assumed that no phenolate ion was present in the first solution and no phenol in the second. The average ratios of phenol to phenolate ion based on three wave lengths (3560, 4000 and 2550 Å.) were 1.2, 0.8 and 0.7 for (3), (4) and (5), corresponding to runs 4, 5 and 7, respectively.

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE AND THE DEPARTMENT OF CHEMISTRY OF SARAH LAWRENCE COLLEGE]

The Hydrolysis of Substituted Benzoic Anhydrides[1]

BY ERNST BERLINER AND LUCILLE HOLLJES ALTSCHUL

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The rates of hydrolysis of substituted benzoic anhydrides in 75% dioxane have been determined at two temperatures. The differences in rates are determined mainly by differences in activation energies and the reaction follows the Hammett equation. The mechanism of anhydride hydrolysis is discussed.

Although the hydrolysis of aromatic esters, acid chlorides and amides has been frequently studied with regard to substituent effects, no corresponding study is available for the hydrolysis of substituted benzoic anhydrides. Such an investigation seemed desirable, because the anhydrides form a logical part of the series of benzoic acid derivatives ArCOR on which hydrolytic cleavages can be performed. Only the hydrolysis of unsubstituted benzoic anhydride is reported,[2] whereas numerous studies have been carried out on aliphatic anhydrides, particularly acetic anhydride.[3] In the following are reported data for the hydrolysis of nine substituted benzoic anhydrides in dioxane–water mixtures at two temperatures.

Experimental

Materials.—Aniline (Reagent Grade) was distilled under reduced pressure in the presence of zinc dust. When stored in a wax-sealed bottle, it could be kept colorless for a period of several months. Dioxane was purified by a standard procedure.[4] It was twice distilled from sodium, and the fraction boiling at 100.5–101° was collected and stored over sodium. All anhydrides, except for the commercially available benzoic anhydride, were prepared by a modification of the method of Autenrieth and Thomae.[5] The appropriate acid was treated with approximately fifteen times the theoretical amount of acetic anhydride. For six hours, periods of reflux were alternated with periods of slow removal of the solvent by distillation. The remainder of the solvent was then removed by distillation *in vacuo*, and the crude anhydrides, with the exception of the two nitro derivatives, were distilled. The nitro derivatives were purified by repeated crystallization. In general two crystallizations of each of the distilled anhydrides yielded a pure product. Relevant data pertaining to the anhydrides are shown in Table I.

The *p*-methoxy-, *m*-methoxy and *p*-chlorobenzoic acid were best commercial products and were used without further purification. The two nitrobenzoic acids were commercial products crystallized to constant melting point. The two toluic acids were prepared from the corresponding toluidines, followed by hydrolysis of the nitriles.[6] The para isomer melted at 179–180° (aqueous ethanol) and the meta isomer at 112–114° (benzene). The *p*-*t*-butylbenzoic acid was obtained from *p*-bromo-*t*-butylbenzene (prepared in 71% yield[7]) by carbonation of the Grignard reagent. The yield of once crystallized acid (m.p. 159–160°, uncor., from aqueous ethanol) was 55%; neutral equivalent 177.6 (theoret. 178.2).

TABLE I[a]

SUBSTITUTED BENZOIC ANHYDRIDES

Substituent	M.p., °C.	B.p., °C.	Mm.	Solvent	Anhydride,[b] %
None	42–44[c]	204–207	8	Benzene-ligroin	99.8
p-Methyl	94.3–94.8	229–230	13	Benzene-ligroin	99.8
m-Methyl	70.0–71.5[c]	195–197	5	Benzene-ligroin	99.9
p-Methoxy	98.5–98.8	304–310	10	Benzene-ligroin	100.0
m-Methoxy	65–66[c]	236–240	2	Benzene	99.7
p-Nitro	192.5–193.0	.....		Benzene-acetone	100.0
m-Nitro	161–162[c]	.....		Benzene-acetone	99.9
p-Chloro	192.9–193.4	248	5	Benzene	99.7
p-*t*-Butyl[d]	78.7–79.0	220	3	Petroleum ether	99.8

[a] All melting points are corrected unless otherwise stated. [b] Accurately weighed samples of the anhydride were dissolved in dioxane, treated with aniline, and the liberated acid was titrated with standard base. [c] Uncorrected melting point. [d] *Anal.* Calcd. for $C_{22}H_{26}O_3$: C, 78.08; H, 7.74. Found: C, 78.22; H, 7.90. Analysis by Miss K. Weiss and Miss L. Carmichael.

Rate Measurements.—The analytical procedure involved a modification of the method introduced by Menschutkin and Wassilieff.[8] Anhydride solutions (0.015–0.045 *M*) were made up by dissolving accurately weighed amounts of solute in anhydrous dioxane and diluting to the mark in a 200-ml. volumetric flask. Aliquot samples (15 ml.) were brought to temperature in a thermostat held constant to ±0.03°. The hydrolysis was initiated by pipetting into each sample 5.0 ml. of water at room temperature, and agitating to ensure homogeneity. Blank tests established that isothermal conditions were invariably restored within less than two minutes after initiation of the introduction of the water. This lapse of time introduced no detectible error into any of the runs except for those of the three most reactive anhydrides. In these latter cases, the first-order linear graph failed to touch the theoretical zero point. The substitute reading for the initial point was the average of three titers, agreeing to within at least 0.04 ml., and obtained from triplicate samples which were prepared for titration at the end of four minutes.

Kinetic points were obtained after measured time periods by pipetting 5 ml. of aniline into the hydrolyzing mixture, which was then shaken and removed from the thermostat, to be stored in a dark place at room temperature. The time necessary for complete reaction of the remaining anhydride with aniline had been determined in advance as follows: solutions containing *p*-nitro-, *m*-nitro- and *p*-chlorobenzoic anhydride were allowed to stand for at least two minutes; solutions of benzoic and *m*-methoxybenzoic anhydride were

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(1) Taken from a dissertation submitted by Mrs. L. Holljes Altschul to the Graduate School of Bryn Mawr College in partial fulfillment of the requirements for the Ph.D. degree.

(2) B. H. Wilsdon and N. V. Sidgwick, *J. Chem. Soc.*, **103**, 1959 (1913); S. C. J. Olivier and G. Berger, *Rec. trav. chim.*, **46**, 609 (1927); S. E. Vles, *ibid.*, **52**, 809 (1933).

(3) For a recent literature survey see V. Gold, *Trans. Faraday Soc.*, **44**, 506 (1948).

(4) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Company, New York, N. Y., 2nd ed., 1941, p. 368.

(5) W. Autenrieth and G. Thomae, *Ber.*, **57**, 431 (1924).

(6) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 514; *ibid.*, Coll. Vol. II, 1943, p. 588.

(7) A. E. Tchitchibabine, S. Elgasine and V. Lengold, *Bull. soc. chim.*, [4] **43**, 238 (1928).

(8) N. A. Menschutkin and M. Wassilieff, *J. Russ. Chem. Soc.*, **21**, 188 (1889) [*J. Chem. Soc. Abs.*, **58**, 359 (1890)]. See also S. E. Vles, ref. 2

eft for five minutes or more, while those of the three alkylbenzoic anhydrides required 30 minutes and *p*-methoxybenzoic anhydride required a minimum of one hour. At the end of the waiting period the solutions were titrated with standard carbonate-free sodium hydroxide, using phenolphthalein as an indicator.

The initial dioxane solutions were analyzed for their anhydride content by treating aliquot portions in a manner analogous to that above, except that no water was added. Two or three such samples were processed in order to check the concentration calculated for the known weight of solute. Agreement was generally excellent. The results of two typical runs are reproduced in Table II.

TABLE II

The hydrolysis of *m*-methoxybenzoic anhydride in 75% dioxane–25% water (by volume); *T*, 58.25°

T (min.)	NaOH (0.05772 N), ml.	$a - x$	$k_1 \times 10^4$, min.$^{-1}$
0	10.36	10.36	
185	11.11	9.61	(4.06)
275	11.92	8.80	5.94
400	12.52	8.20	5.85
574	13.30	7.42	5.82
780	14.14	6.58	5.82
1075	15.16	5.56	5.79
1335	15.96	4.76	5.82
1660	16.82	3.90	5.89
		Av.	5.85 ± 0.04

The hydrolysis of *p*-chlorobenzoic anhydride in 75% dioxane–25% water (by volume); *T*, 79.65°

	NaOH (0.06440 N), ml.		$k_1 \times 10^3$ min.$^{-1}$
0	6.32	6.32	
11	6.91	5.73	(8.90)
25	7.69	4.95	9.77
41	8.43	4.21	9.91
55	8.98	3.66	9.93
80	9.74	2.90	9.74
110	10.37	2.27	9.72
150	11.21	1.43	9.91
		Av.	9.83 ± 0.09

The velocity constants were calculated from the integrated form of the first order equation. The energy of activation was obtained from the Arrhenius equation and the entropy of activation was calculated from the frequency factor *A*.[9] The limits of accuracy recorded for the rate constants represent the average deviation of the individual rate constants from the mean. The errors in the energy of activation and the frequency factor were calculated by combining the lowest velocity constant at the lower temperature with the highest velocity constant at the higher temperature, and *vice versa*. The average error for all compounds, thus estimated, is ±0.26 for log *A* and 1.1 e.u. for the entropy of activation.

Results and Discussion.—Pseudo first-order rate constants for the hydrolysis of substituted benzoic anhydrides at two temperatures are listed in Table III together with the energies of activation and the frequency factors, as well as the entropies of activation obtained from the latter.[9]

It is known qualitatively, and is expected on theoretical grounds, that acid anhydrides hydrolyze faster than acid amides and esters, and slower than acid chlorides, the reactivity decreasing with an increase in nucleophilic character of the group R in the typical acid derivative ArCOR ($Cl > OCOCH_3 > OCH_3 > NH_2$).[10] Direct data for the whole series are not available because of the different experimental conditions under which the various reactions have been studied, but the activation energies offer a sufficient comparison. Values of 18.7 and 17.7 kcal. are reported for the *alkaline* hydrolysis of benzamide[11] and ethyl benzoate[12] in ethyl alcohol–water mixtures. The value for benzoic anhydride is 16.1 kcal. for the *neutral* hydrolysis in 75% dioxane and 14.8 kcal. for the *neutral* hydrolysis of benzoyl chloride in acetone–water.[13] The data are not strictly comparable, because of the different solvents used, but the values for the hydrolysis of the anhydride and the acid chloride would be considerably lower for alkaline hydrolysis, enough lower to compensate for any variations due to solvent composition. The change in energy of activation with structure is considerably larger in the anhydride series than in the hydrolysis of esters or amides. From the *p*-nitro to the *p*-methyl compound the spread for the latter two is 3.7 and 2.8 kcal. in alkaline hydrolysis,[11,12] but 6.9 kcal. for the anhydrides. This must be due in part to the symmetrical structure of the anhydrides and the exaggerated effect of the substituents. A substituent, such as the nitro group, will favor nucleophilic attack on the carbonyl carbon in one ring, and the same substituent in the other ring will favor bond breaking. Each process probably exerts its influence on the activation

TABLE III

RATES OF HYDROLYSIS OF SUBSTITUTED BENZOIC ANHYDRIDES IN 75% DIOXANE–25% WATER (BY VOLUME)

Substituent	$k_1 \times 10^4$ (min.$^{-1}$) T, 58.25°	$k_1 \times 10^4$ (min.$^{-1}$) T, 79.65°	E (kcal.)	log A (sec.$^{-1}$)	ΔS^* (e.u.)
p-Methoxyl	0.547 ± 0.007	3.50 ± 0.10	20.1 ± 0.4	7.22	−27.8
p-Methyl	1.60 ± .04	8.07 ± .06	17.6 ± .4	6.04	−33.1
p-*t*-Butyl	1.77 ± .04	8.74 ± .08	17.3 ± .4	5.89	−33.8
m-Methyl	2.84 ± .04	14.7 ± .4	17.8 ± .4	6.42	−31.4
None	4.55 ± .09	20.0 ± .5	16.1 ± .5	5.50	−35.6
m-Methoxyl	5.86 ± .06	25.2 ± .6	15.8 ± .4	5.42	−36.0
p-Chloro	23.5 ± .3	98.4 ± 1.2	15.5 ± .3	5.82	−34.2
m-Nitro	861 ± 8	354 ± 3[a]	11.6 ± .3	4.81	−38.8
p-Nitro	1380 ± 30[b]	608 ± 6[a]	10.7 ± .4	4.42	−40.5

[a] *T*, 42.35°. [b] At 24.98° k_1 is 22.9×10^{-3} and *E* (24.98–42.35°) is 10.5 ± 0.4 kcal.

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[9] S. Glasstone, K. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 417.

(10) See for instance M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Clarendon Press, Oxford, 1949, p. 120.

(11) I. Meloche and K. J. Laidler, THIS JOURNAL, **73**, 1712 (1951). Solvent: 60–40 by volume ethanol-water.

(12) C. K. Ingold and W. S. Nathan, *J. Chem. Soc.*, 222 (1936); D. P. Evans, J. J. Gordon and H. B. Watson, *ibid.*, 1430 (1937). Solvent: 85% by weight ethanol.

(13) B. L. Archer and R. F. Hudson, *ibid.*, 3259 (1950). Solvent: 75% acetone by volume. This value for *E* refers to the "bimolecular" hydrolysis.

energy, although the former much more than the latter.

Another noteworthy feature is the low frequency factor and large negative entropy of activation for the hydrolysis of the anhydrides (3.2×10^5)[14] as compared to that of aromatic esters (5.32×10^9),[14] amides (2.77×10^7)[14] and acid chlorides (5.4×10^7).[14] The anhydrides are comparatively large molecules and appear to acquire more rigidity in passing from the ground state into the activated state than do the other acid derivatives. A parallelism between the energies of activation and the frequency factors is also evident from the data in Table III. This is not the usual behavior of aromatic side-chain reactions, where the frequency factors are commonly constant, but has nevertheless been observed quite often, for instance in the hydrolysis of benzamides[11] and the acid hydrolysis of ethyl benzoates.[15] Apparently, those groups which favor nucleophilic attack energetically, by withdrawing electrons, lower the probability of the formation of the activated complex.

The Effect of Substituents.—A plot of the logarithm of the rate constants against Hammett's sigma constants[16] shows the usual linear relationship (Fig. 1). The rho value is 3.19 and the mean deviation[17] of the points from the least-square line is 0.034. The rho value is rather high when compared to that of the other hydrolytic reactions, but it should probably be halved (*i.e.*, $\rho = 1.60$) because of the two carbonyl groups available for attack. The substituents place the compounds in the expected order, except for the *t*-butyl group, which causes the compound to react faster than the *p*-methyl compound, while the reverse should have been the case on the basis of their respective sigma values. The relative order of the alkyl groups indicate the operation of hyperconjugation, as has also been observed in other reactions involving a nucleophilic attack.[18] The sigma values obtained from the hydrolysis (*p*-methyl -0.142, *p*-*t*-butyl -0.128) place the two groups in the order expected from hyperconjugation. The *m*-methoxy group favors reaction, while the *p*-methoxy group impedes it more than any other group; this is in line with the effect of the methoxy group operating from the two different positions. The relative order of reactivity of all compounds is determined solely by differences in activation energies; the only exception is the *m*-methyl group, for which E falls out of line. Because of the dependence of k on E, a Hammett relationship is obtained in spite of the variations in the frequency factor. The same correlation has also been observed for certain other reactions for which the Hammett relationship holds.

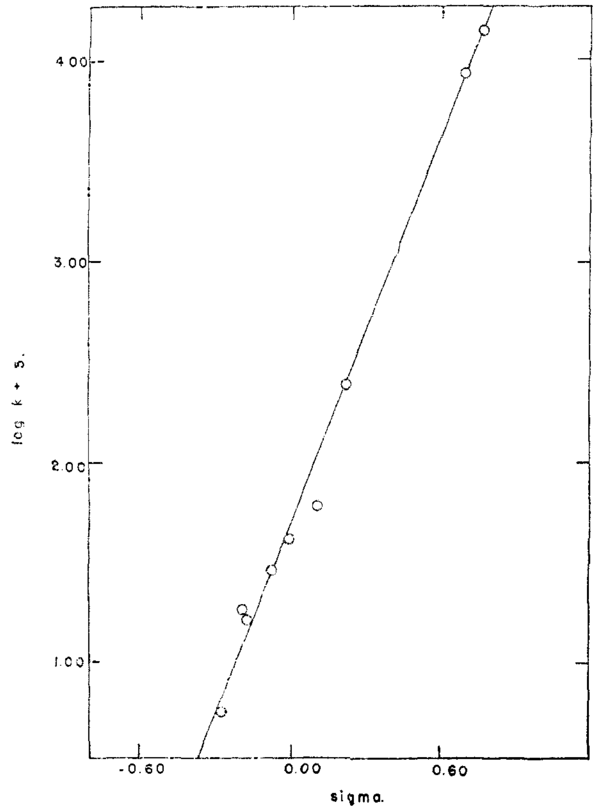

Fig. 1.—A plot of log k against Hammett's sigma constants.

The Mechanism of the Reaction.—The reaction is favored by electron withdrawing groups and impeded by electron donating groups, and therefore involves a nucleophilic attack as the rate-determining step. The effect of substituents does not completely rule out an SN1-type ionization mechanism, because the bond-breaking process might be rate-determining, and the same groups that favor the approach of the nucleophilic reagent will also favor bond-breaking (but not the stability of the ensuing oxocarbonium ion) when situated in the other ring. Such a mechanism, which in the absence of special structural features is very unlikely by analogy with the hydrolysis of esters and amides, has been debated, but rejected for the hydrolysis of certain mixed aliphatic anhydrides.[19] It could conceivably occur when very strong electron-repelling groups are present in one-half of the molecule and electron attracting in the other, as in the ionic breakdown of properly substituted benzoyl peroxides.[20] In the series of acid derivatives ArCOR the incursion of this mechanism in the absence of special structural effects appears only with the compounds in which R is the most electron attracting, namely, the benzoyl chlorides in highly aqueous solution.[21] Aromatic anhydrides are not incapable of ionic splitting, because benzoic anhydride,[22] but not ethyl benzoate,[23] forms the oxo-

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(14) The value for the frequency factor refers to the unsubstituted compound.

(15) E. W. Timm and C. N. Hinshelwood, *J. Chem. Soc.*, 862 (1938); K. J. Laidler and H. Eyring, *Ann. N. Y. Acad. Sci.*, **39**, 303 (1940).

(16) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII.

(17) T. W. Wright and J. F. Hayford, "The Adjustment of Observations," D. Van Nostrand Co., Inc., New York, N. Y., 1906, p. 132.

(18) J. W. Baker, W. S. Nathan and C. W. Shoppee, *J. Chem. Soc.*, 1847 (1935); W. C. L. Bevan, E. D. Hughes and C. K. Ingold, quoted by J. F. Bunnett and R. E. Zahler in *Chem. Revs.*, **49**, 273 (1951); E. Berliner and L. Monack, THIS JOURNAL, **74**, 1574 (1952).

(19) A. R. Emery and V. Gold, *J. Chem. Soc.*, 1443, 1447, 1455 (1950).

(20) J. E. Leffler, THIS JOURNAL, **72**, 67 (1950); P. D. Bartlett and J. E. Leffler, *ibid.*, **72**, 3030 (1950).

(21) Ref. 13. Also R. F. Hudson and J. E. Wardill, *J. Chem. Soc.*, 1729 (1950); E. D. Hughes, *Trans. Faraday Soc.*, **37**, 601 (1941).

(22) R. J. Gillespie, *J. Chem. Soc.*, 2997 (1950).

(23) L. P. Kuhn and A. W. Corwin, THIS JOURNAL, **70**, 3370 (1948).

carbonium ion $ArCO^+$ in concentrated sulfuric acid. It can safely be assumed, however, that the reaction belongs to the type of nucleophilic bimolecular displacement reactions with its analog in ester hydrolysis.[24] This conclusion was also reached by Gold[3] from other evidence. Meloche and Laidler[11] have recently outlined a general scheme for the hydrolysis of acid derivatives, which can be applied also to the hydrolysis of anhydrides (Fig. 2).

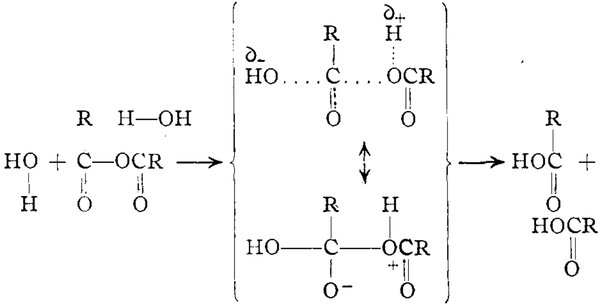
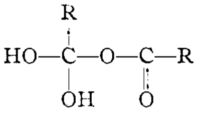


Fig. 2.

The intermediate in Fig. 2 is formulated as an activated complex, *i.e.*, an energy maximum. It may well be an actual intermediate such as I (Fig. 3) as has been suggested for ester hydrolysis.[25] This point is immaterial for this discussion. The position of attachment of the proton, or even the number of protons, is not necessarily unique as shown in Fig. 2. The proton may partake in several fast equilibria, which will not contribute materially to the activation energy.

The attack of the water molecule on the carbonyl carbon followed by the formation of a new covalent bond is the key step which is affected by the presence of the substituents and which requires most of the activation energy. Alkaline hydrolysis proceeds so much faster than neutral hydrolysis (by a factor of 10,000 for acetic anhydride[3]) because the attack is made by the more nucleophilic hydroxide ion and the consequent lowering of the repulsion energy by the carbonyl carbon. Such an explanation was given for the difference in activation energies between acid and alkaline ester hydrolysis.[26] Acid catalysis in anhydride hydrolysis is slight, because the acid by donating a proton to the incipient anion (Fig. 2), or the carbonyl oxygen, takes part in a step which is not as important as the attack by the nucleophilic reagent. The addition of a proton is affected adversely by the same substituents which favor reaction, but this effect is very small compared to the combined favorable influence of the substituents, and the latter outweigh the former. In agreement, it is found that acid catalysis in the hydrolysis of benzoic anhydride is relatively small, even in the presence of 0.1 N hydrochloric acid.[2]

The order of water in the hydrolysis of anhydrides has never been determined,[3] but it is likely to be greater than one. For the transition state pictured in Fig. 2 it is two. The most favorable transition state will be one in which at least two water molecules participate, one to supply a hydroxyl group to the carbonyl carbon, the other to supply a proton to the receding anion. By analogy, third order kinetics have been observed in the hydrolysis of acetyl chloride in aqueous dioxane[27] and the alcoholysis of *p*-nitrobenzoyl chloride in ether.[28] If the reaction is at least of the second-order with respect to water, it has obvious similarities to the mechanism of displacement reactions proposed by Swain and co-workers.[29] It is possible to devise transition states containing more than two molecules of water, but irrespective of the stoichiometric number of water molecules that may enter into the transition state kinetically, the complex must be highly solvated, more than that of ester hydrolysis. The data in Table IV, for example, show that an increase in water concentration increases the rate of hydrolysis of benzoic anhydride far more than that of ethyl benzoate.[30] A highly solvated transition state, relative to a less highly solvated ground state, will be accompanied by a loss of entropy of activation, because of the greater rigidity and the "freezing" of the solvated species and the loss of internal degrees of freedom. Such a process will be more favorable energetically, even if it involves a loss of entropy, and that is found experimentally.



(I)

$$HO{-}\overset{R}{\underset{OH}{C}}{-}O{-}\underset{O}{\overset{\|}{C}}{-}R$$

Fig. 3.

TABLE IV

THE HYDROLYSIS OF ETHYL BENZOATE AND BENZOIC ANHYDRIDES IN SOLVENTS OF VARYING WATER CONCENTRATION AT 25°

Ethyl benzoate[31] Ethanol, % (by weight)	$k \times 10^4$, l./mole^{-1} sec.$^{-1}$	Benzoic anhydride Dioxane, %, (by volume)	$k \times 10^4$, min.$^{-1}$	*p*-Nitrobenzoic anhydride Dioxane, %, (by volume)	$k \times 10^4$, min.$^{-1}$
55.7	15.3	50	2.6		
67.1	12.03	75	0.38	75	229
71.3	10.02	80	0.26	80	165
85.0	6.21				

Acknowledgment.—We gratefully acknowledge the assistance afforded by a Frederick Gardner Cottrell Grant of the Research Corporation.

BRYN MAWR, PENNA.

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[24] J. N. E. Day and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941).

[25] M. L. Bender, THIS JOURNAL, **73**, 1626 (1951).

[26] C. N. Hinshelwood, K. J. Laidler and E. W. Timm, *J. Chem. Soc.*, 848 (1938).

[27] Hudson and Macleod, quoted in ref. 13.

[28] A. A. Ashdown, THIS JOURNAL, **52**, 268 (1930).

[29] C. G. Swain, *ibid.*, **70**, 1119 (1948); *ibid.*, **72**, 4578 (1950); C. G. Swain and R. W. Eddy, *ibid.*, **70**, 2989 (1948).

[30] Data are available for the hydrolysis of both ethyl acetate and acetic anhydride in the *same* solvent (ethanol or acetone), which are in accord with the view expressed above. J. F. M. Caudri, *Rec. trav. chim.*, **48**, 422 (1929); *ibid.*, **49**, 1 (1930); V. Gold, ref. 3.

[31] R. A. Fairclaugh and C. N. Hinshelwood, *J. Chem. Soc.*, 538 (1937), and ref. 12b.