189. *Acylation. Part XV.* The Spontaneous and Acid-catalysed Hydrolysis of Diacetyl Sulphide.*

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Diacetyl sulphide reacts more slowly with water than does acetic anhydride and is much less susceptible to acidic catalysis, the magnitude of which is not related to H_0. The rate of hydrolysis is slightly dependent on the initial anhydride concentration. The effect of added salt has been studied and Arrhenius parameters for the reaction in pure water, in aqueous sodium perchlorate, and in aqueous perchloric acid have been determined. The mechanism of the spontaneous hydrolysis is concluded to involve a slow attack on the anhydride by an hydroxide ion, probably formed locally at the reaction site. It is argued that in acylation generally the kinetic dominance of bond-forming and attack by strongly basic species often go hand in hand. This conclusion is used to resolve apparent anomalies in the literature.

A reason for the low susceptibility of diacetyl sulphide to acid catalysis is given. The acid-catalysed hydrolysis has a bimolecular slow step.

COMPARISONS of the ease of hydrolysis of esters and their thio-analogues have been made.[1] We now report data which permit the first such comparison concerning anhydrides. The

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* Part XIV, Briody and Satchell, *J.*, 1965, 168.

[1] Schaefgen, *J. Amer. Chem. Soc.*, 1948, **70**, 1308; Rylander and Tarbell, *ibid.*, 1950, **72**, 3021; Morse and Tarbell, *ibid.*, 1952, **74**, 416; Noda, Kuby, and Lardy, *ibid.*, 1953, **75**, 913; Connors and Bender, *J. Org. Chem.*, 1961, **26**, 2498.

hydrolysis of acetic anhydride has been thoroughly studied.[2] Our results for diacetyl sulphide are in the Tables. We have measured the spontaneous hydrolysis in an excess of water (*a*) at various initial anhydride concentrations, (*b*) at various concentrations of added sodium perchlorate, and (*c*) at different temperatures (Table 1). We have studied also the effects of added perchloric acid, both in the presence and absence of salt (Table 2). The hydrolyses were always accurately of the first order in diacetyl sulphide. Data for acetic anhydride and diacetyl sulphide are compared in Table 3.

(a) *Spontaneous Hydrolysis.*—The observed first-order rate constant for the hydrolysis of acetic anhydride in an excess of water is slightly dependent on the initial anhydride concentration,[3] though this fact is often ignored. We have found a similar effect for diacetyl sulphide (Table 1). Below *ca.* 0·01M the effect is probably negligible. When calculating Arrhenius parameters for diacetyl sulphide we have used data pertaining to the lowest available initial concentrations (Table 3). The origin of the phenomenon probably lies in the deceleration of the reaction by the products. Addition of quite small concentrations of acetic acid reduce the rate of the hydrolysis [2c] of acetic anhydride (presumably by some variety of salt effect) and therefore, in any particular solvolysis, as the products build up

$$Ac_2O + H_2O \longrightarrow 2AcOH \qquad (1)$$

$$Ac_2S + H_2O \longrightarrow AcOH + AcSH \qquad (2)$$

this effect will increase. That the first-order course of the reaction is not detectably disturbed is probably due to the smallness of the effect. Very low concentrations of added acetic acid appear [2c] to increase the rate slightly, perhaps owing to catalysis by acetate ions, from the dissociation of the acid ($K_a^{25°} = 1·8 \times 10^{-5}$) at such concentrations, but again this effect, which must be present in the initial stages, does not significantly disturb the spontaneous hydrolysis in the absence of added acid. For diacetyl sulphide the product, thioacetic acid ($K_a^{25°} = 4·7 \times 10^{-4}$), will often be appreciably dissociated throughout the course of the reaction, but any catalytic effect of thioacetate ions is clearly outweighed by the negative salt effects of this and the other product species.

TABLE 1.

Spontaneous hydrolyses.

$k_{obs.}$ = observed first-order rate constant (sec.$^{-1}$), and square brackets represent molarity in all Tables.

(i) In water at 25°.

$[Ac_2S]_{init.}$	0·074	0·052	0·047	0·040	0·011	0·005
$10^3k_{obs.}$	1·37	1·45	1·45	1·46	1·49	1·50

(ii) In water at 35°.

$[Ac_2S]_{init.}$	0·045	0·040	0·02	0·004	0·003
$10^3k_{obs.}$	2·26	2·29	2·47	2·66	2·67
$[Ac_2O]_{init.}$	0·05	0·04			
$10^3k_{obs.}$	5·10	5·14			

(iii) In aqueous sodium perchlorate at 0°.

$[Anhydride]_{init.} \approx 0·08$

$[NaClO_4]$	0	0·5	1·0	1·5	2·0	3·0
$10^3k_{obs.}$ (Ac_2O)	0·46	0·35	0·28	—	0·16	0·089 [a]
$10^3k_{obs.}$ (Ac_2S)	0·26	0·17	0·16	0·12	0·072	0·035

[a] Data from refs. 2*d* and 2*c*.

From Table 1 it may be seen that diacetyl sulphide reacts about half as fast as does acetic anhydride in the temperature range studied. The activation energy (E_a) is similar for both compounds and is somewhat temperature dependent for both, though in opposite

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[2] (*a*) Gold, *Trans. Faraday Soc.*, 1948, **44**, 506; (*b*) Gold and Hilton, *J.*, 1955, 844; (*c*) Butler and Gold, *J.*. 1961 2305; (*d*) Bunton and Perry, *J.*, 1960, 3070; (*e*) Bunton, Fuller, Perry, and Pitman, *J.*, 1962, 4478; (*f*) Bunton, Fuller, Perry, and Shiner, *J.*, 1963, 2918; (*g*) Koskikallio, *Acta. Chem. Scand.*, 1960, **14**, 1343.

[3] Rivett and Sidgwick, *J.*, 1910, **97**, 739; Vles, *Rec. Trav. chim.*, 1933, **52**, 809.

senses in the ranges considered (Table 3). The entropy of activation (ΔS^*) is also similar for both compounds and its value probably implies that the motions of one or more water molecules are restricted in forming the transition state.[4] It is generally considered that a molecule (or molecules) of water, other than that actually acylated, is involved as an acidic or basic catalyst in the acetic anhydride reaction.[2c,5] Hydrogen bonding between the anhydride and solvent is likely to be more important in the transition state (whatever its exact nature) than in the undisturbed (and therefore less polar) reactant. It is clearly not possible to distinguish sharply between such hydrogen bonding and more formal catalytic roles of the solvent molecules.[2f] However, the similarity of the entropy data for acetic anhydride and diacetyl sulphide (Table 3) implies that similar effects are involved for both compounds. We return to this point below.

TABLE 2.

Acid-catalysed hydrolysis.

$[Ac_2S] \approx 0{\cdot}08$

(*a*) In aqueous $HClO_4$ at 0°.

$[HClO_4]$	0·0	0·5	1·0	1·5	2·0	3·0
$10^3k_{obs.}(Ac_2O)$	0·46	0·61	0·84	1·1	1·7	4·9 *
$10^3k_{obs.}(Ac_2S)$	0·26	0·30	0·34	0·31	0·31	0·30
†$10^3k_a(Ac_2O)$	0·0	0·15	0·38	0·64	1·24	4·4
$10^3k_a(Ac_2S)$	0·0	0·04	0·08	0·05	0·05	0·04

(*b*) In aqueous $HClO_4$–$NaClO_4$ mixtures.

	0°					25°	
$[HClO_4]$	0·0	1·0	2·0	3·0	2·0	0·0	2·0
$[NaClO_4]$	3·0	2·0	1·0	0·0	3·0	3·0	3·0
$10^3k_{obs.}(Ac_2S)$	0·035	0·14	0·20	0·30	0·14	0·29	1·57
10^3k_a	0·0	0·10	0·16	0·26	0·13(?)	0·0	1·3(?)

* Interpolated from data from ref. 2*b*. † k_a = Apparent contributions of acid catalysis to $k_{obs.}$.

The decrease in rate produced by sodium perchlorate is of the same order of magnitude for both acetic anhydride and diacetyl sulphide, being somewhat greater for the latter (Table 1). The effect of this salt is thought [2e] to be two-fold: it " salts in " the anhydride and it also destabilises the transition state by making water less available. The reality

TABLE 3.

Comparison of Arrhenius parameters for acetic anhydride and diacetyl sulphide.

		Ac_2O	Ac_2S
(*a*) Spontaneous hydrolysis.			
	E_a (0—25°)	11·3 [a]	11·4
	E_a (25—35°)	12·0	10·5
	ΔS^* (0—25°)	−35 [b]	−35
	ΔS^* (25—35°)		−37
(*b*) Hydrolysis in 3N-$NaClO_4$.			
	E_a (0—25°)		13·5
	ΔS^*		−32
(*c*) Acid-catalysed hydrolysis.			
(~0·1N-acid)	E_a (0—25°)	17 [c]	
	ΔS^*	−12 [c]	
(1·0N-acid)	E_a (0—25°)	21 [d]	16·5
	ΔS^*	+2 [d]	−19

E_a in kcals. mole^{-1}; ΔS^* in e.u.

[a] From data in reference 2*c* and 2*d*. [b] Ref. 2*f*. [c] Ref. 2*g*. [d] Ref. 2*d*.

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[4] Schaleger and Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1.

[5] Johnson, *J. Amer. Chem. Soc.*, 1962, **84**, 1729.

of this second role is supported by the larger activation energy and the smaller entropy of activation obtained for diacetyl sulphide in the presence of salt (Table 3).

We have noted above that the closeness of the ΔS^* values implies similar changes in ambient solvent molecules on forming the transition state in the two reactions. Since the departure of the leaving group is much less likely † to involve assistance from acid catalysis, or hydrogen bonding, in the diacetyl sulphide reaction than in that of acetic anhydride, it seems probable that bond-forming is the kinetically dominant phase in these reactions. This phase is likely to be similar in its demands on ambient water molecules in the two cases. This conclusion supports that of Bunton, Fuller, Perry, and Shiner [2f] who argue that because acetic, acetic benzoic, and acetic mesitoic anhydrides hydrolyse at similar rates, leaving-group departure can only have slight kinetic importance. We can use this argument also: the rate for diacetyl sulphide only differs from that of acetic anhydride by a factor of *ca.* 2. It is significant (and superficially unexpected) that the sulphur compound actually hydrolyses more slowly than its oxygen analogue. Similar results are sometimes found in comparisons of ester hydrolyses.[1] Generally, in acylation, the better the leaving group the faster the bimolecular hydrolysis.[6] Such is obviously the likely circumstance when bond-breaking is at all important. We consider that the few exceptions to the generalisation can be reasonably attributed to an unusual dominance of the bond-forming process, coupled with a particular relationship between the inductive effects of the respective leaving groups. A good example is the pair benzoyl fluoride and chloride. In neutral aqueous acetone solution the chloride hydrolyses the faster.[7] Here we assume bond-breaking (which reflects the stability of the anion formed) to be an important component of the reaction, and the attacking species probably molecular water. In aqueous alkali, where the reagent is hydroxide ion, the fluoride's rate exceeds that of the chloride.[7] Since the carbonyl carbon atom will carry a greater charge in the fluoride (because of the relative inductive effects) and because this charge controls the rate of approach of the hydroxide ion, it is therefore very probable that bond-forming is dominant in these reactions in alkaline solution. This is a sensible conclusion: with a powerful reagent, bond-breaking will not need to have made so much progress in reaching the transition state.

An analogous situation, which has received various interpretations, appears in comparisons of the hydrolyses of benzoyl and mesitoyl chlorides.[8,9a] In neutral alcoholic or aqueous acetone solutions the latter compound hydrolyses the faster. This is anomalous, since there is evidence that both reactions are bimolecular,[2f,9b] and thus the approach of a water molecule should be hindered both sterically and electronically in mesitoyl chloride. However, if as we suggest above, bond-breaking is important for acyl halides in neutral solution then, since the expulsion of the chloride ion is favoured in mesitoyl chloride, the faster rate for this compound is understandable. (There is no need to postulate the extreme of bond-breaking dominance—a unimolecular mechanism—to rationalise examples which show *some* characteristics of this type of reaction.[9a,c]) On the other hand, in alkaline solution, where we suggest that bond-forming is dominant, the mesitoyl compound should hydrolyse the more slowly. This is, in fact, the case.[8]

In the above discussion we attribute significant bond-breaking components to solvolyses involving molecular water (or alcohol) as attacking agent, and we therefore consider that the dominance of bond-forming in anhydride solvolyses in neutral solution is to be attributed to basic catalysis by additional solvent molecules which provide incipient hydroxide ions as the attacking species (3).

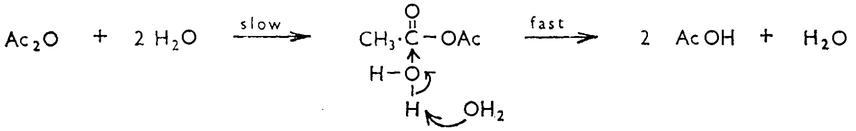
† Because thioacetic acid is a notably stronger acid than acetic acid and thioacetate a better leaving group than acetate.

[6] Satchell, *Quart. Rev.*, 1963, **17**, 160.

[7] Swain and Scott, *J. Amer. Chem. Soc.*, 1963, **75**, 246.

[8] Peeling, *J.*, 1959, 2307.

[9] (*a*) Ugi and Beck, *Ber.*, 1961, **94**, 1839; (*b*) Gold, Hilton, and Jefferson, *J.*, 1954, 2756; (*c*) Hudson and Moss, *J.*, 1962, 5157.



$$Ac_2O + 2\,H_2O \xrightarrow{slow} \underset{\underset{H\curvearrowleft OH_2}{\underset{|}{H-O}}}{CH_3\cdot\overset{O}{\overset{\|}{C}}-OAc} \xrightarrow{fast} 2\ AcOH + H_2O \qquad (3)$$

In such circumstances the slower rate for diacetyl sulphide compared with acetic anhydride may be thought of as an analogue of the benzoyl fluoride–benzoyl chloride comparison in alkaline solution.

Our conclusions about the mechanism are in keeping with those of Johnson.[5] An earlier scheme [2c] including a tetrahedral intermediate involved in a rapid pre-equilibrium with water is excluded by oxygen-exchange studies of Bunton *et al.*[2f,5] Very little, or no, exchange is observed during the hydrolysis of acetic anhydride. We go further than Bunton in thinking there is no real need to include a tetrahedral intermediate in these solvolyses at all. The present cases of acetic and similar anhydrides can be regarded as synchronous processes in which bond-forming is the important phase. Even when concurrent exchange *is* observed (in anhydrides like benzoic,[2f] with poorer leaving groups) there is no logical imperative for the assumption that exchange and hydrolysis involve a common intermediate. Although exchange is generally most easily detectable (as would be expected) with poor leaving groups,[10,11] nevertheless the absence of a systematic correlation between the exchange and hydrolysis data supports the idea that they involve distinct mechanisms.

A necessary corollary of the foregoing is that the rate of acylation by an acyl-oxygen compound relative to that of its thio-analogue will depend on the relative importance of bond-forming and breaking in the reaction concerned. Thus we are not surprised that Connors and Bender [1] find that while the rates of reaction of esters and their thiol counterparts with hydroxide ions are similar, the sulphur compound reacts much more readily with a weaker base, such as an amine. In the latter reaction the capacity for bond-breaking in the acylating agent is at more of a premium, and this gives the thiol ester the advantage. The change from amine to hydroxide ion with esters is another parallel to that from water to hydroxide ions with acyl halides. Analogous considerations explain the more general observation [12] that esters with activating substituents in their acyl portion usually suffer what is called general base catalysis [which we interpret as attack by hydroxide ions formed under the influence of any other (weaker) base added as catalyst] whereas esters with good leaving groups tend to suffer what is termed nucleophilic catalysis, *i.e.*, direct attack by whatever base is present. The reason seems clear: with a very poor leaving group bond-breaking will not appreciably advance and only bases as powerful as hydroxide can successfully attack the acylating agent. Bond-forming will be dominant kinetically. With a very good leaving group, bond-breaking will have considerable kinetic significance and the base's approach will be easier; therefore any base may be directly effective. Acylating agents with intermediate (moderately good) leaving groups will show intermediate behaviour.[13] Our rationalisations of these acylations differ from those of Jencks and Carriuolo.[12]

(b) *Acidic Catalysis.*—Thiol esters are much less subject to acid catalysis than their oxygen analogues.[1] Table 2 shows the same effect for anhydrides. While in aqueous perchloric acid acetic anhydride suffers a considerable increase in hydrolysis rate [2b] (which may be correlated with H_0), diacetyl sulphide is apparently unaffected by acid over a wide concentration range. When, however, measurements are made at constant ionic strength, a small positive catalysis appears. It is difficult to estimate this exactly, for it is not certain that sodium perchlorate and perchloric acid have identical salt effects. The last

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[10] Bunton, Lewis, and Llewellyn, *Chem. and Ind.*, 1954, 1154.

[11] Bender, in " Technique of Organic Chemistry," Vol. 8, Interscience, 1963, p. 1500.

[12] Jencks and Carriuolo, *J. Amer. Chem. Soc.*, 1961, **83**, 1743; Bender, *Chem. Rev.*, 1960, **60**, 53.

[13] Butler and Gold, *J.*, 1961, 2305.

line in Table 2 assumes that they have. It probably represents therefore the maximum catalysis and it is clear that this is very feeble and certainly no more than proportional to $[H_3O^+]$. The acid-catalysed hydrolysis of diacetyl sulphide in strongly acidic solution is therefore different from that observed [2b, f] for acetic anhydride. It is more like that found for acetic anhydride in very dilute aqueous acid: [2g] a bimolecular reaction (4). The Arrhenius parameters support this view.

$$Ac_2S + H_3O^+ \rightleftharpoons Ac_2SH^+ + H_2O \qquad \text{Fast} \qquad (4a)$$

$$Ac_2SH^+ + H_2O \longrightarrow \text{Products} \qquad \text{Slow} \qquad (4b)$$

We attribute the low sensitivity of the diacetyl sulphide reaction towards acid catalysis to the inability of this compound's leaving group to accept a proton.

Since acetic anhydride displays similar salt effects to those of diacetyl sulphide a negative salt effect (due to mineral acid) must operate in acid catalysed hydrolyses of acetic anhydride. Any such catalysis proceding by a bimolecular route will therefore be partly concealed. This may be the reason that in strongly acidic solutions the hydrolysis appears predominantly unimolecular.

Experimental

Materials.—Diacetyl sulphide, prepared by Bonner's method,[14] was fractionally distilled, b. p. 62—63°/20 mm. AnalaR acetic anhydride, purified by distillation from magnesium, had b. p. 140°. Aniline was purified by fractional distillation and had b. p. 185°. B.D.H. thioacetic acid, fractionally distilled in nitrogen, had b. p. 87·5—87·8°. B.D.H. sodium perchlorate was dried at 150°. Perchloric acid was AnalaR.

Kinetic Measurements.—Measurements were made at three temperatures. Most of the spontaneous hydrolyses were conducted at 25 or 35°. For these the reaction was followed conductimetrically.[2a, c] Some difficulty arose in the later stages of the diacetyl sulphide reaction owing to the further hydrolysis of the product thioacetic acid into acetic acid and hydrogen sulphide. This is a comparatively slow process, but made the infinity reading uncertain. This difficulty could be overcome by using Guggenheim's procedure,[15] or by using a calculated infinity value assuming 100% solvolysis of diacetyl sulphide. All the evidence pointed to the correctness of this assumption. The rate constants were reproducible within ±1%.

Most of the reactions at 0° involved acid catalysis and a conductivity technique was therefore impracticable. Bunton and Perry's [2d] titration procedure also failed owing to concurrent solvolysis of thioacetic acid which appeared exaggerated under such conditions. The following spectrophotometric method (developed in conjunction with MR. J. M. BRIODY) proved satisfactory. It is not dependent on acidimetry. Samples (1 ml.) of reaction mixture [0·08M (or less) diacetyl sulphide in 25 ml. aqueous acid (or water)] were run into aniline–water containing sufficient aniline to both neutralise the sample's acid content and react rapidly (and stoicheiometrically) with any unhydrolysed diacetyl sulphide (to give acetanilide). The mixture was made up to 25 ml. and further diluted by a factor of 25, this final solution being acidified ($HClO_4$). The acetanilide formed was estimated spectrophotometrically at 2500 Å, by using a blank of similar constitution except for the omission of the reaction sample. Acetanilide has an absorption maximum close to 2500 Å, but this will be obscured by the absorption of the excess of aniline present unless this substance is converted into the anilinium ion by added acid. Some small absorption due to anilinium ion then remains, but this can be accurately balanced by a suitable blank, as described above. Infinity values showed some irreproducibility, but this difficulty could again be overcome by following the Guggenheim procedure. Good first-order plots were always obtained and individual rate constants were reproducible to within ±4%.

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[14] Bonner, *J. Amer. Chem. Soc.*, 1950, **72**, 4270.

[15] Guggenheim, *Phil. Mag.*, 1926, **2**, 538.