542. *The Hydrolysis of Carboxylic Anhydrides. Part III.* Reactions in Initially Neutral Solution.*

By C. A. Bunton, N. A. Fuller, S. G. Perry, and V. J. Shiner.

The rates of hydrolysis of various carboxylic anhydrides have been compared in water or in aqueous dioxan, and are in the sequence: maleic > homophthalic ≈ phthalic > cyclohex-1-ene-1,2-dicarboxylic > *cis*-cyclohex-3-ene-1,2-dicarboxylic > succinic, glutaric, acetic > acetic benzoic, acetic mesitoic > tetramethylsuccinic > mesitoic > benzoic > camphoric.

These structural effects can be explained in terms of the steric and electronic effects of substituents, on the assumption that bond-breaking is not kinetically important. Reaction is slower in the less aqueous solvents, and the large deuterium solvent isotope effect is also found for the hydrolyses of other carboxyl derivatives. There is some oxygen exchange between the water and benzoic anhydride during hydrolysis; and appreciable exchange during the hydrolysis of methyl trifluoroacetate.

Hydrolyses of carboxylic anhydrides in initially neutral solution have been studied extensively. Reaction is retarded by the addition of non-polar organic solvents to the water, and values of the energies of activation are lower, and the entropies more negative, than those observed for nucleophilic substitution at a saturated carbon atom.[1,2] These observations suggest that solvation of the transition state by water molecules is important. The reactivities of symmetrical anhydrides of both aliphatic and aromatic carboxylic acids are increased by electron-attracting substituents.[3,4] We have compared the rates of hydrolysis of some symmetrical and unsymmetrical anhydrides with those of cyclic anhydrides. All our evidence indicates that the rate-limiting step is a nucleophilic attack by water upon an acyl-carbon atom, but an S_N2 displacement at a saturated carbon atom is not a good model for the reaction mechanism.[5,6]

Results

The first-order rate constants for hydrolyses of various anhydrides in initially neutral solution are given in Table 1; the deuterium solvent isotope effects for several anhydrides and related compounds are given in Table 2. Some of these values have been reported previously.[7a,8,9] We made no special effort to measure the entropies and energies of activation to high precision. Our values are in reasonable agreement with those of others,[1,2] and because only two temperatures were used we quote the activation energy to the nearest kcal. mole^{-1} (Table 3).

The results of exchange experiments with ^{18}O are given in Table 4. (The acetyl–oxygen bond is broken during hydrolysis of the unsymmetrical open-chain anhydrides.[7])

The oxygen-exchange results are expressed in terms of the ratio k_h/k_e, where k_h is the first-order rate constant for hydrolysis, and $k_e = (2{\cdot}303)/t.\log[100/(100 - \%\ \text{exchange})]$. If we assume that the oxygen atoms attached to the reaction centre become equivalent in the intermediate (I), then $k_h/k_e = 2k_2/k_{-1}$.

In the earlier work on the hydrolysis of carbonyl compounds this factor of 2 was included

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* Part II, *J.*, 1962, 4478.

[1] Gold, *Trans. Faraday Soc.*, 1948, **44**, 506.

[2] Koskikallio, *Ann. Acad. Sci. Fennicae*, 1954, AII, **57**, 1, and refs. therein.

[3] Rivett and Sidgwick, *J.*, 1910, **97**, 1677; Wildson and Sidgwick, *J.*, 1913, **103**, 1959; Kilpatrick, *J. Amer. Chem. Soc.*, 1930, **52**, 1410.

[4] Berliner and Altschul, *J. Amer. Chem. Soc.*, 1952, **74**, 4110.

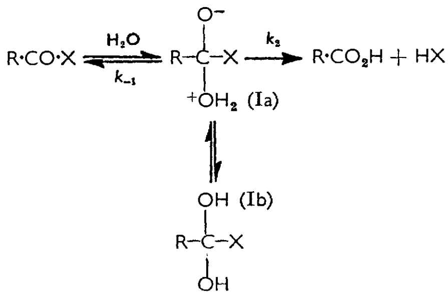
[5] Bunton, Lewis, and Llewellyn, *Chem. and Ind.*, 1954, 1154.

[6] Bunton and Shiner, *J. Amer. Chem. Soc.*, 1961, **83**, 3207.

[7] (*a*) Bunton and Perry, *J.*, 1960, 3070; (*b*) Bailey and Chang, *J. Org. Chem.*, 1962, **27**, 1192.

[8] Bunton, Fuller, Perry, and Shiner, *Chem. and Ind.*, 1960, 1130.

[9] Cf. Butler and Gold, *Proc. Chem. Soc.*, 1960, 15; *J.*, 1961, 2305; 1962, 2212.



in the tabulated value of k_h/k_e.[5] The change brings our method of presenting the results into line with that of other workers.[10]

TABLE 1.

Hydrolysis in initially neutral solution.

First-order rate constants expressed as 10^5k_1 (sec.$^{-1}$). Relative rates are at 25·1°.

In water

Anhydride	Acetic	Succinic	Glutaric	Maleic	Tetramethylsuccinic
At 0°	46·9	34·7	42·3	348	—
25·1°	267[a]	269	270	3140[b]	22·7 (47·3[c])
Rel. rate	1	1	1	11·8	0·087

In dioxan–water, 12·5 : 87·5 v/v

Anhydride	Succinic	Camphoric
At 25·1°	183	0·162[d]

In dioxan–water, 60 : 40 v/v

Anhydride	Acetic	Acetic benzoic	Acetic mesitoic	Benzoic	Mesitoic
At 0°	1·22 (5·81[e])	0·90	—	—	—
25·1°	6·60 (35·8[e])	4·85	4·89	0·22 (0·397[c])	0·386[f]
Rel. rate	1	0·74	0·74	3×10^{-2}	0·058

Anhydride	Succinic	Glutaric	Maleic	Phthalic	Homophthalic	Tetramethylsuccinic
At 0°	1·22	1·39	—	—	7·27	—
25·1°	11·4	11·1	165	42·9	49·3	1·18
Rel. rate	1·7	1·7	25	6·5	7·5	0·18

Anhydride	*cis*-Cyclohex-3-ene-1,2-dicarboxylic	Cyclohex-1-ene-1,2-dicarboxylic
At 25·1°	15·7 (32·0[c])	27·5 (52·3[c])
Rel. rate	2·4	4·2

[a] Value obtained by Mr. J. H. Fendler. [b] From $10^5k_1 = 1830$ sec.$^{-1}$ at 18·55°. [c] At 35·0°. [d] From $10^5k_1 = 4{\cdot}72$ sec.$^{-1}$ at 72·9°, and 22·5 sec.$^{-1}$ at 101°. [e] In dioxan–water 40 : 60 v/v. [f] From $10^5k_1 = 5{\cdot}17$ sec.$^{-1}$ at 60·0°, and 58·7 sec.$^{-1}$ at 101°.

TABLE 2.

Solvent deuterium isotope effects.

Temp. 25·1°, except where specified. Co-solvent = dioxan.

Compound	Ac_2O		Bz_2O	AcOBz	$AcO{\cdot}CO{\cdot}C_6H_2Me_3$
Water (vol. %)	100	40	40	40	40
k_{H_2O}/k_{D_2O}	2·9 *	2·6	3·45 †	3·4	2·8

Compound	Succinic anhydride	Glutaric anhydride		$Ph{\cdot}COCl$		$C_6H_2Me_3{\cdot}COCl$	$CF_3{\cdot}CO_2Me$
Water (vol. %)	100	100	40	40	15	5	40
k_{H_2O}/k_{D_2O}	2·8	2·8	3·0	1·7	1·6	1·7	1·8

* Ref. 9. † At 35·0°.

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[10] Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626; *Chem. Rev.*, 1960, **60**, 53; Bender, Ginger, and Unik, *J. Amer. Chem. Soc.*, 1958, **76**, 1044; Bender, Matsui, Thomas, and Tobery, *ibid.*, 1961, **83**, 4193.

TABLE 3.

Entropies and energies of activation.

Dioxan–water 60 : 40 v/v, unless specified otherwise.

Anhydride	Acetic			Acetic benzoic	Benzoic	Mesitoic	Succinic		Glutaric		Maleic
E (k cal. mole^{-1})	11,†	11,‡	11	11	11	14·5	13 †	14	12 †	13·5	14 †
ΔS^* (e.u.)	−35,	−37,	−43	−44	−50	−36	−28	−31	−31	−33	−20

Anhydride	Tetramethyl-succinic	Homophthalic	Cyclohex-1-ene-1,2-dicarboxylic	*cis*-Cyclohex-3-ene-3,4-dicarboxylic	Camphoric
E (k cal. mole^{-1})	13·5 †	12·5	12	13	14·5 §
ΔS^* (e.u.)	−32	−34	−37	−34	−39

† Water. ‡ Dioxan–water, 40 : 60 v/v. § Dioxan–water, 12·5 : 87·5 v/v.

We consider that in searching for small amounts of oxygen exchange it is desirable to have the tracer in the water rather than in the reactant. With our equipment it is easier to compare the (low) abundance of the isolated sample with that of an isotopically normal sample than to measure a small difference between two high abundances. Our experience with initially isotopically enriched samples of acetic anhydride (Table 4) illustrates this.

TABLE 4.

Oxygen exchanges during the uncatalysed hydrolysis.

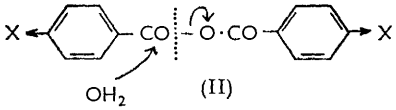
Solvent, dioxan–water 60 : 40 (v/v) unless specified: N_{H_2O} and $N_{R\cdot CO\cdot X}$ are excesss abundances in atom %, relative to the isotopically normal compound.

Compound	Ac_2O				Bz_2O			Camphoric anhydride *	$CF_3\cdot CO_2Me$
Temp.	0°		25·1°		25·1°	35·0°	80·8°	10.1°	25·1°
Hydrolysis (%)...	58 †	50 †	76 †	50	60	64	51	70	50
N_{H_2O}	1·40	0 ‡	1·30	0 ^{c}	1·40	1·30	1·58	$0{\cdot}91_6$	$0{\cdot}54_4$
$N_{R\cdot CO\cdot X}$	$0{\cdot}00_2$	$0{\cdot}44_5$	$0{\cdot}00_5$	$0{\cdot}44_5$	$0{\cdot}00_7$	$0{\cdot}01_2$	$0{\cdot}02_9$	$0{\cdot}00_7$	$0{\cdot}02_9$
$k_h/2k_e$...............	>150				~100	~50	18	~100	6·3

* Dioxan–water, 12·5 : 87·5 v/v. † H_2O. ‡ Abundance of Ac_2O initially = $0{\cdot}45_5$ atom % excess.

DISCUSSION

Structural Effects.—Open-chain anhydrides. Electron-attracting substituents assist, and electron-repelling substituents hinder, the hydrolysis of 3,3′- and 4,4′-disubstituted benzoic anhydrides,[4] and the rate constants fit a linear free-energy relation with Hammett σ constants, and $\rho = 3{\cdot}2$. This high sensitivity to electronic substituent effects is reasonable because electron-withdrawal could assist both attack of a nucleophile and expulsion of a carboxylate group (II). Similar structural effects are observed for the hydrolyses of symmetrically substituted acetic anhydrides.[3]



(II)

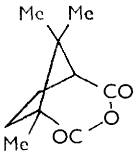
Our results suggest that it is the first effect which is the more important, because the rates of hydrolysis of acetic, acetic benzoic, and acetic mesitoic anhydride are very similar in initially neutral aqueous dioxan (Table 1). The acetyl group is attacked by the water,[7] and these limited changes in the nature of the displaced group have little effect upon the rate of reaction. More drastic changes in the chemical nature of the displaced group are important, *e.g.*, acid chlorides are more reactive than anhydrides, and esters are less reactive.

Replacement of the methyl group at the reaction centre by an aryl group decreases the reactivity considerably, *e.g.*, acetic benzoic anhydride is 220 times as reactive as benzoic anhydride, and acetic mesitoic anhydride is 190 times as reactive as mesitoic anhydride. The retarding effect of an aryl substituent is general for reactions of acyl and carbonyl compounds, and arises because conjugation between an aryl and a carbonyl group deactivates the latter to nucleophilic attack.

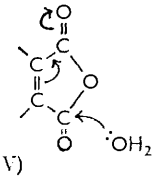
Cyclic anhydrides. In water or aqueous dioxan at 0° or 25°, the rates of hydrolysis of acetic, succinic, and glutaric anhydride are similar (Table 1 and ref. 2). The relative rates are, however, affected by solvent changes, and the activation energies are generally higher for the cyclic anhydrides. The hydrolyses of *cis*-cyclohex-3- and cyclohex-1-ene-1,2-dicarboxylic anhydride were studied only in aqueous dioxan because these materials are sparingly soluble in water. The rate for the former anhydride is similar to that of succinic anhydride (Table 1). These results, and the similar reactivities of succinic anhydride and its mono- and di-alkyl substituted derivatives,[2,11] show that neither introduction of an alkyl group adjacent to the reaction site nor fusion of a carbocyclic system, has a large steric or polar effect on the rate. More extensive alkyl-substitution decreases the reactivity, *e.g.*, tetramethylsuccinic anhydride is *ca.* one-tenth as reactive as succinic anhydride; the relative rates depend upon the solvent (Table 1 and ref. 11). The effect is probably both steric and electronic; alkyl groups generally decrease the reactivity of acetyl compounds to hydrolysis.[12] The low reactivity of 2,2′-dimethylglutaric anhydride (relative to glutaric anhydride) is predominantly steric in origin.[2,11] A much more striking example of steric hindrance to nucleophilic attack is the hydrolysis of camphoric anhydride (III). The congested structure so restricts attack that this compound is *ca.* 10^3 times less reactive than the simple cyclic anhydrides (Table 1 and ref. 13); and the activation energy is larger, and the Arrhenius non-exponential term less.

Maleic, phthalic, and cyclohex-1-ene-1,2-dicarboxylic anhydride are more reactive than the saturated cyclic anhydrides, probably because one acyl group can activate the other to nucleophilic attack by electronic relay through the double bond (IV).

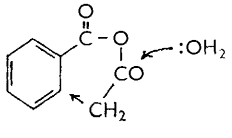
Homophthalic anhydride is activated by the $-I$ effect of the phenyl group (V) and, except for having only one reactive centre, can be compared with phenylacetic anhydride.



(III)



(IV)



(V)

The reactivity of these unsaturated cyclic anhydrides contrasts strikingly with the unreactivity of benzoic anhydride.

Although open-chain and cyclic anhydrides are hydrolysed at similar rates in initially neutral solution, lactones and thiolactones (but not lactams) are more reactive than the corresponding open-chain compounds.[14] Both the formation of cyclic anhydrides from the salts of monoesters of some dicarboxylic acids, and the hydrolysis of these anhydrides, have been studied by Bruice and Pandit.[11] They point out that the rules for the ease of opening of five- and six-membered rings, which can be applied to the hydrolysis of esters and lactones,[14] are unsatisfactory for anhydride hydrolysis. The similarity of the reactivities of cyclic and open-chain anhydrides suggests that there is no great change in the shape of the molecule during formation of the transition state.

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[11] Bruice and Pandit, *J. Amer. Chem. Soc.*, 1960, **82**, 5858.

[12] Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 757.

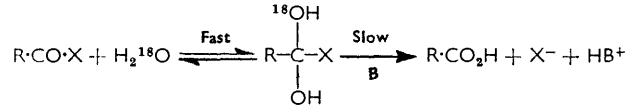
[13] Wilsdon and Sidgwick, *J.*, 1915, **107**, 679.

[14] Brown, Brewster, and Schechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467; Huisgen, *Angew. Chemie*, 1957, **69**, 345; Schjanberg, *Ber.*, 1942, **75**, 468; Hall, Brandt, and Mason, *J. Amer. Chem. Soc.*, 1958, **80**, 6420.

Bruice and Pandit used aqueous ethanol as solvent,[11] and our values for the relative reactivities differ slightly from theirs, probably because our reaction is hydrolysis and theirs was a simultaneous hydrolysis and ethanolysis. They found succinic to be slightly more reactive than glutaric anhydride, and suggested that this difference was due to an inductive effect relayed through two carbon atoms in succinic and three in glutaric anhydride; our evidence suggests that this effect is unimportant in water or aqueous dioxan.

Solvent Isotope Effect.—The solvent isotope effect is large for the spontaneous hydrolysis of carboxylic anhydrides and $k_{H_2O}/k_{D_2O} \approx 3$.[8,9] The values for water and aqueous dioxan are similar, and do not depend markedly on the structure of the anhydride. Much smaller effects are found for nucleophilic substitution at a saturated carbon atom,[9,15] where $k_{H_2O}/k_{D_2O} < 1{\cdot}4$, and they depend on the nature of the displaced group, being least for hydrolysis of alkylsulphonium ions and greatest for alkyl nitrates and phosphates. There is some disagreement as to the causes of these isotope effects, but it is probable that the formation or distribution of charge during hydrolysis changes the structure of the water around the reacting molecules, thus changing the low-frequency vibrations of the water (cf. refs. 15 and 16).

The large solvent isotope effect for the hydrolysis of anhydrides suggests that other factors are at work here, and moreover comparatively large values of k_{H_2O}/k_{D_2O} (relative to alkyl halide hydrolysis) are generally observed when water attacks an acyl group, as in hydrolysis of acid chlorides or esters.[8,17] Large deuterium isotope effects have often been associated with slow proton transfers, and it has been suggested that the solvent isotope effect for anhydride hydrolysis should be explained in these terms.[9] Thus one could suppose that some fast reversible reaction was followed by a rate-limiting reaction involving a slow proton transfer. This hypothetical slow proton transfer cannot involve proton loss from the α-carbon atom, because there is no exchange of hydrogen with the solvent,[9] and, moreover, these large solvent isotope effects appear with compounds which have no exchangeable hydrogen atom (*e.g.*, benzoic anhydride, benzoyl chloride, and methyl trifluoroacetate). Nor can we invoke a rapid reversible hydration of the carbonyl group followed by some slow proton transfer to a base B, *e.g.*,



$$R{\cdot}CO{\cdot}X + H_2{}^{18}O \overset{\text{Fast}}{\rightleftharpoons} R-\overset{^{18}OH}{\underset{OH}{C}}-X \xrightarrow[\text{B}]{\text{Slow}} R{\cdot}CO_2H + X^- + HB^+$$

because such a reaction scheme requires considerable oxygen exchange with the solvent, and it is difficult to envisage prior hydration without extensive oxygen exchange.[*]

However, arguments based on slow proton transfers seem to be unnecessary. The solvent isotope effect upon the dissociation of oxy-acids can be explained in terms of the hydrogen bonding between water and the acids and bases concerned.[18] Strong hydrogen bonding between water and an acid or base should reduce the vibrational stretching frequency of the hydrogen or deuterium involved, and the changes in the zero-point energies will give a solvent isotope effect. By counting the number of hydrogen bonds in reactants and products, and making various approximations, it is possible to account for the solvent isotope effect upon these acid–base equilibria.[18] A similar treatment can be applied to reaction rates, provided that we assume that solvation equilibrium is maintained between the transition state and the solvent.[6]

Expressed qualitatively, this theory states that for hydrolysis of an oxygen-containing

[*] It is unlikely that proton transfer between oxygen atoms could be slower than formation of a carbon–oxygen covalency.

[15] Heppolette and Robertson, *J. Amer. Chem. Soc.*, 1961, **83**, 1834, and refs. therein.

[16] Swain and Thornton, *J. Amer. Chem. Soc.*, 1962, **84**, 822.

[17] Jencks and Carriuolo, *J. Amer. Chem. Soc.*, 1961, **83**, 1743.

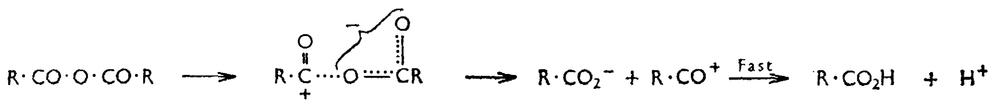
[18] Bunton and Shiner, *J. Amer. Chem. Soc.*, 1961, **83**, 42.

compound there will be a solvent isotope effect if formation of the transition state involves formation of acidic and basic centres which form a strong hydrogen bond with water. For hydrolysis of a carboxylic anhydride we can postulate that the transition state is that for the formation of the tetrahedral intermediate and is very close in structure to (Ia).

The hydrogen-bonding interactions in the initial state between water molecules and the anhydride will be much weaker than those in the transition state between water and those atoms which are shown as bearing charges. The treatment outlined elsewhere[6] gives a calculated value for acetic anhydride of $k_{H_2O}/k_{D_2O} = 3$ at 25° in water. The isotope effects are larger than this value for benzoic and acetic benzoic anhydride (Table 2 and ref. 9), possibly because the theory assumes that all the solvent isotope effect is caused by changes in the activation energy and in these examples neglects interactions between the solvent and the initial state. Therefore the differences between the solvent isotope effects for the various anhydrides may depend on changes in the entropies of activation and in the interactions in the initial state, which will depend upon the shapes of the groups attached to the reaction centre, rather than upon the mechanism. The general agreement between experiment and theory does not, of course, prove the correctness of (Ia) as a model for the transition state. It is an over-simplification to assume that the negative charge is localised completely upon the carbonyl-oxygen atom; some of it may be transferred to the displaced carboxylate group. However, the insensitivity of reaction rate to the nature of the displaced carboxylate group and the similar reactivities of open-chain and cyclic anhydrides suggests that this transfer is small.

For the mutarotation of glucose $k_{H_2O}/k_{D_2O} \approx 3$. This reaction can be compared with anhydride hydrolysis, because both can be written as involving formation of acidic and basic centres in the transition state, and these centres can be linked through a Grotthus chain of hydrogen-bonded water molecules.[6] This hypothesis incidentally requires that proton transfer between the oxygen atoms in (I) should be rapid.

We should expect a unimolecular mechanism to lead to a much smaller solvent isotope effect:



because the only hydrogen-bonding sites in the transition state are upon the displaced carboxylate group. It should also be very sensitive to the nature of the displaced group and the conformation of the anhydride.

Similar arguments can be applied to the uncatalysed hydrolysis of acid chlorides, and of carboxylic esters with acyl–oxygen fission.[6] (We might expect the theory to be less satisfactory for the acid chlorides, because the ease of breaking of the carbon–halogen bond should make bond-breaking relatively more important than it is for other acyl compounds.) The solvent isotope effects for hydrolyses of acid chlorides are greater than those found for alkyl halides[8,15,16] because there is a transfer of electrons from the incoming water molecule to the carbonyl-oxygen atom in the transition state, and for the hydrolysis of mesitoyl and benzoyl chloride ($k_{H_2O}/k_{D_2O} \approx 1{\cdot}7$).

Mesitoyl chloride is more reactive than benzoyl chloride in solvolysis.[19] For this reason, and because the 2,6-dimethyl groups might sterically hinder an approaching nucleophile, it has been suggested that the mechanism of hydrolysis is unimolecular for mesitoyl chloride and bimolecular for benzoyl chloride.[19a] The high value of the entropy and energy of activation (relative to those for other acid chlorides) are explicable on this hypothesis, but the solvent isotope effect and the enhancement of rate by added nucleophiles are not.[19b,20] Moreover, reactions in which there is almost certainly a unimolecular

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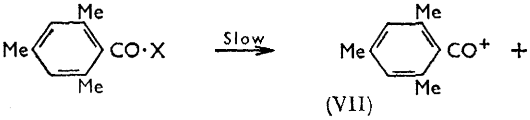
[19] (*a*) Brown and Hudson, *J.*, 1953, 3352; Ugi and Beck, *Chem. Ber.*, 1961, **94**, 1839; (*b*) Peeling, *J.*, 1959, 2307.

[20] Bunton and Lewis, *Chem. and Ind.*, 1956, 180.

rate-limiting formation of a mesitoylium ion (VII) (mechanism $A_{Ac}1$) are slower than the bimolecular ($A_{Ac}2$) reactions of the corresponding benzoyl compounds:[21]



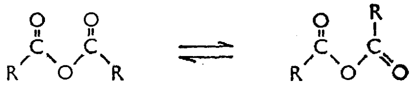
(VII)

($X = ROH^+$, H_2O^+)

Because these reactions are acid-catalysed, it may be unreasonable to compare them with solvolyses of acid chlorides and anhydrides.

Bulky substituents in the 2,6-positions will prevent the aryl group and the carbonyl group from becoming coplanar and will destabilise the initial state. Therefore these steric effects of the di-*ortho*-substituents should destabilise both the initial and the transition state, and it is not obvious which effect will dominate in a given reaction. It is possible that mesitoyl chloride may be hydrolysed by a mechanism different from that followed by the simpler acid chlorides, but it is far from certain that the S_N1 reaction is the appropriate model.

The behaviour of mesitoic anhydride is similar to that of mesitoyl chloride, because although this anhydride is only slightly more reactive than benzoic anhydride the activation energy is higher and the entropy of activation more positive (Table 3). For this anhydride we must consider also the di-*ortho*-substituents in the displaced group. These groups may further alter the conformations of the initial state, *e.g.*, by changing the populations of (VIIIa) and (VIIIb). This effect is apparently not important for the unsymmetrical anhydrides, as can be seen from rate comparisons of acetic benzoic and acetic mesitoic anhydride.



(VIIIa) (VIIIb)

(R = Me, Ph, $C_6H_2Me_2$-2,4,6)

The hydrolysis of methyl trifluoracetate[8] (and of similar esters[17]) also shows a solvent isotope effect larger than those found for alkyl halides or other inorganic esters. Again we can suppose that the transition state for this reaction involves formation of acidic and basic centres.

In discussing the solvent isotope effect we have assumed that there is no major effect upon the initial state, *i.e.*, that the free energies of solvation of the reactants are similar in water and deuterium oxide. Solubility studies of other organic compounds suggest that this effect will be small,[22] and that these compounds dissolve in water or deuterium oxide without materially affecting the structure of the solvent. Hydrogen bonding should decrease the enthalpy of the transition state, and these reactions have low activation energies, but because several water molecules are clustered around the transition state they have large negative entropies of activation. They are often catalysed by general bases,[3,9,23] which presumably stabilise the transition state by taking the place of a water molecule that would be hydrogen-bonded to the incoming water molecule, *i.e.*, the positive charge on this molecule can be donated partially to water or to a general base by hydrogen bonding. Conclusions similar to these have been drawn by Jencks and Carriuolo[17] and by Johnson.[23]

It is not surprising that in this reaction we observe so many phenomena characteristic of slow proton transfers, because in all these reactions one or more protons are shared

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[21] Chmiel and Long, *J. Amer. Chem. Soc.*, 1956, **78**, 3326; Bunton, James, and Senior, *J.*, 1960, 3364.

[22] Rabinovich, Fedorov, Pashkin, Avdesnyak, and Pimenov, *Doklady Akad. Nauk S.S.S.R.*, 1955, **105**, 108; *Chem. Abs.*, 1956, **50**, 9845.

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

between bases. To this extent it may not be necessary to attempt to distinguish between mechanisms in which a specific hydrogen atom is transferred to or from an oxygen atom and those in which there are strong hydrogen-bonding interactions. The absence of extensive oxygen exchange with the water of the solvent (Table 4) suggests that an initial, reversible hydration followed by a slow proton transfer is unimportant for acid anhydrides and chlorides [5] and for trifluoroacetates.

Oxygen Exchange.—Some hydrolyses of acyl compounds are accompanied by exchange between the carbonyl-oxygen atom and water of the solvent which, except for the alkaline hydrolysis of amides,[5,10] is much slower than hydrolysis. Exchange is barely detectable during the hydrolyses of acetic and camphoric anhydride, *i.e.*, $k_h/2k_e > 150$. The activation energy for exchange is greater than for hydrolysis, as in the alkaline hydrolysis of carboxylic esters. The ratio $k_h/2k_e$ for the hydrolysis of benzoic anhydride decreases from *ca.* 100 at 25° to 18 at 81°; in a slightly less aqueous solvent (dioxon–water 75 : 25 v/v) at 62·6° $k_h/2k_e \approx 20$.[5]

It is usually assumed that oxygen exchange during hydrolysis demonstrates formation of an intermediate which dissociates to form the products or to regenerate the reactant, and provided that the oxygen atoms at the reaction centre can become equivalent by proton transfer this regeneration will lead to oxygen exchange. It is therefore surprising that there is very little exchange during the hydrolysis of camphoric anhydride, because the rigidity of the molecule should hold the two carboxyl groups close together and so favour oxygen exchange, as should the comparatively high temperature and high water content of the solvent. Ester hydrolysis provides other examples of the different behaviours of cyclic and open-chain compounds, because there is no oxygen exchange during the alkaline hydrolysis of β-butyrolactone and phthalide whereas there is appreciable exchange during the hydrolyses of several alkyl benzoates; [10] and, because of the complex requirements for the observation of oxygen exchange, it is difficult to be certain that the small amounts of exchange which we observe here prove the existence of an intermediate of finite life.[24]

The ratio k_h/k_e for the hydrolysis of methyl trifluoroacetate is similar to those observed for the acid and alkaline hydrolyses of alkyl benzoates.[10] The situations are not strictly comparable, because our reaction is in initially neutral solution, and the transition state is formally unchanged.

EXPERIMENTAL

Materials.—The preparation of the open-chain anhydrides has been described.[7]

Succinic, maleic, phthalic, cyclohex-1-ene-1,2-dicarboxylic, and camphoric anhydride were commercial samples, purified by recrystallisation to constant m. p.

cis-Cyclohex-3-ene-1,2-dicarboxylic anhydride was prepared from butadiene and maleic anhydride.[25] The other cyclic anhydrides were prepared from the acids by cyclisation with acetic anhydride or acetyl chloride. They were purified by crystallisation, followed, for tetramethylsuccinic anhydride, by vacuum-sublimation.

Glutaric and homophthalic acid were commercial samples and tetramethylsuccinic acid was prepared as a mixture of acid and anhydride by the method of Verkade and Hartmann.[26]

The cyclic anhydrides had the following m. p.s: succinic 120°; glutaric 55—56°; maleic 56°; tetramethylsuccinic 152°; phthalic 131°; homophthalic 141°; cyclohex-1-ene-1,2-dicarboxylic 74°; *cis*-cyclohex-3-ene-1,2-dicarboxylic 103°; camphoric 223°.

Benzoyl chloride was purified by vacuum-distillation. Mesitoyl chloride prepared from the acid by treatment with thionyl chloride had b. p. 143—145°/60 mm.[27] Methyl trifluoroacetate, prepared from the acid and methanol,[28] had b. p. 41·5° and gave a single peak after gas–liquid chromatography (Found: Equiv., 128. Calc. for $C_3H_3F_3O_2$: Equiv., 128).

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[24] Bunton, *Ann. Reports*, 1958, **55**, 186.
[25] Kohler and Jansen, *J. Amer. Chem. Soc.*, 1938, **60**, 2144.
[26] Verkade and Hartmann, *Rev. Trav. chim.*, 1933, **52**, 951.
[27] Barnes, *Org. Synth.*, 1941, **21**, 77.
[28] Moffat and Hunt, *J. Amer. Chem. Soc.*, 1957, **79**, 54.

The aqueous-dioxan solvent was made up by weight to give the appropriate volume composition. Dioxan–D_2O was made up to give the same molecular composition as the corresponding dioxan–H_2O solvent.

Kinetics.—Hydrolysis of the anhydrides was followed by titration (Part II and ref. 7*a*). Aniline was added to portions of the reaction mixture (5 c.c.), and the carboxylic acid was titrated with standard alkali.[29] Where comparison could be made, our rate constants and values of k_{H_2O}/k_{D_2O} agree with those of others.[1,2,9] Camphoric anhydride reacts sufficiently slowly with dilute alkali for the acid to be titrated directly with M/20-sodium hydroxide, provided that the titration is done quickly. The hydrolyses of methyl trifluoroacetate and the acid chlorides were followed dilatometrically.[30]

The rate constants for the hydrolysis of acetic and succinic anhydride, determined dilatometrically, were within 3% of those determined by titration. For acetic benzoic anhydride four runs (followed up to 80% completion) gave rate constants within ±3% of the mean, and for acetic anhydride in water duplicate runs agreed within 2%.

Tracer Experiments.—The evidence on the bond fission of the unsymmetrical anhydrides was given in ref. 7.

Oxygen exchange between acetic or benzoic anhydride and water was studied by stopping the hydrolysis by addition of aniline. The anilide was extracted and purified by recrystallisation from aqueous ethanol. Camphoric anhydride was extracted from a reaction mixture and purified by recrystallisation from a mixture of benzene and light petroleum.

Oxygen exchange between $CF_3{\cdot}CO_2Me$ and $H_2{}^{18}O$ was measured in dioxan–$H_2{}^{18}O$. After partial hydrolysis the unchanged ester was extracted with pentane, and the organic layer washed quickly with cold aqueous sodium hydrogen carbonate and then with cold water, and dried (Na_2SO_4). The ester was converted into the anilide by treatment with anilinomagnesium iodide.

The ^{18}O content of trifluoroacetanilide, and of the acetanilide from the experiments with initially enriched acetic anhydride, was determined by the method of Dahn, Moll, and Menassé.[31] A variation of this method, in which the anilide is heated with a mixture of phenylenediamine hydrochloride and guanidine hydrochloride, was used for all the other samples. The carbon dioxide was analysed mass-spectrometrically.

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[29] Vlès, *Rec. Trav. chim.*, 1933, **52**, 809.
[30] Bunton and Hadwick, *J.*, 1958, 3248.
[31] Dahn, Moll, and Menassé, *Helv. Chim. Acta*, 1959, **42**, 1225.