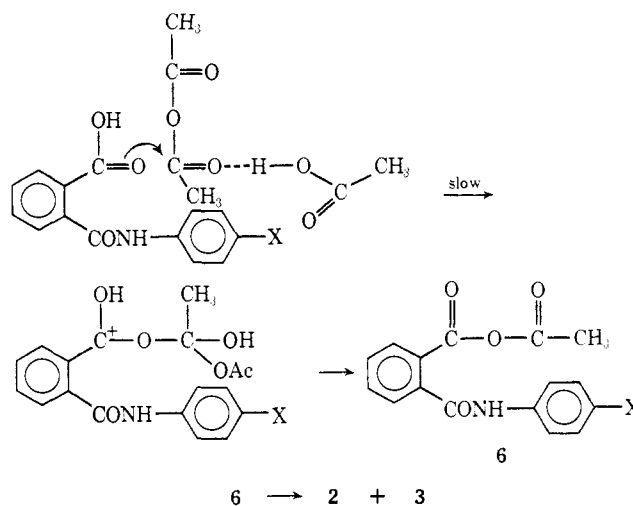
(15) J. Brown, S. C. K. Su, and J. A. Shafer, *J. Amer. Chem. Soc.*, **88**, 4468 (1966).
(16) T. Higuchi, L. Eberson, and J. McRae, *ibid.*, **89**, 3001 (1967).
(17) T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, p 119.
(18) M. Sheinblatt and S. Alexander, *J. Amer. Chem. Soc.*, **87**, 3905 (1965).

Scheme II

$$6 \longrightarrow 2 + 3$$

The magnitude of the substituent effect ($\rho = -1.5 \pm 0.2$) seems inconsistent with the mechanism in Scheme II. The neighboring amide group may enhance the nucleophilicity of the carboxylic acid by partial removal of the acid hydrogen through hydrogen bonding or through the formation of the zwitterion 7. The acidities of protonated acetanilides ($\rho = +1.66$)[7b] offer support for this possibility.

Little work has been done on the reactions of carboxylic acids with anhydrides to form mixed anhy-

drides.[19] It appears, however, that the carboxylic acid behaves as a nucleophile attacking the anhydride carbonyl carbon.[20] The postulated action of the acetic acid catalyst in Scheme II is in accord with the evidence that acetic acid forms hydrogen bonds to acetic anhydride in dilute solutions of the acid in the anhydride; acetic acid dimers become more important in concentrated solutions.[21] In contrast, the work of Sheinblatt and Alexander provides evidence of first-order perchloric acid catalysis of the rate of exchange of acetic acid with the acetyl groups of acetic anhydride and the kinetic analysis leads to the conclusion that protonation occurs on the acetic acid prior to the exchange reaction.[18] The kinetics of this rapid reaction (mean lifetime <2 sec at 22°) are not comparable to the work described herein since the nmr method used by Sheinblatt and Alexander would not detect slower exchange reactions in the acetic acid–acetic anhydride system.[18]

Alternative mechanisms to the one portrayed in Scheme II are not ruled out and it is possible that the action of acetic acid in the present work is the result of a solvent effect. If 7 is the reactive species, rate enhancement would be expected in a more polar medium, and charge separation which would develop in the transition state for the attack of neutral amic acid on neutral acetic anhydride would similarly be aided by an increasingly polar medium.

The product studies show that the yields of phthalic anhydride increase with increasing acetic acid concentration. Previous work on N-phenylmaleamic acid has shown that the carboxylic acid oxygens are preserved during the transformation to phthalic anhydride. It is possible that the mixed anhydride 6 is an intermediate in the transacylation process or that the reaction proceeds through the zwitterion 7. The concentration of 7 would be increased by the increased polarity of the medium.

The inhibition of the rate of the reactions of the nitro compound 1e in the presence of increasing amounts of acetic acid suggests that a rapid equilibrium between the amic acid 1e and the mixed anhydride 6e may exist followed by rate determining ring closure to imide and isoimide.

$$1e + Ac_2O \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} 6e + HOAc$$

$$6e \xrightarrow{\text{slow } k_2} \text{products}$$
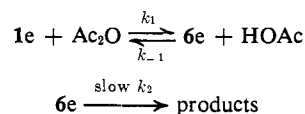
The rate equation predicted by this mechanism is given by eq 1

$$\frac{d(\text{products})}{dt} = k_2 \left[\frac{\dfrac{k_1 [Ac_2O]}{k_{-1}[AcOH]}}{1 + \dfrac{k_1 [Ac_2O]}{k_{-1}[AcOH]}} \right] [1e]_{\text{total}} \quad (1)$$

where $[1e]_{\text{total}} = [1e] + [6e]$.

An independent determination of k_2 could be made if the $k_1[Ac_2O]/k_{-1}[AcOH]$ term were much larger than unity so that the rate equation would reduce to k_2·

(19) D. P. N. Satchell and R. S. Satchell in "The Chemistry of the Carboxylic Acids and Esters," S. Patai, Ed., Interscience, New York, N. Y., 1969, p 406.

(20) T. G. Bonner, E. G. Gabb, P. McNamara, and B. Smeshhurst, *Tetrahedron Lett.*, 21, 463 (1965).

(21) (a) N. Muller and P. I. Rose, *J. Amer. Chem. Soc.*, 85, 2173 (1963); (b) G. Allen and E. F. Caldin, *Quart. Rev., Chem. Soc.*, 7, 278 (1953).
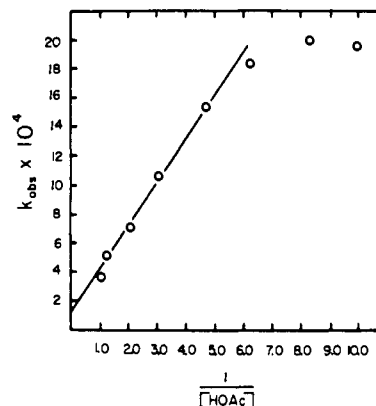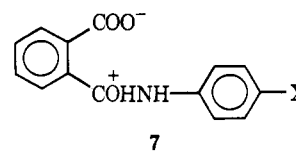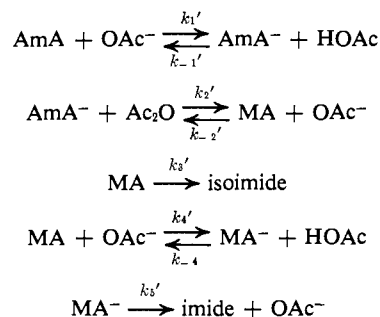
Figure 5. Observed rate constants for the reaction of N-p-nitrophenylphthalamic acid containing variable amounts of acetic acid. The line represents the empirical relationship $k_{\text{obsd}} = k_0 + k_{NO_2}/$ [HOAc], where $k_0 = 1.3 \times 10^{-4}$ sec^{-1} and $k_{NO_2} = 2.8 \times 10^{-4}$ sec^{-1} M which is valid from 0.16 to 0.93 M acetic acid.
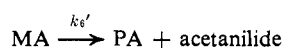

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$[1e]_{\text{total}}$. Freshly distilled acetic anhydride contains about 0.1 M acetic acid. In this range of acetic acid concentrations, some leveling of the rate constants is observed (see Figure 5 and Table II). However, use of a value for k_2 of 2×10^{-3} sec^{-1} does not lead to a constant value for k_1/k_{-1} calculated from the remainder of the experiments and eq 1. The change in solvent polarity between 0.10 and 1.0 M acetic acid might be expected to have a further effect on the rate constants for this reaction.

The difference in dependence of the rate constants on acetic acid concentration is striking and reflects a basic change in the mechanism or rate determining step for the reaction. However, firm conclusions about the acetic acid catalysis and inhibition await studies concerning the reaction of simple carboxylic acids with acetic anhydride.

Acetate Catalysis. The inclusion of sodium acetate in the reaction system has a remarkable effect on both the product distribution and the speed of the reactions. Thus the amounts of phthalic anhydride and isoimide are both decreased and the yield of imide is increased. Furthermore the rates of the reaction are markedly increased. The results are consistent with the following mechanism where AmA = phthalamic acid 1, AmA$^-$ = phthalamate anion, MA = mixed anhydride 6, MA$^-$ = the mixed anhydride amide anion, PA = phthalic anhydride 4, $K_{\text{AmA}} = K_a$ for the phthalamic acid, and $K_{\text{HOAc}} = K_a$ for acetic acid

$$\text{AmA} + \text{OAc}^- \underset{k_{-1}'}{\overset{k_1'}{\rightleftarrows}} \text{AmA}^- + \text{HOAc}$$

$$\text{AmA}^- + \text{Ac}_2\text{O} \underset{k_{-2}'}{\overset{k_2'}{\rightleftarrows}} \text{MA} + \text{OAc}^-$$

$$\text{MA} \xrightarrow{k_3'} \text{isoimide}$$

$$\text{MA} + \text{OAc}^- \underset{k_{-4}}{\overset{k_4'}{\rightleftarrows}} \text{MA}^- + \text{HOAc}$$

$$\text{MA}^- \xrightarrow{k_5'} \text{imide} + \text{OAc}^-$$

and possibly

$$MA \xrightarrow{k_6'} PA + \text{acetanilide}$$

If k_2' is slow compared to the product forming steps and k_{-2}' is much slower than k_2' and the product forming steps then

$$\frac{d(\text{products})}{dt} = k_2'[\text{AmA}^-][\text{Ac}_2\text{O}]$$

Application of the steady-state treatment to AmA⁻ and the material balance relationship

$$[\text{AmA}]_{\text{total}} = [\text{AmA}] + [\text{AmA}^-]$$

leads to

$$\frac{d(\text{products})}{dt} =$$

$$k_2'[\text{Ac}_2\text{O}]\left\{\frac{\dfrac{K_{\text{AmA}}}{K_{\text{HOAc}}}\dfrac{[\text{OAc}^-]}{[\text{HOAc}]}}{1 + \dfrac{K_{\text{AmA}}}{K_{\text{HOAc}}}\dfrac{[\text{OAc}^-]}{[\text{HOAc}]}}\right\}[\text{AmA}]_{\text{total}} \quad (2)$$

The pK_a values of the phthalamic acids in acetic anhydride cannot be measured spectrophotometrically because of the speed of the dehydration reaction. The measurement of the pK_a values of the phthalamic acids in water is hindered by the rapid catalysis of amide hydrolysis by the neighboring carboxyl group.[22] From the dependence of this reaction on pH, Morawetz and Shaefer have determined a value of 2.4×10^{-4} M for the K_a of **1c**.[23] This then would fix the ratio of $K_{\text{AmA}}/K_{\text{HOAc}}$ in water at a value close to 10 for **1c** and presumably less than 10 for **1a** if it is assumed that the *relative* acidities remain similar in acetic anhydride compared to water.[24] For most of the values of [OAc⁻]/[HOAc] in the present study, the term $K_{\text{AmA}}[\text{OAc}^-]/K_{\text{HOAc}}[\text{HOAc}]$ is small compared to 1 and eq 2 can be reduced to eq 3. This is the form of the experimentally

$$\frac{d(\text{products})}{dt} = k_2'[\text{Ac}_2\text{O}]\frac{K_{\text{AmA}}[\text{OAc}^-]}{K_{\text{HOAc}}[\text{HOAc}]}[\text{AmA}]_{\text{total}} \quad (3)$$

observed equation where

$$k_{\text{B}} = k_2'\frac{K_{\text{AmA}}}{K_{\text{HOAc}}}[\text{Ac}_2\text{O}]$$

Table III shows that the values for k_{B} are 0.22 and 0.27 sec⁻¹ for the methoxy-substituted **1a** and the unsubstituted **1c**, respectively. The fact that the values lie close together is not unexpected. The greater nucleophilicity of the anion of **1a** compared to that from **1c** would lead to $k_2'(\text{a}) > k_2'(\text{c})$ whereas K_{AmA} for **1a** would be expected to be less than K_{AmA} for **1c**. Similar results have been observed in other systems.[5a,25]

Hegarty and Bruice have shown that oxygen attack of ionized and un-ionized ureido groups upon neighboring benzoate esters becomes important at low pH and when the pK_a of the conjugate acid of the leaving group Y falls below 11 or 10, respectively.[25] Similarly,

(22) M. L. Bender, F. Chloupek, and M. C. Neveu, *J. Amer. Chem. Soc.*, **80**, 5380 (1958).

(23) H. Morawetz and J. Shafer, *ibid.*, **84**, 3783 (1962).

(24) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 58.

(25) A. F. Hegarty and T. C. Bruice, *J. Amer. Chem. Soc.*, **92**, 6575 (1970).
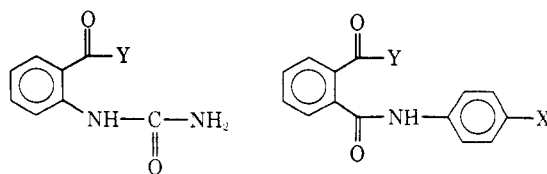
participation by the oxygen is favored for neighboring amide groups when Y is a good leaving group. Trifluoroacetic anhydride dehydrations of **1a–1e** produce isoimides;[4e] acetic anhydride dehydrations yield both the isoimides and imides. The isoimides are favored when the substituent X is such that the ionization of the amide is more difficult. When Y is a poor leaving group such as OCH₃, imide formation appears to be exclusive.[5a,b] These observations make it highly probable that the leaving group in N,N'-dicyclohexylcarbodiimide dehydrations of amic acids (which produce isoimides in good yields from **1a–1d** but not from **1e**) is the neutral dicyclohexylurea rather than its anion.[26,27]

The effect of added acetate ion on the product distribution is also dramatic. Both the phthalic anhydride yield and the isoimide yields are severely cut and, in the preparative scale runs, imides can be isolated. We postulate that acetate ion behaves as a base to remove a proton from the amide group and that subsequent ring closure leads primarily to imide.

The chloro compound produces imide directly even in the absence of added acetate ion. It would be expected that the contribution to the amide resonance hybrid of structure A below would be less important when X is the electron withdrawing chloro or nitro group.
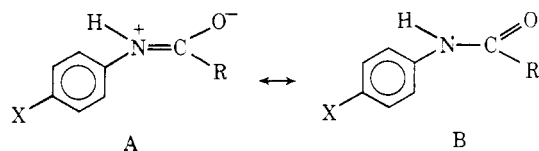
In conclusion it can be stated that acetate ion can enhance the direct formation of imide and in addition can increase the yield of imide formed by the rearrangement of the major kinetic product, the isoimide. The yield of imide is larger when substituents on the ring attached to nitrogen are electron withdrawing. The dehydration process appears to proceed through a rate-determining formation of a mixed anhydride followed by rapid ring closure steps.

Experimental Section

Materials. Acetic anhydride (Matheson Coleman and Bell, 99+ %) was distilled in an all glass apparatus before use. Approximately one-fourth of the material was collected as a forerun; the main fraction was collected and stored in dry bottles previously rinsed with the distillate. Reagent grade fused sodium acetate was dried in a vacuum oven and weighed amounts were dissolved in appropriate small amounts of reagent grade glacial acetic acid before the addition of acetic anhydride. The molarity of the acetic acid was calculated from the comparison of the area under

(26) D. V. Kashelikar and C. Ressler, *ibid.*, **86**, 2467 (1964).

(27) R. Paul and A. S. Kende, *ibid.*, **86**, 4162 (1964).

the methyl resonance peak for the acetic acid with the area under the C-13 satellite peak for the acetic anhydride according to the method of Muller and Rose.[21a] These solutions were stable over a period of several days with respect to acetic acid concentration when stored in stoppered volumetric flasks.

The phthalamic acids were prepared from phthalic anhydride and the substituted anilines each dissolved in dichloromethane. Crude products were recrystallized from 95% alcohol. The phthalisoimides 2a-2d were prepared by the dehydration of the corresponding acids with N,N'-dicyclohexylcarbodiimide and were either recrystallized from acetone–water or chromatographed on Florisil in benzene to effect purification.[4a] Treatment of 1e with the carbodiimide did not lead to a clean preparation of 2e; this isoimide was prepared by the method of Roderick and Bhatia,[4e] mp 172–174° (change to needles which remelt at 260°) (lit. mp 173° (isoimide),[4e] mp 262–263° (imide)[28]). The compound had absorption bands in the infrared at 1820 and 1790 cm^{-1}. The phthalimides were prepared by treatment of the corresponding phthalamic acids with acetic anhydride containing sodium acetate and acetic acid.

The uv spectra of the imides, isoimides, and phthalic anhydride were measured in acetic anhydride and are summarized in Table V.

Table V. Ultraviolet Spectra in Acetic Anhydride at 40°

Substituent	—Imide[a]— λ		—Isoimide— λ_{max}	
CH$_3$O	300	1,340	350	12,100
H	300	3,350	325	7,290
Cl	300	2,240	330	9,640
NO$_2$	300	14,800	321	12,700
Phthalic anhydride	300	2,170		

[a] Maxima for the imides lie at 300 nm or below. Extensive absorbance by the solvent also occurs in this region and the slit widths required for readings make the measurements uncertain below 300 nm.

(28) M. L. Sherrill, F. L. Schaeffer, and E. P. Shoyer, J. Amer. Chem. Soc., 50, 474 (1928).

Kinetic Measurements. Solutions of the phthalamic acids or phthalisoimides (0.100 ml) dissolved in scintillation grade dioxane were injected into solutions of 2.40 ml of the acetic anhydride solutions which were prewarmed in glass-stoppered cuvettes in the sample chamber of the recording spectrophotometer. When the circulating bath temperature was maintained at 41.5° the solutions in the cuvettes were maintained at 40.0°. These temperatures were monitored by a thermistor manufactured by Yellow Springs Instrument Co. Changes in the absorbance vs. time were recorded and infinity readings were recorded after 10 or more half-lives. No differences in rate constants were observed when dioxane was replaced with reagent grade acetonitrile[29] nor when different wavelengths were used to monitor the kinetic runs. Calculations were made on a Wang Model 142 programmable calculator according to the method of least squares and correlation coefficients for rate constants calculated from 10 to 20 experimental points were generally 0.995 or higher. Average deviations from the average values of k_{obsd} from duplicate or triplicate runs were less than ±6%.

Product Studies. Isoimide yields for the kinetic runs of 1a, 1c, and 1d were estimated from infinity absorbance measurements made on the solutions. The infinity measurements made on the N-p-nitrophenylphthalamic acid runs so closely paralleled the curves for pure N-p-nitrophenylphthalimide that no more than 5% isoimide could be formed in these reactions. Phthalic anhydride yields were measured using gas phase chromatography of the reaction mixtures after 10 half-lives. The more concentrated solutions were studied on an Aerograph 90-P thermal conductivity apparatus while the dilute solutions were studied on an F&M Model 810 with flame ionization detector. Solutions of known concentration of phthalic anhydride were used for calibrations. Columns used were $^1/_4$ in. × 10 ft, 3% SE-30 on 80–100 Gas Chromosorb Q, and $^1/_{16}$ in. × 6 ft 10% SE-30 on Chromosorb S.

(29) A. F. Hegarty and T. C. Bruice, ibid., 92, 6561 (1970).