357. *Acylation. Part VI.* A Kinetic Study of Friedel–Crafts Acylation by Monocarboxylic Acid Anhydrides in Carbon Tetrachloride as Solvent with Stannic Chloride as Catalyst.*

By D. P. N. SATCHELL.

At 25°, the stannic chloride-catalysed acylation of phenols by mono-carboxylic acid anhydrides in carbon tetrachloride leads to an ester rather than a ketone. At [anhydride]/[catalyst] ratios below *ca.* 40 the reaction kinetics are simple, the acylation being of the first-order in each component. At ratios greater than 40, however, the kinetics are complex.

Changes in anhydride structure reveal competing substituent effects. The observed order of reactivity is $Ac_2O > (C_3H_7 \cdot CO)_2O \gg (CH_2Cl \cdot CO)_2O$. Steric effects may be prominent.
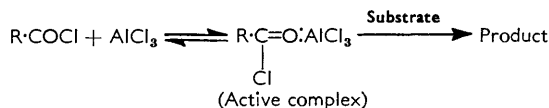
The reaction is compared generally with the analogous acylation by acyl chlorides. The latter is found to be far simpler though, in the system studied, a given phenol is acylated at the same stannic chloride concentration at least 50 times faster by the anhydride than by the corresponding acyl chloride.

The reaction mechanism for stannic chloride-catalysed acylation by anhydrides bears no resemblance to that currently accepted for catalysis by aluminium chloride, for the former is truly catalytic, involving acylation by anhydride–catalyst complexes rather than decomposition of the catalyst.

THERE appears to be no previous kinetic study of Friedel–Crafts acylation by anhydrides. There exists, nevertheless, much preparative work,[1] chiefly concerning dicarboxylic acid anhydrides. Some of this constitutes enquiry into the best preparative recipes and from it deductions about mechanism have also been made.[2] Most previous study has involved aluminium chloride and this catalyst appears to exhibit the following behaviour. In the presence of anhydrides replacement of halogen occurs, *e.g.*:

$$(R \cdot CO)_2O + AlCl_3 \longrightarrow R \cdot COCl + R \cdot CO \cdot O \cdot AlCl_2$$

The acyl halide produced may then interact with more catalyst to form the active acylating agent, *e.g.*:

$$R \cdot COCl + AlCl_3 \rightleftharpoons \underset{\underset{\text{(Active complex)}}{\overset{|}{Cl}}}{R \cdot C}=O \vdots AlCl_3 \xrightarrow{\text{Substrate}} \text{Product}$$

Best yields are obtained when three equivalents of aluminium chloride are present, and further reaction may therefore occur:

$$R \cdot CO \cdot O \cdot AlCl_2 + AlCl_3 \longrightarrow \underset{\overset{|}{Cl}}{R \cdot C}=O \vdots AlCl_3 + AlOCl$$
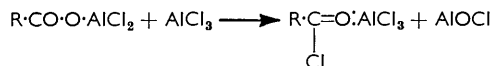
There seem, however, to be other possible explanations for the efficacy of an excess of catalyst: for instance, some catalysts will doubtless be engaged by the product. This reaction scheme for aluminium chloride, if correct, makes it clear that with this catalyst the reaction is only an elaboration of Friedel–Crafts acylation by an acid chloride. Since the scheme has, in fact, been generally accepted by reviewers a kinetic study of acylation by anhydrides must have seemed less urgent to many than a study of the acyl halide reaction.

* Part V, preceding paper.

[1] (*a*) Thomas, " Aluminium Chloride in Organic Chemistry," Reinhold Publ. Co., New York, 1944; (*b*) Berliner, " Organic Reactions," Wiley and Sons, Inc., New York, 1949, Vol. V, p. 232; (*c*) Gore, *Chem. Rev.*, 1955, **55**, 229; (*d*) Baddeley, *Quart. Rev.*, 1954, **8**, 355.

[2] See, *e.g.*, Groggins and Nagel, *Ind. Eng. Chem.*, 1934, **26**, 1313.

However, as Burton and Praill [3] have pointed out, in work which has been largely neglected, some Lewis acids (*e.g.*, boron trifluoride, zinc chloride, or stannic chloride) do not decompose in the presence of anhydrides at ordinary temperatures. There is good evidence that both boron trifluoride and zinc chloride form addition complexes of some kind with anhydrides and then acylate aromatic compounds without displacement of halide from the Lewis acid. For such catalysts the reaction mechanism must differ from that accepted for aluminium chloride but, apart from the work of Burton and Praill, this has received little attention. The present paper reports a preliminary kinetic study of catalysis by stannic chloride in carbon tetrachloride. Various monocarboxylic acid anhydrides have been used to test the effect of structural change on their reactivity. Friedel–Crafts acylations usually concern the production of ketones from aromatic substrates. Here we have studied instead the acylation of phenols under conditions which lead predominantly to an ester rather than a ketone. The overall reaction has been
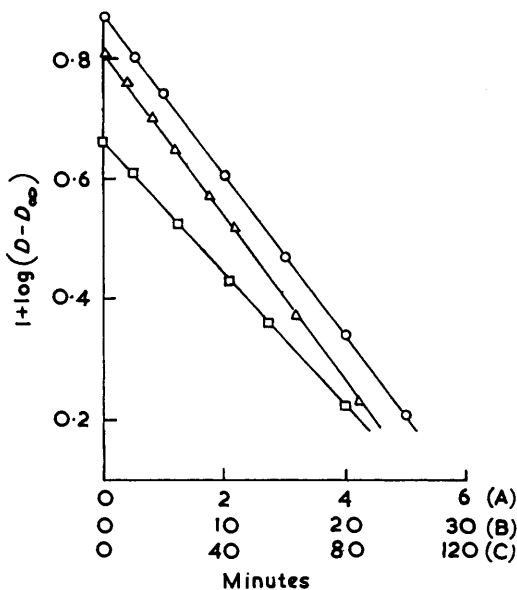
Examples of first-order loss of phenol.

$[Ac_2O] = 0.012M;$ $[SnCl_4] = 7.0 \times 10^{-4}M.$
D = Optical density.

$\bigcirc$, β-Naphthol (scale A); $\triangle$, *m*-nitrophenol (scale B); $\square$, 2,4-dibromophenol (scale C).

$(R \cdot CO)_2O + ArOH \longrightarrow ArO \cdot COR + R \cdot CO_2H.$ Our earlier studies of the analogous acylation by acid chlorides in carbon tetrachloride,[4] and of acylation by anhydrides, catalysed by stannic chloride in acetic acid,[5] form the background to the present work.

Preliminary Experiments and Choice of System.—Some preliminary experiments were conducted with β-naphthol at an initial concentration of *ca.* $5 \times 10^{-3}M$. With an excess (*ca.* $10^{-2}M$) of acetic anhydride, the half-life for loss of naphthol was only a few minutes at stannic chloride concentrations as low as $7 \times 10^{-4}M$. In these experiments, with the stannic chloride concentration considerably below that of the substrate, reaction nevertheless went to completion. This fact indicates that this Friedel–Crafts acylation cannot depend on the quantitative production of an acylating agent from the catalyst by replacement of chlorine atoms: there were not sufficient chlorine atoms available, even if all four were substituted, in the experiments described above. [Such a mechanism for stannic chloride was in any event unlikely, for this substance is not solvolysed in acetic acid solvent [6] but gives addition complexes such as $(AcOH)_2SnCl_4$; see also ref. 5.]

[3] Burton and Praill, *Chem. and Ind.*, 1954, 90; 1951, 726.
[4] Satchell, *J.*, 1961, 5404.
[5] Satchell, *J.*, 1962, Part V, 1894.
[6] Satchell, *J.*, 1958, 3910.

Plots of the kinetic data for individual runs at constant catalyst and anhydride concentrations, when the catalyst concentration was well below that of the initial naphthol concentration, as above, did not show accurate first-order behaviour for loss of naphthol: the reaction become somewhat slower with time. This was attributed to the production of acetic acid (one of the products), which could co-ordinate with the stannic chloride or solvate–stannic chloride complexes, in competition with the anhydride.* Because of this it was thought desirable to work at a lower initial naphthol concentration, so that the acetic acid concentration produced would be small, or, at least, only comparable with that of the catalyst. The reactions were followed by measuring the loss of phenol spectrophotometrically in the concentration range from 5×10^{-4} to 10^{-5}M, and in order actually to use such concentrations for the reacting solutions it was found desirable to conduct the reaction in the spectrophotometric cells themselves (see Experimental section). Under these conditions, with the substrate concentration comparable with, or less than, that of the catalyst, the loss of substrate showed good first-order kinetics (a typical plot is shown in

TABLE 1.

Acylation of β-naphthol by acetic anhydride catalysed by stannic chloride at 25°.

Initial [β-naphthol] $\approx 5 \times 10^{-4}$M; k_{obs} = First-order rate constant, in min.$^{-1}$.
Square brackets represent molarity in all Tables.

[Ac$_2$O]	10^4[SnCl$_4$]	$10^2 k_{obs}$
0·012	3·5	14·0
0·012	7·0	30·0

TABLE 2.

Acylation of *m*-nitrophenol by acetic anhydride catalysed by stannic chloride at 25°.

Initial [*m*-nitrophenol] $\approx 5 \times 10^{-4}$M; k_{obs} = First-order rate constant, in min.$^{-1}$; $t_{\frac{1}{2}}$ = reaction half-life, in min.

[Ac$_2$O]	10^4[SnCl$_4$]	$t_{\frac{1}{2}}$	Reaction order *	$10^2 k_{obs}$ *	[Ac$_2$O]	10^4[SnCl$_4$]	$t_{\frac{1}{2}}$	Reaction order *	$10^2 k_{obs}$ *
0·003	7·0	49	1	1·4	0·10	7·0	30	Z	—
0·006	7·0	23	1	3·0	0·20	7·0	30	Z	—
0·012	7·0	11	1	6·3	0·003	14·0	26	1	2·7
0·024	7·0	10	Z/1	—	0·012	14·0	6	1	12·0
0·048	7·0	17	Z/1	—	0·10	14·0	3	Z/1	—

* 1 = First-order; Z = approximately zero order; Z/1 = between first and zero order. The rate constants are not calculated for the zero-order plots.

TABLE 3.

Acylation of 2,4-dibromophenol by acetic anhydride catalysed by stannic chloride at 25°.

Initial [dibromophenol] $\approx 5 \times 10^{-4}$M.

[Ac$_2$O]	10^4[SnCl$_4$]	$t_{\frac{1}{2}}$	Reaction * order	$10^2 k_{obs}$	[Ac$_2$O]	10^4[SnCl$_4$]	$t_{\frac{1}{2}}$	Reaction * order	$10^2 k_{obs}$
0·006	7·0	108	1	0·64	0·012	14·0	26	1	2·7
0·012	7·0	55	1	1·3	0·036	14·0	12	Z/1	—
0·028	7·0	65	Z/1	—	0·1	14·0	14	Z/1	—
0·1	7·0	65	Z	—	0·3	14·0	13	Z	—
0·2	7·0	64	Z	—	0·012	28·0	12	1	6·0
0·5	7·0	64	Z	—	0·024	28·0	5·5	1	13·0

* See Table 2.

the Figure). At most, negligible engagement of the catalyst by the products can therefore occur under these conditions.

Only a few experiments were undertaken with β-naphthol because the reaction was a little too fast for convenient study, but some evidence for first-order dependence on the catalyst concentration can be seen in Table 1. A more detailed study was made with

* It is known that the phenolic substrate does not do this in the concentration ranges concerned.[4]

dibromophenol and *m*-nitrophenol, and the results of experiments directed towards the determination of reaction orders are given below.

Reaction Orders.—Results for stannic chloride-catalysed acetylation of 2,4-dibromo-phenol and *m*-nitrophenol by acetic anhydride are given in Tables 2 and 3. The observed phenomena are reproducible and straightforward but, as we shall see, their complete interpretation is not clear-cut.

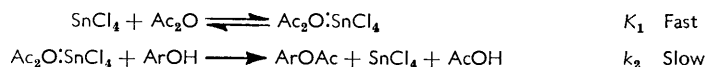For both substrates the following behaviour was found:

(*a*) Reaction in the absence of catalyst was negligibly slow.

(*b*) When the anhydride concentration was less than 20—40 times that of the catalyst the observed loss of phenol was an accurately first-order process (Figure) and the first-order constants (k_{obs}) depended on the first powers of both anhydride and catalyst concentrations.

(*c*) When the anhydride concentration exceeds that of the catalyst by a factor of 20—40, then, rather suddenly, the loss of phenol changes to an approximately zero-order process, while the rate decreases slightly and then becomes largely independent of the anhydride concentration but strongly dependent on catalyst concentration.

(*d*) In the latter region, in spite of the approximately zero-order loss of substrate, the rate constant is nevertheless somewhat dependent on the nature of phenol used.

The simple behaviour (*b*) probably implies a reaction scheme such as:

$$SnCl_4 + Ac_2O \rightleftharpoons Ac_2O \cdot SnCl_4 \qquad\qquad K_1 \quad Fast$$

$$Ac_2O \cdot SnCl_4 + ArOH \longrightarrow ArOAc + SnCl_4 + AcOH \qquad k_2 \quad Slow$$

If the pre-equilibrium lies to the left, then the observed reaction rate is given by:

$$-d[ArOH]/dt = k_2[Ac_2O \cdot SnCl_4][ArOH] = k_2 K_1[Ac_2O][SnCl_4][ArOH],$$

or
$$-d \log [ArOH]/dt = k_{obs}.$$

In the above expression K_1 is the equilibrium constant for complex formation, k_2 the rate constant of the slow step, and square brackets represent concentrations. This scheme provides for the observed first-order dependence on each reactant. The complex between stannic chloride and anhydride is perhaps a dipolar oxonium complex at one of the carbonyl-oxygen atoms, rather than the fully ion-paired acylonium complex $Ac^+[SnCl_4(OAc)]^-$.

The observations noted under (*c*) and (*d*), which apply to the region where the anhydride is in more than 40-fold excess over the catalyst, are difficult to rationalise convincingly.

TABLE 4.

Reactivity of different phenols to stannic chloride-catalysed acetylation at 25°.

k_{obs} = First-order rate constant, in min.$^{-1}$; $[Ac_2O] = 0.012$M; $10^4[SnCl_4] = 7.0$M.

Phenol..............	β-C$_{10}$H$_7$·OH	*m*-NO$_2$·C$_6$H$_4$·OH	2,4-Br$_2$C$_6$H$_3$·OH
$10^2 k_{obs}$	30.0	6.3	1.3

TABLE 5.

Acylation of *m*-nitrophenol by benzoic anhydride catalysed by stannic chloride at 25°.

Initial [*m*-nitrophenol] $\approx 5 \times 10^4$M.

[Bz$_2$O]	10^4[SnCl$_4$]	$t_{\frac{1}{2}}$	Reaction order *	$10^2 k_{obs}$ *	[Bz$_2$O]	10^4[SnCl$_4$]	$t_{\frac{1}{2}}$	Reaction order *	$10^2 k_{obs}$ *
0.0055	14.0	46	1	1.5	0.21	14.0	18	Z/1	—
0.0110	14.0	22	1	3.2	0.011	7.0	54	1	1.3
0.0225	14.0	11	1	6.3	0.011	28.0	9	1	7.7
0.067	14.0	6.5	Z/1	—					

* See Table 2.

More detailed work is planned for this concentration region where it at least seems clear that the mechanism becomes appreciably more involved and doubtless concerns poly-associated species.

Effects of Phenol Structure.—The reactivities of the different phenols towards acetylation under the same conditions are compared in Table 4. β-Naphthol is 5 times more reactive than *m*-nitrophenol. In acylation by acetyl chloride catalysed by stannic chloride the factor was *ca.* 8. This similarity is to be expected for, as found in the latter reaction, it is likely that the greater the electron density on the phenolic oxygen atom the faster the rate of acylation, nucleophilic attack on the acylating agent being facilitated. The low reactivity of dibromophenol may be partly steric in origin.

Effect of Anhydride Structure.—Besides acetic anhydride, n-butyric anhydride, mono- and di-chloroacetic anhydride, and benzoic anhydride were studied as acylating agents for *m*-nitrophenol.

Benzoic anhydride. Sufficient results (Table 5) were obtained for this compound to show that the kinetic pattern with it (and therefore presumably with other aromatic anhydrides) was very similar to that found for acetic anhydride.

At the same catalyst concentration benzoic anhydride is *ca.* 5 times less reactive than acetic anhydride.

Aliphatic anhydrides. Chloro- and dichloro-acetic anhydride proved too unreactive to give measurable rates under the conditions used. (A very small amount of reaction was observed with dichloroacetic anhydride but experiment showed that this was entirely due to an uncatalysed reaction, which is favoured for this compound.) n-Butyric anhydride gave measurable rates but was less reactive than acetic anhydride (cf. Table 6), which is interesting because it indicates that not only the kinetics but also substituent effects are more complex in the present reaction than in acylation by acid chlorides.[4] Both reactions seem very likely to involve polar complexes, between catalyst and acetylating compound, which suffer nucleophilic attack by the substrate. Such a process can involve at least

TABLE 6.

Comparison of acetic and butyric anhydride.

k_{obs} = First-order rate constant, in min.$^{-1}$.   Initial [phenol] $\approx 5 \times 10^{-1}$M.

	[Anhydride]	10^4[SnCl$_4$]	k_{obs}	[Anhydride]	10^4[SnCl$_4$]	k_{obs}
		2,4-Dibromophenol			*m*-Nitrophenol	
Ac$_2$O	0·012	14·0	2·7	0·012	7·0	6·3
Ac$_2$O	0·012	28·0	6			
Bu$_2$O	0·012	14·0	1·2	0·012	7·0	5·3
Bu$_2$O	0·012	28·0	2·7			

three separate effects from the viewpoint of substituents in the acylating agent. (*a*) Electron-withdrawing substituents reduce the electron density on the carbonyl-oxygen atom and so reduce the facility of co-ordination with the catalyst; electron-repelling substituents increase this facility. (*b*) Electron-repelling substituents stabilise any positive charge developed on the co-ordinated carbonyl-carbon atom in the complex, thus hindering attack by the substrate; electron-attracting substituents increase this charge, and therefore facilitate nucleophilic attack (this is why dichloroacetic anhydride exhibits a detectable uncatalysed reaction). (*c*) Bulky substituents may have steric effects which hinder both complex formation and attack by the substrate.

In the stannic chloride-catalysed acylation by acid chlorides we found [4] that the effects noted under (*a*) were dominant. Thus the order of reactivity was CH$_2$Cl·COCl < CH$_3$·COCl < CH$_3$·CH$_2$·COCl < CH$_3$·CH$_2$·CH$_2$·COCl. In the present reaction the order is (CH$_2$Cl·CO)$_2$O < Ac$_2$O > (C$_3$H$_7$·CO)$_2$O. Since effects (*a*) and (*b*) appear likely to have similar relative importance for both reactions it seems possible that the difference in

behaviour between chlorides and anhydrides is to be attributed to the greater importance of steric effects for the latter.   Whatever the exact nature of the reactive complexes there will always be the additional acyl group to be accommodated.   Thus the combination of effects (*b*) and (*c*) must just outweigh effect (*a*) in the comparison between acetic and butyric anhydride.

It should be noted that substituent effects recorded for aluminium chloride-catalysed acylation by anhydrides will not necessarily be similar to those now found.   The aluminium chloride reaction is a different process and is likely to resemble acylation by acid chlorides rather than the present reaction.   (In fact, our present knowledge of substituent effects in the aluminium chloride-catalysed reaction is very confused.[1a,b]   This is largely because the results apply to a variety of solvents and conditions.)

Catalytic Effect of Germanium Tetrachloride.—Because stannic chloride proved so powerful a catalyst for the present type of reaction, the less powerful Lewis acid germanium tetrachloride was studied.   However, this substance produced negligible reaction over long periods under the conditions used with stannic chloride.

Effect of the Products on the Kinetics.—Friedel–Crafts reactions are frequently complicated by the engagement of catalyst by the product which thus removes some of the former from its useful sphere of influence.   As shown above, in the present systems the products do not form appreciable amounts of complex with the catalyst in the concentration ranges used. However, evidence was also quoted which implies that, when present in excess of the catalyst, they do inhibit the reaction to some extent.   The importance of the inhibition by acetic acid was examined with deliberately added carboxylic acid (Table 7).   These showed that concentrations of acid comparable with that of the catalyst produced little effect on the rate, but that retardation is noticeable when a considerable excess of acid over catalyst is present.   It will be recalled (Table 2) that, when the concentration of anhydride is greatly increased the rate of loss of phenol, instead of increasing also, falls somewhat and then tends to independence of anhydride concentration.   While this effect in any case does not

TABLE 7.

Effect of added acetic acid on the acylation of 2,4-dibromophenol by acetic anhydride catalysed by stannic chloride at 25°.

Initial [dibromophenol] $\approx 5 \times 10^{-4}$M;   [Ac$_2$O] $= 0{\cdot}04$M;   [SnCl$_4$] $= 7{\cdot}0 \times 10^{-4}$M; $t_{\frac{1}{2}} =$ reaction half-life, in min.

Added [AcOH]	0·0	5×10^{-4}	6×10^{-3}	2×10^{-2}
t	68	68	130	240

seem likely to be due to carboxylic acid as an impurity in the anhydride, the results in Table 7 may nevertheless be used to deduce that, for the acetic system, even 3% of impurity would not suffice to produce the observed loss of dependence on acetic anhydride concentration.

Comparison with Acylation by Acid Chlorides.—It should be noted (see p. 1905) that the products are esters and not hydroxy-ketones.   In principle, the phenolic substrates could undergo acylation at one, or both, of two sites.   Acylation of the hydroxyl group gives esters and of the aromatic ring gives ketones, the more usual Friedel–Crafts product.   However, as pointed out previously,[4] Friedel–Crafts acylation of phenols by acid chlorides in carbon tetrachloride may be expected, and does, lead, at least initially, to predominant ester formation.   The same now appears true for acylation by anhydrides.   Comparison of present with previous work shows that for a given phenol, at the same catalyst concentration, the anhydride reaction is at least 50-fold the faster.   (This is good, additional evidence against acyl chlorides as intermediates in this latter reaction.)   The effect, on reactivity, of changes in substrate structure is the same for both reactions, but alterations in the acetylating species appear to have more serious steric effects for the anhydride reaction.   Also the products for this reaction are likely to hinder its completion, when a

deficit of catalyst is used, more seriously than will the products of the acyl chloride reaction. Thus acylation by acid chlorides is undoubtedly the simpler process both kinetically and from the viewpoint of predicting the effects of structural changes in the reactants.

EXPERIMENTAL

Materials.—Dry carbon tetrachloride and acetic acid were prepared as previously described.[4,7] Acetic anhydride and butyric anhydride, purified by fractional distillation from magnesium, had b. p. 139° and 198°, respectively. Dichloroacetic anhydride was a previous sample.[8] Chloroacetic anhydride was fractionally distilled and had m. p. 46°. Benzoic anhydride was a pure, dried commercial sample of m. p. 42°. β-Naphthol, *m*-nitrophenol, and 2,4-dibromophenol were recrystallised samples, of m. p. 122°, 95°, and 39°, respectively. Samples of β-naphthyl acetate, *m*-nitrophenyl acetate, dibromophenyl acetate, and *m*-nitrophenyl benzoate for comparison were prepared by Vogel's method;[9] they had m. p. 69°, 55°, 36°, and 95°, respectively.

All reagents were stored permanently in a dry box, in which solutions and reaction mixtures were made up (see below).

Stoicheiometry.—For each phenol, acylation essentially resulted in esterification only, this product being obtained in high yield. This was established (*a*) by noting that the ultraviolet spectrum of the products, for each phenol–anhydride combination, was in quantitative agreement with that expected on the basis of spectra of synthetic product mixtures containing the expected esters (this was so no matter what the anhydride/catalyst concentration ratio) and (*b*) by conducting independent preparative-scale reactions under conditions similar to those used in the kinetic experiments and isolating the products. The infrared spectrum always corresponded to that of the expected ester.

Kinetic Arrangements.—The reaction studied being of the Friedel–Crafts type, care was taken to avoid contamination with atmospheric moisture. All the reagents were carefully dried (see above). Any residual water in the carbon tetrachloride will have been rapidly transformed into the carboxylic acid corresponding to the anhydride used. This acid must have had some effect on the observed rate constant (see p. 1904) though the simplicity of some of the kinetic data, their reasonable (~10%) reproducibility with different samples of solvent and reagents, and the study of the effects of deliberately added carboxylic acid (Table 7), all show that this effect was probably small.

In order to work with very low phenol concentrations the reaction mixtures were placed in the quartz cells of 1 cm. path (*ca.* 3 ml. capacity) used with a Beckman spectrophotometer. These cells had inverted ground caps, which effectively exclude atmospheric moisture for reasonable periods. The spectrophotometer was fitted with a thermostat-controlled cell compartment, and the filled cells were left in this during a run so that measurements could be taken continuously (this was especially convenient for the faster reactions). The cell compartment was maintained at 25° ± 0·5° for all measurements.

The reaction mixtures were made up by volume, in 10-ml. graduated flasks, from solvent and stock solutions of the anhydride and catalyst. A sample was then transferred to a spectrophotometer cell. All these operations were carried out in a dry box. The filled, stoppered cells were removed from the box, placed in the instrument, and allowed to reach the thermostat temperature. A small (*ca.* 0·05 ml.) sample of a suitable solution of the relevant phenol in carbon tetrachloride was then rapidly added to the cell, with the minimum exposure to the atmosphere, and spectrophotometric measurements of the loss of phenol were begun. These were taken as previously described.[3]

KING'S COLLEGE, STRAND, LONDON, W.C.2.

[7] Satchell, *J.*, 1956, 3911.
[8] Satchell, *J.*, 1960, 1752.
[9] Vogel, " Practical Organic Chemistry," Longmans, Green and Co., London, 1948.

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