

355. *Acylation. Part IV.¹ The Mechanism of Acylation by Carboxylic Anhydrides in Non-aqueous Media Catalysed by Sulphuric acid and by Sulphoacetic Acid.*

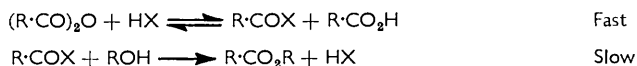
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Kinetic experiments are reported on the acylation of *m*-nitrophenol by acetic anhydride in acetic acid, and by *n*-butyric anhydride in *n*-butyric acid, catalysed by sulphuric acid. A study of catalysis by sulphoacetic acid in acetic acid is also described.

With both catalysts the active acylating agent is the acyl derivative of the catalyst, formed from the anhydride in a rapid pre-equilibrium. For the dibasic sulphuric acid, evidence is presented for the production of both mono- and di-acyl derivatives. The equilibrium constant for the reaction $(R\cdot CO)_2O + H_2SO_4 \rightleftharpoons R\cdot CO\cdot HSO_4 + R\cdot CO_2H$ is 10 ± 2 for the acetic system and 20 ± 3 for the butyric system.

The behaviour of the present catalysts is related to that of other strong acids, and their action in effecting acetylation by acetic anhydride is compared with that in acetylation by the related compound isopropenyl acetate.

PART I of this series ² comprises the essential background to the present work. We there reported a kinetic study of the mineral acid-catalysed acylation of β -naphthol by carboxylic anhydrides in the parent carboxylic acid as solvent. If HX represents the catalyst, and ROH the naphthol, the mechanism of acylation was found to be:



For the halogen acids the pre-equilibria lie well to the right, but for perchloric acid only a small amount of acyl perchlorate is present.

It was noted in Part I that the sulphuric acid-catalysed reaction would be liable to exhibit complications because of the special reaction known to occur between this acid and anhydrides. With acetic anhydride, for instance, it gives sulphoacetic acid, a process which, it has been suggested,³ involves rearrangement of the expected intermediate for acylation, namely acetyl hydrogen sulphate.



Because of the expected complexities we have made a separate study of catalysis by both sulphuric and sulphoacetic acid. In the event, sulphuric acid-catalysis did prove

¹ Part III, preceding paper.

² Satchell, *J.*, 1960, 1752.

³ Murray and Kenyon, *J. Amer. Chem. Soc.*, 1940, **62**, 1230.

more complex than that of other acids, but the complications were not those expected, for the special side reactions noted above proved slow in comparison with acylation under the conditions chosen (see Experimental section).

To avoid the obvious and trivial difficulty of loss of sulphuric acid by sulphonation of the hydroxylic substrate, which would be serious with the reactive β -naphthol, we chose for study the nuclear-deactivated, but otherwise equally suitable, *m*-nitrophenol.

EXPERIMENTAL

Materials.—Acetic acid, *n*-butyric acid, acetic anhydride, and *n*-butyric anhydride were purified as previously described.² They had b. p. 118°, 163—164°, 140°, and 198°, respectively. Sulphuric acid was of "AnalaR" quality. Sulphur trioxide was prepared by the distillation of oleum in an all-glass apparatus. A stock solution of sulphoacetic acid in acetic acid was prepared as before.¹ *m*-Nitrophenol was a recrystallised sample, of m. p. 97°. *m*-Nitrophenyl acetate was prepared by Vogel's method⁴ and had m. p. 54°.

Stoichiometry of the Reactions.—Independent preparative-scale reactions, with concentrations similar to those used in the kinetic work, were undertaken. These showed that the product ester was formed in nearly quantitative (>90%) yield.

Kinetic Methods.—Acylation was studied in both the acetic anhydride-acetic acid and the butyric anhydride-butyric acid systems. As for β -naphthol, the reaction was followed by observing the rate of loss of phenol by spectroscopy. *m*-Nitrophenol has an absorption band at 3300 Å which is largely absent from the spectrum of the derived acetate and butyrate. Measurements were made with a Beckman spectrophotometer and quartz cells of 1 cm. path.

Reaction mixtures were made up, and sampling carried out, essentially as previously described.² The kinetic experiments were at 40°. With acetic acid as solvent and sulphuric acid as catalyst, it was shown that there was negligible loss of free sulphate from the mixtures in periods corresponding to several half-lives for loss of phenol. Formation of sulphoacetic acid was therefore inappreciable during the acylation for the concentration ranges used (Table 1). Possible complication of this nature also proved absent in the butyric system.

TABLE 1.

Acetylation by acetic anhydride catalysed by sulphuric acid at 40°.

k_{obs} = first-order rate constant, in min.⁻¹.

Square brackets represent concentrations (molarity) in all Tables.

(a) Order in sulphuric acid. Initial [Ac ₂ O] = 0.405M.		(b) Order in anhydride. Initial [H ₂ SO ₄] = 0.0076M.		
[H ₂ SO ₄]	10 ² k_{obs}	[Ac ₂ O]	[Ac ₂ O]/[AcOH]	10 ² k_{obs}
0.00140	0.231	0.124	0.0072	0.200
0.00280	0.457	0.186	0.0109	0.375
0.00420	0.674	0.280	0.0165	0.670
0.00652	1.03	0.346	0.0206	0.935
0.0131	1.85	0.451	0.0270	1.38
0.0211	2.78	0.490	0.0295	1.64
		0.658	0.0406	2.53
		0.832	0.0502	3.74

In general, concentrations were kept as low as practicable to minimise possible medium effects.

Infrared Spectra.—These were made with a Grubb-Parsons double-beam instrument, fitted with rock-salt optics and sample cells possessing either rock-salt or silver chloride windows.

Attempts to Prepare Acetyl Hydrogen Sulphate.—As in the method of van Peski,⁵ acetic acid was slowly added to sulphur trioxide at a temperature below 0°. The products of this preparation and others are discussed below.

RESULTS AND DISCUSSION

Catalysis by Sulphuric Acid.—(i) *Kinetic form.* For the acetic system experiments directed towards the determination of reaction orders are reported in Table 1. The initial

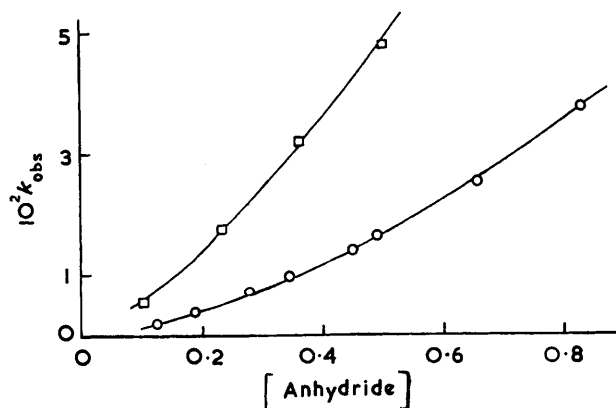
⁴ Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1948.

⁵ van Peski, *Rec. Trav. chim.*, 1921, **40**, 103.

m-nitrophenol concentration was very low compared with the anhydride's and its removal was, in all cases, an accurately first-order process. The reproducibility of the observed first-order rate constants (k_{obs}) was within 1%. It was found (Table 1 and Fig. 1) that k_{obs} was closely proportional to the stoichiometric catalyst concentration but depended on acetic anhydride concentration to a power greater than unity. In fact, k_{obs} was approximately proportional to $[\text{Ac}_2\text{O}]^{1.5}$.

FIG. 1. Plots showing order in anhydride.

○, Ac_2O . □, $(\text{C}_3\text{H}_7\cdot\text{CO})_2\text{O}$.



For the butyric system the same general features were found as for the acetic system (Table 2 and Fig. 1) though the apparent kinetic order in anhydride was here 1.3.

TABLE 2.

Acylation by butyric anhydride catalysed by sulphuric acid at 40°.

k_{obs} = First-order rate constant, in min^{-1} .

(a) Order in sulphuric acid.

Initial $[(\text{C}_3\text{H}_7\cdot\text{CO})_2\text{O}] = 0.232\text{M}$.

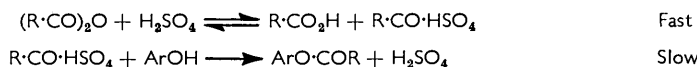
$[\text{H}_2\text{SO}_4]$	$10^2 k_{\text{obs}}$
0.00364	0.834
0.00728	1.73
0.0109	2.71
0.0146	3.54

(b) Order in anhydride.

Initial $[\text{H}_2\text{SO}_4] = 0.00728\text{M}$.

$[(\text{C}_3\text{H}_7\cdot\text{CO})_2\text{O}]$	$[(\text{C}_3\text{H}_7\text{CO})_2\text{O}]/[\text{BuOH}]$	$10^2 k_{\text{obs}}$
0.099	0.0165	0.548
0.232	0.0394	1.73
0.365	0.0634	3.17
0.498	0.0888	4.76

If the mechanism for sulphuric acid-catalysis were like that for other mineral acids² it would be basically as follows, it being remembered that in carboxylic acid solvents strong acids are little dissociated: *

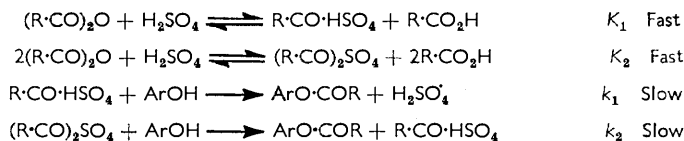


This scheme predicts the first-order loss of phenol. However, since the sulphuric acid was always in considerable deficit compared with the anhydride (see Tables), if the pre-equilibrium lay to the right an order of less than unity in the anhydride would be expected. Such is the case for the halogen acid catalysts. On the other hand, if the pre-equilibrium lay largely to the left, then an order of unity would be expected, as found for perchloric and for sulphoacetic acid (see below). An order greater than unity, as observed, is not explicable in terms of the above mechanism. An explanation based on a large, general medium effect due to the increasing anhydride concentration seems ruled out by the absence of this phenomenon in catalysis by perchloric² and sulphoacetic acid. It appears, therefore, that a modified mechanism is needed for sulphuric acid-catalysis.

A significant feature of this acid is its dibasic nature (other catalysts studied so far

* They exist to some extent as solvated ion pairs (e.g., $\text{AcOH}_2^+\text{HSO}_4^-$) though this detail has been omitted in the present paper.

have been monobasic) and, as shown in the extended mechanism below, this may lead to the production of a potential acylating agent whose concentration is dependent on the second power of the anhydride concentration:



k_1 and k_2 represent the respective rate constants for the product-forming reactions, and K_1 and K_2 the constants for the pre-equilibria. In the following, K_2 is assumed to have a value such that, for the concentration ranges involved, only a trace of the catalyst is converted into diacyl sulphate. Then, if C is the stoichiometric catalyst concentration and square brackets represent concentration generally,

$$C = [\text{H}_2\text{SO}_4] + [\text{R}\cdot\text{CO}\cdot\text{HSO}_4]$$

$$\begin{aligned}
 \text{and } [\text{R}\cdot\text{CO}\cdot\text{HSO}_4] &= K_1(C - [\text{R}\cdot\text{CO}\cdot\text{HSO}_4])[(\text{R}\cdot\text{CO})_2\text{O}]/[\text{R}\cdot\text{CO}_2\text{H}] \\
 &= K_1C[(\text{R}\cdot\text{CO})_2\text{O}]/[\text{R}\cdot\text{CO}_2\text{H}](1 + K_1[(\text{R}\cdot\text{CO})_2\text{O}]/[\text{R}\cdot\text{CO}_2\text{H}])
 \end{aligned}$$

$$\text{Also } [(\text{R}\cdot\text{CO})_2\text{SO}_4] = K_2 \left(\frac{[(\text{R}\cdot\text{CO})_2\text{O}]}{[\text{R}\cdot\text{CO}_2\text{H}]} \right)^2 C / \left\{ 1 + K_1 \frac{[(\text{R}\cdot\text{CO})_2\text{O}]}{[\text{R}\cdot\text{CO}_2\text{H}]} \right\}$$

$$\text{Since } -d[\text{ArOH}]/dt = k_1[\text{ArOH}][\text{R}\cdot\text{CO}\cdot\text{HSO}_4] + k_2[\text{ArOH}][(\text{R}\cdot\text{CO})_2\text{SO}_4]$$

we have:

$$-2.3 \, d \log [\text{ArOH}]/dt = \left\{ k_1 K_1 + k_2 K_2 \frac{[(\text{R}\cdot\text{CO})_2\text{O}]}{[\text{R}\cdot\text{CO}_2\text{H}]} \right\} C \frac{[(\text{R}\cdot\text{CO})_2\text{O}]}{[\text{R}\cdot\text{CO}_2\text{H}]} / \left\{ 1 + K_1 \frac{[(\text{R}\cdot\text{CO})_2\text{O}]}{[\text{R}\cdot\text{CO}_2\text{H}]} \right\}$$

Since $[\text{ArOH}] \ll [(\text{R}\cdot\text{CO})_2\text{O}] < [\text{R}\cdot\text{CO}_2\text{H}]$ the above expression satisfactorily predicts the observed first-order loss of phenol: $-d \log [\text{ArOH}]/dt$ is a constant (k_{obs}) at given values of C and $[(\text{R}\cdot\text{CO})_2\text{O}]$. Letting $[(\text{R}\cdot\text{CO})_2\text{O}]/[\text{R}\cdot\text{CO}_2\text{H}] = A$, we obtain:

$$2.3 \, k_{\text{obs}}(1 + K_1 A)/A = k_1 K_1 C + k_2 K_2 C A, \quad (1)$$

$$\text{or } \{(2.3 \, k_{\text{obs}}/A) - k_1 K_1 C\}/A = -2.3 \, K_1 k_{\text{obs}}/A + k_2 K_2 C. \quad (2)$$

The adequacy of expression (2) for representing the results may be tested by plotting the left-hand side against $2.3 \, k_{\text{obs}}/A$, at constant C , when a straight line of slope $-K_1$ should be obtained. However, in order to evaluate the left-hand side it is necessary to know the magnitude of $k_1 K_1 C$. It is possible to estimate this in the following way. Unless K_1 is quite large, $K_1 A$ will be small compared with unity at the lower acetic anhydride concentrations. Under these conditions it follows from equation (1) that a plot of $2.3 \, k_{\text{obs}}/A$ against A , at constant C , will be linear at low anhydride concentrations. The intercept is $k_1 K_1 C$. For the acetic system this plot was possible. With $k_1 K_1 C$ known, a plot of equation (2), for all values of A , can be made. This yielded a fairly straight line for the acetic system, from which a rough value of K_1 was obtained. This value was refined by using slight variants of it in re-plots of equation (1) aimed at producing the best straight line. In this way it was found that $K_1 = 10 \pm 2$ for the acetic system. For the butyric system the initial plot of equation (1) at low anhydride concentrations was less successful (because K_1 is larger), and a rough value of K_1 was obtained essentially by inspection. This was refined by trial plots of equation (1). An excellent straight line was eventually obtained, showing $K_1 = 20 \pm 3$. The final plots of equation (1) for both the acetic and the butyric system are given in Fig. 2. The best values for $k_1 K_1 C$ (and hence k_1) are obtained from the intercepts, and values of $K_2 k_2$ from the slopes. Values of these various constants are collected in Table 3. They are now considered in turn.

TABLE 3.

Comparison of acetylation with butyrylation at 40°.

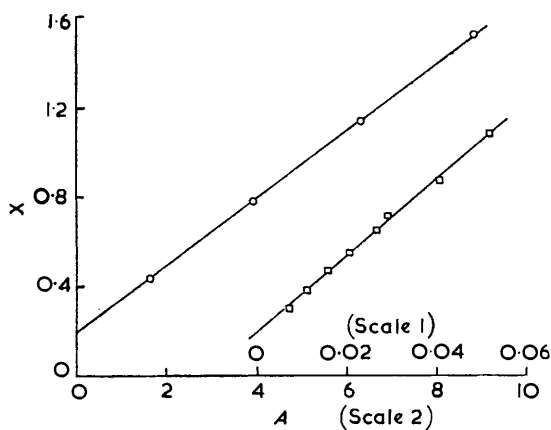
For definitions of k_1 , k_2 , and K_2 see text.

Reactant	k_1	$10^{-3}k_2K_2$
$(C_3H_7\cdot CO)_2O$	1.39	4.89
Ac_2O	5.89	5.14

(a) It is difficult to predict *a priori* how the pre-equilibrium which controls K_1 will be affected by the change from acetic to butyric acid. A change in K_1 from 10 to 20 seems reasonable.

(b) The values of the second-order constants k_1 , which refer to acylation of *m*-nitrophenol by acetyl hydrogen sulphate and butyryl hydrogen sulphate in the respective parent acids, are best compared with the corresponding values found for acetyl and butyryl chloride in acylation of β -naphthol.² In the latter reaction acetyl chloride is 8 times as reactive as butyryl chloride. In the present reaction acetyl hydrogen sulphate is *ca.* 4 times as reactive as the butyryl derivative. This result again seems reasonable. (Reasons for expecting the butyryl compound to be of lower reactivity have been discussed previously.²)

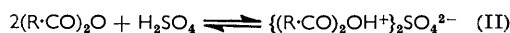
FIG. 2. Final plot of equation (1).
 $\times = (k_{obs}/A)(1 + K_1A)$. \circ , Butyric system, scale 1, $K_1 = 20$. \square , Acetic system, scale 2, $K_1 = 10$.



(c) Comparisons of k_2K_2 are not particularly meaningful. The value of K_2 is perhaps <1 . If so, k_2 will be *ca.* 1000 times larger than k_1 . Since there seems every reason to suppose the diacyl derivative will be notably more reactive than the monoacyl derivative, this tentative conclusion is again reasonable.

It may be concluded that the very satisfactory plots (Fig. 2), and the acceptable constants to which they lead, seem together reasonable evidence that the mechanism is basically of the type suggested. The active entities could be written as ion-pairs ($Ac^+HSO_4^-$ and $Ac^+AcSO_4^-$) if this were preferred. The present paper provides no evidence on this point.

(ii) *Related work on similar systems.* While the reaction may be formulated in terms of acyl derivatives it could equally, from the purely kinetic viewpoint, be formulated in terms of addition complexes (presumably ion-pairs) between catalyst and anhydride:

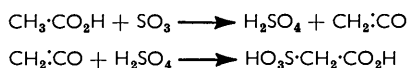


While (I) is a reasonable structure (1 : 1 complexes are postulated by Mal'kova⁶), species (II) (and possible variants) are unattractive. An intermediate such as (I) was considered for perchloric acid-catalysis² and was then judged less likely to be the active acylating

⁶ Mal'kova, *Zhur. obshei Khim.*, 1960, **30**, 2113.

agent than the acyl perchlorate. Another argument against (I) and (II) as active intermediates is that the reaction between sulphuric acid and acetic anhydride to give sulphoacetic acid probably involves the same intermediates. This will be demonstrated in a subsequent paper, where it will be argued that structures (I) and (II) are unattractive as intermediates for sulphoacetic acid formation. In view of these considerations, and the facts noted in the following paragraphs, we favour the particular mechanism given on p. 1890.

The values of K_1 (Table 3) imply appreciable conversion of sulphuric acid into acyl hydrogen sulphate (or other intermediate) in the reaction mixtures. Spectroscopic examination should, therefore, reveal a new species. In fact, the infrared spectra of suitable mixtures of acetic acid, acetic anhydride, and sulphuric acid show a strong absorption band at 13.4μ , not present in spectra of the original components, in excellent confirmation of the kinetic analysis. Attempts were made to identify this new absorption with acetyl hydrogen sulphate (whose presence has^{3,5,7} been postulated in such mixtures) by preparation of this compound. However, the literature contains no convincing preparation of this substance in a free condition. It is claimed as formed by the action of sulphur trioxide on cold acetic acid,⁵ but significantly the only salts of it (*e.g.*, AcNaSO_4) to have been isolated and analysed have come from mixtures of sulphuric acid and acetic anhydride.⁵ We have tried to prepare free acetyl hydrogen sulphate from sulphur trioxide and acetic acid, but the product had only very faint absorption at 13.4μ . While this could be taken to imply that the main species in sulphuric acid-acetic anhydride-acetic acid mixtures is not acetyl hydrogen sulphate, nevertheless the corresponding salts have been isolated from just such mixtures. We, therefore, consider that little acyl sulphate is formed from acetic acid and sulphur trioxide but that, instead, the reaction results in the direct formation of sulphoacetic acid (which is claimed as the product when low temperatures are not used⁵) perhaps by reactions involving dehydration to keten and sulphuric acid, followed by addition to the double bond:



A similar addition is suggested in Part III for the reaction of isopropenyl acetate with sulphuric acid.

Our conclusions as to the fate of sulphuric acid in acetic anhydride-acetic acid mixtures may be significant for the catalysed anomerisation of sugars in such mixtures.⁸ Painter⁸ suggests, and we note, that the kinetics of anomerisation are not explicable in terms of equilibria such as $\text{Ac}_2\text{O} + \text{H}_2\text{SO}_4 \rightleftharpoons \text{Ac}_2\text{OH}^+\text{HSO}_4^-$. Following Mackenzie and Winter,⁹ he proposes the participation of Ac^+ ions (playing an acidic role). We suggest that the complex kinetic phenomena of acid-catalysis produced by this system for anomerisation are probably as explicable in terms of the equilibria proposed in this paper as by any alternative proposed so far. We hope to make the acidic properties of this solvent system, as distinct from its acylating power, a subject of further study.

TABLE 4.
Acylation by acetic anhydride catalysed by sulphoacetic acid at 40° .

k_{obs} = First-order rate constant, in min.^{-1} ; k = overall third-order constant, in $l.^2 \text{ mole}^{-2} \text{ min.}^{-1}$.							
$[\text{Ac}_2\text{O}]$	[Catalyst]	$10^2 k_{\text{obs}}$	k	$[\text{Ac}_2\text{O}]$	[Catalyst]	$10^2 k_{\text{obs}}$	k
0.923	0.0111	4.42	4.31	0.492	0.0056	1.20	4.35
0.705	0.0111	3.33	4.26	0.492	0.0167	3.47	4.23
0.492	0.0111	2.41	4.41	0.492	0.0222	4.62	4.24
0.281	0.0111	1.34	4.29				

⁷ See, *e.g.*, Russell and Cameron, *J. Amer. Chem. Soc.*, 1938, **60**, 1345; Franchimont, *Rec. Trav. chim.*, 1888, **7**, 27.

⁸ See, *e.g.*, Bonner *J. Amer. Chem. Soc.*, 1951, **73**, 2659; Painter, *ibid.*, 1953, **75**, 1139.

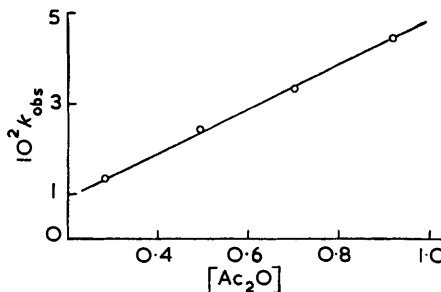
⁹ Mackenzie and Winter, *Trans. Faraday Soc.*, 1948, **44**, 159, 171, 243.

Catalysis by Sulphoacetic Acid.—This catalyst was studied in the acetic acid system only. Experiments to determine the reaction orders are reported in Table 4 and Fig. 3. The loss of phenol was always accurately a first-order reaction. The first-order constant, k_{obs} , also proved proportional to the first powers of both the catalyst and anhydride concentration. Thus:

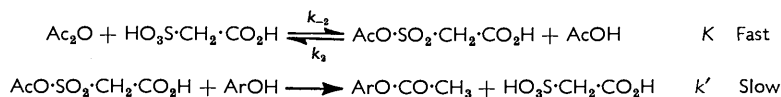
$$(2.3/t) \log([\text{ArOH}]_o/[\text{ArOH}]_t) = k[\text{Ac}_2\text{O}][\text{Catalyst}] \\ = k_{\text{obs}},$$

where subscripts o and t refer to zero time and time t , respectively. The constant k is $4.30 \text{ l.}^2 \text{ mole}^{-2} \text{ min.}^{-1}$. The results are very similar in form to those previously obtained with perchloric acid as catalyst,² and a similar mechanism is therefore suggested, though

FIG. 3. Plot showing order in anhydride for catalysis by sulphoacetic acid (0.0111M).



it is recalled that a seemingly less likely alternative scheme may, in fact, operate² (see, however, below for further evidence for the correctness of the chosen mechanism):



K is the pre-equilibrium constant. If this equilibrium lies well on the left-hand side, then the rate of loss of phenol is given by

$$-d[\text{ArOH}]/dt = Kk'[\text{Ac}_2\text{O}][\text{ArOH}][\text{Catalyst}]/[\text{AcOH}]$$

or, since $[\text{AcOH}]$ is effectively constant,

$$(2.3/t) \log([\text{ArOH}]_o/[\text{ArOH}]_t) = k[\text{Ac}_2\text{O}][\text{Catalyst}]$$

This is the equation empirically observed. Sulphoacetic acid is, after perchloric, the strongest acid catalyst studied. It is also monobasic (from the strong-acid viewpoint). The similarity of its behaviour to that of perchloric acid is therefore satisfactory.

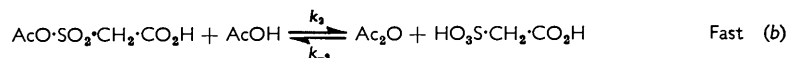
A Comparison of Acetylation by Isopropenyl Acetate and by Acetic Anhydride, Catalysed by Sulphoacetic and by Sulphuric Acid.—*Sulphuric acid.* Compared with other strong-acid catalysts, sulphuric acid behaves uniquely.

(i) With isopropenyl acetate,¹ instead of forming acetone and acetyl hydrogen sulphate in a first step, it provides quantitatively a sulphononic acid, probably by addition to the double bond, to give acetonesulphonic acid. The latter acid then acts as a normal catalyst for subsequent acetylation by any excess of isopropenyl acetate (see Part III and below).

(ii) As noted in the present paper, sulphuric acid behaves abnormally with anhydrides, this time because of its dibasic nature.

Sulphoacetic acid. This acid behaves as a normal sulphononic acid catalyst with both isopropenyl acetate and anhydrides.

(i) With isopropenyl acetate¹ the mechanism for acetylation of acetic acid is probably



The equilibrium lies well to the right.

(ii) With acetic anhydride we are now (see p. 1893) independently led to postulate a pre-equilibrium identical with (b) above. The further self-consistency of the various studies is illustrated by the fact that, if the reasonable assumption is made that the rates of attack of sulphoacetic acid on the structurally similar isopropenyl acetate and acetic anhydride are of the same order of magnitude, then, since k_1 is known,¹ k_{-2} (p. 1893) is known roughly. This value turns out to be large compared with that of k' , as it should be if the second step is rate-controlling in the anhydride reaction.

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