Kinetics of the Acid Hydrolysis of Substituted Benzoic Anhydrides in Dioxan-Water Mixtures

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The rate constants of the hydrolysis of benzoic and p-nitro-, p-chloro-, and p-methoxybenzoic anhydrides catalysed by perchloric acid in dioxan-water mixtures containing small amounts of water were measured. It is concluded from the observed solvent effects and the values of the activation entropy that the acid hydrolysis of p-methoxybenzoic anhydride occurs by the A1 mechanism and the acid hydrolysis of p-nitrobenzoic anhydride by the A2 mechanism in all dioxan-water mixtures from 0.05 M to 10 M in water. Benzoic anhydride and p-chlorobenzoic anhydride hydrolyse mainly by the A2 mechanism in water-rich solvent mixtures but the mechanism partly changes into the A1 mechanism when the concentration of water in dioxan decreases. The large differences observed in the solvent effects of A1 and A2 hydrolysis reactions catalysed by perchloric acid in dioxan containing less than about two moles of water per litre was found to be a useful criteria when choosing between the two mechanisms. Electron attracting substituents slightly accelerate the acid hydrolysis of anhydride by the A2 mechanism but strongly retard the hydrolysis by the A1 mechanism.

B erliner and Altschul[1] measured the rates of the spontaneous hydrolysis of substituted benzoic anhydrides in a 75 vol. % dioxan-water mixture. The large negative values of the activation entropy and the substituent effects that were in accordance with the Hammett equation indicate a bimolecular S_N2 mechanism for the hydrolysis of all anhydrides studied from the most reactive p-nitrobenzoic anhydride to the least reactive p-methyxybenzoic anhydride.

Results obtained by Bunton and Perry[2] show that acid-catalysed hydrolysis of p-methoxybenzoic anhydride occurs by a unimolecular A1 mechanism, whereas the acid hydrolysis of benzoic anhydride occurs by a bimolecular A2 mechanism in 40 % and 60 % dioxan-water mixtures. Previous results[3] show that the acid hydrolysis of acetic anhydride occurs by the A1, A2, or a mixed mechanism in dioxan-water mixtures depending on the composition of the latter. In order to get more information about the effect of the solvent

on reactions occurring by a borderline mechanism the rates of acid catalysed hydrolysis of several substituted benzoic anhydrides were studied over a wide range of dioxan-water mixtures.

EXPERIMENTAL

With the exception of p-nitrobenzoic anhydride which was obtained in low yields, the anhydrides were prepared from the corresponding acids by heating them with an excess of acetic anhydride as described by Berliner and Altschul.[1] p-Nitrobenzoic anhydride was prepared by warming slowly an equimolar mixture of p-nitrobenzoyl chloride and sodium p-nitrobenzoate. The anhydrides were purified by repeated crystallisation until the purity as determined by the aniline method was at least 99 %. The following melting point ranges were recorded: benzoic anhydride 40−41°, p-methoxybenzoic anhydride 96−98°, p-chlorobenzoic anhydride 193−195° and p-nitrobenzoic anhydride 191−193°C. Dioxan (Fluka AG, purum) was purified by the method of Hess and Frahm.[4] Perchloric acid, 70 % (E. Merck AG, guaranteed reagent), was used as received.

The kinetic experiments were carried out in thermostats controlled electrically to $\pm 0.01°C$. The aniline method [3] was used to analyse the anhydride contents of the samples. Because the reaction between aniline and anhydride is slow in solutions of low water content, a 4-ml sample initially about 0.05 M in the anhydride was mixed with about 0.5 ml of aniline and 1 ml of water and heated to 60°C for about 2 h in the case of p-methoxybenzoic anhydride and for shorter times in the case of the other anhydrides before titrating with 0.02 N barium hydroxide. The final value was obtained as usual by adding an excess of barium hydroxide to the sample and titrating back with 0.02 N hydrochloric acid.

The rate constants were calculated from the first-order rate equation. A good constancy was obtained over the whole range, usually from 15 % to 80 % change, of the reaction studied. The first-order rate constants of the spontaneous hydrolysis of the anhydrides were determined separately and subtracted from the first-order rate constants for the reactions in solutions containing perchloric acid and the differences were divided by the the concentrations of perchloric acid. These second-order rate constants are shown in Table 1.

DISCUSSION

The first-order rate constant of the acid hydrolysis of p-nitrobenzoic anhydride remains almost unaltered in dioxan-water mixtures containing 0.05 to 5 moles of water per litre, whereas the rate constant of the acid hydrolysis of p-methoxybenzoic anhydride decreases about 7000-fold as the water content increases in this range. The solvent effect observed with p-nitrobenzoic anhydride is very similar to that found [5] in the acid hydrolysis of ethyl acetate in the same solvent mixtures and both these reactions then react by the same bimolecular A2 mechanism. The large effect of the solvent on the acid hydrolysis of p-methoxybenzoic anhydride is similar to that on the acid hydrolysis of diethoxymethane in the same solvent mixtures [6] and these two reactions then react by the same unimolecular A1 mechanism.

Acid-catalysed hydrolysis reactions involve a fast proton transfer pre-equilibrium and the experimentally obtained first-order rate constant k is equal to the product of the rate constant k' of the reaction of the protonated anhydride and the acid constant of the protonated anhydride K_{BH^+}. It can be expected that the rate constant k' of the protonated anhydride is approximately independent of the water content in the dioxan-water mixtures for unimolecular A1 reactions in mixtures containing only low concentrations of

water. The changes in the experimental rate constant are thus caused by changes in the acid constant K_{BH^+} when the composition of the solvent mixture is changed. The plot of log K_{BH^+} of amines [7,8] and amides [9] versus log $[H_2O]$ in dioxan-water mixtures when $[H_2O] < 2$ M is linear with a slope

Table 1. First-order rate constants k_a of the spontaneous hydrolysis and second-order rate constants k_w of the acid catalysed hydrolysis of substituted benzoic anhydrides in dioxan-water mixtures.

Anhydride	$t°$	$[H_2O]$ M	$[HClO_4]$ M	$10^5 k_a$ M sec^{-1}	$10^6 k_w$ sec^{-1}
p-NO$_2$-benzoic	40	0.051	0.019	11.0	
	40	0.094	0.036	14.2	1.62
	60	0.142	0.016	114.	4.03
	80	0.142	0.016	640	12.4
	40	0.177	0.067	12.5	
	40	0.225	0.192	10.2	1.65
	40	0.530	0.096	11.5	1.90
	20	0.875	0.096	3.02	0.58
	40	0.872	0.096	15.8	2.22
	60	0.872	0.096	78.3	8.90
	40	1.07	0.019	17.7	2.70
	40	2.14	0.038	30.8	8.74
	20	5.55			31.6
	40	5.37			106
	60	5.55			284
	40	11.1			545
p-Cl-benzoic	60	0.043	0.0049	3600	
	60	0.089	0.0099	1650	1.4
	60	0.176	0.0195	485	1.6
	60	0.482	0.049	177	1.8
	60	0.867	0.096	86.7	2.3
	60	1.98	0.096	32.6	2.7
	60	5.32	0.096	24.0	7.35
	60	10.9	0.096	21.9	27.5
benzoic	40	0.044	0.0049	1780	
	25	0.098	0.0110	44.8	
	40	0.098	0.0110	470	
	60	0.098	0.0110	8260	
	40	0.120	0.0041	362	
	40	0.177	0.0250	173	
	40	0.183	0.0201	183	
	40	0.365	0.046	63.5	
	40	0.453	0.050	40.4	
	40	0.88	0.045	14.9	
	20	1.11	0.028	0.91	
	40	1.11	0.023	12.5	0.087
	60	1.11	0.038	77.6	
	40	2.22	0.076	4.18	0.138
	20	5.55	0.098	0.44	0.170
	40	5.55	0.150	2.42	0.633
	60	5.55	0.098	15.0	2.91
	40	11.1	0.198	2.64	1.38
	20	22.2	0.099	1.06	1.57
	60	22.2	0.150	5.01	7.14
	50	22.2	0.099	24.4	26.7

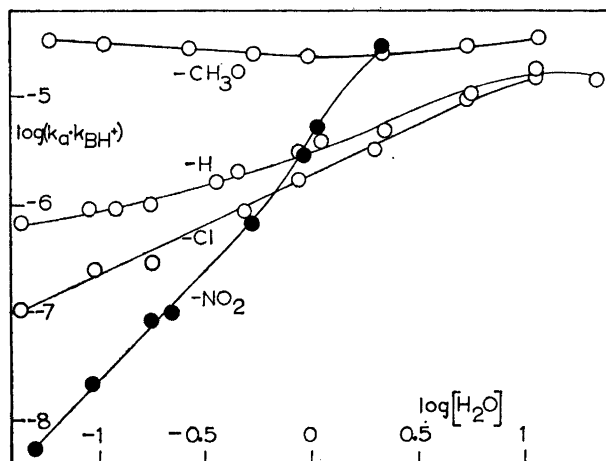| p-CH$_3$O-	40	0.058	0.0012	53900	
benzoic	40	0.107	0.0021	14000	
	40	0.267	0.0053	2340	
	25	0.540	0.0113	82.5	
	40	0.530	0.0105	430	
	60	0.540	0.0113	8600	
	25	1.04	0.0216	7.26	
	40	1.05	0.0209	91	
	60	1.05	0.0220	1245	
	40	2.12	0.0421	23.2	
	25	5.28	0.110	0.625	
	40	5.27	0.107	7.28	0.4
	60	5.24	0.109	72.3	
	40	11.3	0.112	3.97	0.9

Fig. 1. The logarithms of the products of the rate constants k_a of the acid-catalysed hydrolysis reactions of benzoic anhydride and p-methoxy-, and p-nitrobenzoic anhydrides and the acid constants $K_{BH}+$ of dichloroaniline in dioxan-water mixtures at 40°. For p-chlorobenzoic anhydride the values plotted are those of log $(k_a K_{BH}+)-1$ at 60°.

of approximately 2. The plot of log k versus log [H$_2$O] in the same solvent mixture range is linear also for the acid hydrolysis of p-methoxybenzoic anhydride and diethoxymethane [6] and the slope has the same value. The product of the experimental rate constant and the acid constant of dichloroaniline,[8] $k \cdot K_{BH}+$, is almost constant in dioxan-water mixtures in the range from 0.05 M to 11 M water as shown in Fig. 1.The slope of the plot of log $(k \cdot K_{BH}+)$ versus [H$_2$O] is -0.14 for the reaction in dioxan-water mixtures when the water concentration is less than 1 M. The acid hydrolysis of p-methoxybenzoic anhydride occurs by the A1 mechanism and the reaction of the protonated anhydride to the products is approximately independent of the water concentration. The positive values of the activation entropy also support the A1 mechanism (Table 2). Bunton and Perry [2] showed that the acid hydrolysis of p-

Table 2. Activation ethalpies and entropies of the acid hydrolysis reactions of benzoic, *p*-nitrobenzoic and *p*-methoxybenzoic anhydrides at 40°C.

Anhydride	$[H_2O]$ M	E kcal	ΔH^* kcal	ΔS^* cal.deg.$^{-1}$
p-Nitro-benzoic	0.142	22.0	21.4	− 9.3
	0.875	17.7	17.1	−20.4
Benzoic	0.098	29.3	28.7	16.6
	1.11	21.4	20.8	−10.3
	5.55	17.2	16.6	−26.6
	22.2	15.2	14.6	−31.4
p-Methoxy-benzoic	0.540	26.4	25.8	13.5
	1.05	29.1	28.5	17.9
	5.26	27.0	26.4	6.3

methoxybenzoic anhydride occurs by the A1 mechanism in 40 % and 60 % dioxan-water mixtures. The hydrolysis reaction thus proceeds by a unimolecular mechanism over a wide range of dioxan-water mixtures.

The acid hydrolysis of *p*-nitrobenzoic anhydride in dioxan water mixtures takes place by the A2 mechanism. The plot of log $(k \cdot K_{BH}+)$ *versus* log $[H_2O]$ is linear with slope 2.0 at low water concentrations in dioxan-water mixtures. A similar value of the slope has been obtained [5] for the acid hydrolysis of ethyl acetate in dioxan-water mixtures. Two water molecules therefore participate in the hydrolysis of the protonated anhydride or ester. The negative values of the activation entropies obtained for *p*-nitrobenzoic anhydride also support the bimolecular A2 mechanism (Table 2).

A change in the reaction mechanism from A1 to A2 occurs somewhere between *p*-methoxybenzoic anhydride and *p*-nitrobenzoic anhydride when the nature of the substituent changes. A change in reaction mechanism was observed by Buton and Perry [2] between *p*-methoxybenzoic anhydride and benzoic anhydride in 40 % and 60 % dioxan-water mixtures; the former reacts by the A1 and the latter by the A2 mechanism. The change may occur between other anhydrides in dioxan-water mixtures containing low concentra-

Table 3. Relative rates of benzoic and *p*-nitro- and *p*-methoxybenzoic anhydrides at 40°C and those of *p*-chlorobenzoic anhydride at 60°C.

$[H_2O]$ M	-NO$_2$	Cl-	H-	CH$_3$O-
0.120	0.034	0.185	1	31
1.11	1.0	0.87	1	6.5
5.55	6.9*	1.60	1	2.8

* $[H_2O]$ = 2.14.

tions of water. Table 3 shows the relative rates of the four anhydrides studied. The rate of acid hydrolysis increases with decreasing electron-attracting properties of the substituent, $NO_2 < Cl < H < CH_3O$, in the dioxan-water mixture, 0.11 M in water, whereas with the exception of p-methoxybenzoic anhydride the order is reversed in dioxan 5.4 M in water. The acid hydrolysis of benzoic anhydride is mainly an A2 reaction in dioxan, 5.4 M in water, as can be deduced from the large negative activation entropy $\Delta S^* = -26.6$ cal. deg.$^{-1}$ (Table 2). The change in mechanism thus occurs between benzoic anhydride and p-methoxybenzoic anhydride as can be expected from the reversal of the reaction rates (Table 3). If the hydrolysis of benzoic anhydride proceeds by an A2 mechanism in dioxan, 5.4 M in water, it is even more likely that the reactions of p-chloro- and p-nitrobenzoic anhydrides do so also. The effect of the substituent upon the rate of acid hydrolysis of benzoic anhydrides by the A2 mechanism is hence very weak. For example, p-nitrobenzoic anhydride reacts only about 7 times faster than benzoic anhydride.

The activation entropy of the acid hydrolysis of benzoic anhydride decreases rapidly as the concentration of water in dioxan decreases. The positive value of the activation entropy obtained at low water concentration indicates changes from the A2 to the A1 mechanism. The reversal of the order of the reactivities in dioxan containing 0.11 mole of water per litre also indicates a large contribution of the A1 mechanism. The slope of the plot of log ($k \cdot K_{BH^+}$) versus log $[H_2O]$ is about 0.48 for benzoic anhydride in dioxan-water mixtures of low water content and indicates that there may be still some contribution of the A2 mechanism. The slope is about 0.86 for the acid hydrolysis of p-chlorobenzoic anhydride. This value is roughly the mean of the values of the slopes for p-methoxy- and p-nitrobenzoic anhydrides and indicates a borderline mechanism for p-chlorobenzoic anhydride. The slope 0.22 obtained [10] for the acid hydrolysis of acetic anhydride at low water concentrations shows that this reaction takes place almost exclusively by the A1 mechanism in dioxan-water mixtures of low water content, whereas this reaction occurs mainly by an A2 mechanism in dioxan water mixtures of high water content according to previous results.[3] A change of the reaction mechanism from A2 to A1 as the amount of water in dioxan is decreased is to be expected because the rate constant of the reaction of the protonated anhydride by the A2 mechanism is approximately proportional to the second power of the water concentration, whereas the rates of reactions occurring by the A1 mechanism are largely independent of water concentration.

The rates of acid hydrolysis of substituted benzoic anhydrides by the A2 mechanism decrease when the substituent becomes less electronegative, but the decrease is small. For reactions occurring by an A1 mechanism an opposite and strong effect is observed when the substituent is changed (Table 3), the rate of hydrolysis of p-methoxybenzoic anhydride being 37 times the rate of hydrolysis of benzoic anhydride in dioxan containing 0.11 mole of water per litre. These substituents effects are explained by the expected different stabilities of the transition states in the two reactions. In an A1 reaction the carbonyl carbon atom becomes positively charged when the transition state is formed whereas only small changes are expected to occur in the charge of the carbonyl carbon atom in an A2 reaction a positive charge

developing at the oxygen atom of the attacking water molecule. Electron-releasing substituents therefore increase the rate of a reaction occurring by the A1 mechanism and either weakly accelerate or retard a reaction occurring by the A2 mechanism depending on the nature of the charge that develops on the carbonyl carbon atom. The effect of an electronegative substituent in the leaving group increases the rates of reactions occurring by both the A1 and the A2 mechanisms and electron-attracting substituents at both ends of a reacting anhydride molecule retard the reaction by effecting a decrease in the concentration of protonated anhydride molecules because of decreased basicity. These two effects partly cancel each other and the result is a weak substituent effect as is observed for reactions occurring by the A2 mechanism.

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