Studies on Cyclic Anhydrides

I. Rate Constants and Activation Parameters for the Solvolysis of Alkylsubstituted Cyclic Anhydrides in Aqueous Solution by the pH-stat Method

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Rate constants have been determined for the solvolysis of a series of alkylsubstituted succinic and glutaric anhydrides in aqueous solution at 20.0, 25.0, and 30.0°. The kinetic measurements have been done by the pH-stat method, which gives rate constants in good agreement with otherwise determined rate constants provided the titrating liquid is not too strongly basic. With sodium hydroxide as the titrating liquid rate constants exhibited a systematic error, being 5—10 % too high, which could be eliminated by a change of titrating liquid to the weaker base, Na_2HPO_4. This error is probably due to a pH gradient around the base inlet tube, giving the experimental rate constant a small contribution from the hydroxide ion catalyzed reaction.

The activation parameters E_a and $\Delta S\neq$ satisfy two sets of isokinetic relationships. The possible significance of this fact is discussed.

The spontaneous hydrolysis of carboxylic anhydrides has been studied extensively from a mechanistic point of view during recent years.[1-8] According to these investigations the rate-determining step is a nucleophilic attack by water upon one of the acyl-carbon atoms.[1] Since oxygen exchange between solvent and anhydride is much slower than hydrolysis,[1] there is no definite proof for the existence of an intermediate of finite life; at least the transition state for the over-all reaction must precede the formation of any intermediate species. The energy of the transition state is lowered by hydrogen bonding with solvent molecules[1,6] with the result that anhydride hydrolyses generally have large negative entropies of activation and a large solvent isotope effect[1,4,5,7] ($K_H/K_D \approx 3$). There does not seem to be any mechanistic difference between the hydrolysis of open-chain and cyclic anhydrides.[1]

On the other hand, studies on the variation in solvolysis rate with the introduction of substituents in the anhydride molecule have been restricted mainly to alkylsubstituted anhydrides.[1,8,9-11] There exist some crude estimates

of the rates of hydrolysis of aliphatic chlorine[12] and acetyl[13] substituted anhydrides as well as data for several unsaturated anhydrides[9],[10],[14],[15] In the aromatic series Berliner and Altschul[16] obtained a satisfactory correlation between hydrolysis rates of symmetrically meta and para substituted benzoic anhydrides and Hammett's σ-constants. The high ϱ value for this reaction implies a high sensitivity to inductive and resonance effects.

The present state of prevailing theories of substituent effects has been amply summarized by Dewar and Grisdale[17] From measurements of ionization constants of 1-substituted naphthoic acids,[18] they proposed a quantitative theory[19] based on σ-constants expressed in terms of two parameters calculated from data for benzene. These parameters are related to the inductive field effect and the net sum from π-inductive and mesomeric effects. The σ-inductive effect was assumed to be unimportant and the treatment was limited to cases where there is no mutal conjugation between the substituent and the reacting center. The need for more data on the effects of substituents in rigid molecules of known geometry, other than benzene, was also emphasized.

Five- and six-membered cyclic anhydrides have properties which may make them suitable for a quantitative study of substituent effects and their transmission in saturated molecules. One of the prime requisites is molecular rigidity in order to make possible the evaluation of distance parameters within the molecule and to ascertain that the molecule cannot exist in several conformations. This demand is fulfilled by the succinic anhydride molecule where the coplanarity of the CO-O-CO system rigidly locks the methylene groups in an eclipsed position. The six-membered cyclic anhydride, glutaric anhydride, is somewhat more flexible since in its deformed chair conformation it can locate substituents in axial or equatorial positions. This difficulty may easily be overcome, either by a proper choice of substitution patterns or by incorporating the glutaric anhydride molecule in a bicyclic ring system.

Cyclic anhydrides are also suitable objects for a study of the gem-dialkyl effect,[20-23] which is the common denomination for the influence of alkyl groups on ring closure reactions, although the alkyl groups actually need not be geminally positioned in the carbon chain. There are many reports on cases where the anhydride appears to be the stable species in aqueous or non-aqueous solution or to exist in equilibrium with the corresponding dicarboxylic acid. [21],[24-26] The position of the equilibrium has been established in one case, namely dimethylmaleic acid.[26]

It is the purpose of this series to exploit the properties of the carboxylic anhydride system with respect to these problems. The first paper is a study of the hydrolysis rates of alkylsubstituted succinic and glutaric anhydrides, mainly with the intention to develop a reliable and convenient kinetic method. It is found that with certain precautions, to be discussed below, the pH-stat technique gives excellently reproducible rate constants in good agreement with those determined by other methods.

Kinetic method. Rate constants for anhydride solvolyses in aqueous solution have been determined by a variety of methods, *e.g.* by conductometric,[1],[8] spectrophotometric,[27] dilatometric,[1],[3] and titrimetric techniques.[8],[10] The method adopted here is the pH-stat method in which the hydrolytic process is followed by recording automatically against time the amount of standard

base required to keep the pH of the reaction mixture constant. This method has the advantage of being convenient and satisfactorily reproducible; in addition, it allows rate measurements to be performed at different hydrogen ion concentrations, which is desirable in the equilibrium measurements (anhydride + water $\rightleftharpoons$ dicarboxylic acid). However, the nature of the titrating liquid appears to be a critical point.

Anhydride hydrolyses are know to be extremely sensitive towards hydroxide ion catalysis[8]. If the titrating liquid was 0.02-0.1 N standard sodium hydroxide and the reaction was run at pH 5.50 or below, it was consistently found that the measured rate constants were 5-10 % higher than those determined by other methods (the conductometric or aniline-water method). Since the literature values were in good agreement with each other, the pH-stat method must give rise to a systematic error probably due to a hydroxide ion gradient around the base inlet tube, giving a small contribution from the hydroxide ion catalyzed reaction. Attempts to eliminate or diminish this error by varying the stirring rate, the volume of the solution, or the pH of the solution failed. Only by changing the titrating liquid could rate constants in reasonable agreement with literature values be obtained. The hydrogen phosphate ion (HPO_4^{2-}) was found to be suitable for this purpose both with respect to the pH of the titrating liquid (about 9) and to the hydrogen concentration at which the hydrolyses were run (pH usually 5.20). A comparison between rate constants determined with 0.1 N sodium hydroxide and 0.1 N sodium hydrogen phosphate as titrating liquid, and literature values is given in Table 1. With sodium hydrogen phosphate as base, agreement with literature values is good and there is no indication of systematic errors since deviations are both positive and negative (see also Table 2). It may be noted

Table 1. Comparison between rate constants obtained by the pH-stat method using sodium hydroxide or sodium hydrogen phosphate as titrating base

| Anhydride | Tempera-ture °C | Rate constant, min⁻¹ | | Difference | Literature value |
		0.1 N OH⁻	0.1 M HPO₄²⁻		
Acetic	20.0	0.127	0.115	0.012	0.114[8]
Acetic	25.0	0.168	0.158	0.010	0.153[8], 0.159[31] 0.160[32], 0.160[1]
Succinic	20.0	0.119	0.109	0.010	0.110[8]
Succinic	25.0	0.185	0.159	0.026	0.159[33], 0.161[1]
Glutaric	20.0	0.124	0.113	0.011	0.121[8]
Methylsuccinic	20.0	0.173	0.151	0.022	0.151[8]
3,3-Dimethyl-glutaric	20.0	0.00860	0.00781	0.00079	0.00840[8]

that Bender and Feng[28] have determined the rate of hydrolysis of acetic anhydride in water by the pH-stat method at 20.0° with 0.02 N hydroxide ion as the titrating base[29], and obtained a value of 0.124 $\pm$ 0.006 min⁻¹. Within the limits of error, this value is identical with that obtained in this investiga-

tion with the same base, 0.127 ± 0.001 min^{-1}, indicating that this systematic error is not very much dependent on the apparatus design.

There is no indication that the $H_2PO_4^-$ ion in the concentrations employed has a catalytic effect upon the reaction since all reactions show excellent pseudo first-order kinetics. Several anions are known to have a weak catalytic effect on anhydride hydrolyses but this is detectable only at considerably higher concentrations.[2,30]

Next, the pH-dependence of the hydrolysis of succinic anhydride at 20.0° was investigated in order to find where hydroxide ion catalysis has a

Fig. 1. Plot of experimental rate constant *versus* pH (solid line) for succinic anhydride at 20.0° The broken line was calculated from a value of the rate constant for the water reaction of 0.109 min^{-1}, and a rate constant[8] for the hydroxide ion catalyzed reaction of 1.4×10^6 l mole^{-1} min^{-1}.
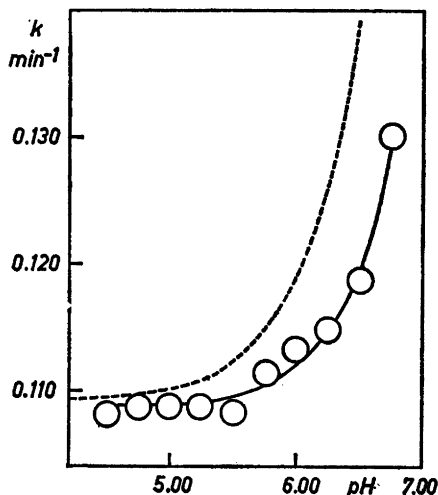
negligible effect upon reaction rate. This is shown in Fig. 1, where experimental rate constants have been plotted against pH (solid curve). Below pH 5.50, the value of the rate constant does not change, which cannot be estimated from Koskikallios' value[8] of k_2 for the hydroxide ion catalyzed reaction (estimated to be about 1.4×10^6 l mole^{-1} min^{-1} at 20°) The curve calculated from a rate constant for the spontaneous reaction of 0.109 min^{-1} and a k_2 value of 1.4×10^6 l mole^{-1} min^{-1} is shown in Fig. 1. (broken curve *). This curve lies considerably above the experimentally found curve, probably due to the uncertainty in the k_2 value. A k_2 value of about 6×10^5 l mole^{-1} min^{-1} gives a good fit with the experimental curve. The same behavior was exhibited by other anhydrides and in one case, *cis*-caronic anhydride, the kinetics could be followed down to a pH value of 3.30. No change in rate constant was observed in the pH region 5.50-3.30, which shows that hydrogen ion catalysis is negligible in this pH interval. This is in agreement with previous

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* *Note added in proof.* It was recently reported by Kirsch and Jencks (*J. Am. Chem. Soc.* **86** (1964) 837) that Koskikallios' k_2 value for acetic anhydride was 30-fold greater than that obtained by the pH-stat method.

Table 2. Rate constants for the hydrolysis of cyclic anhydrides at 20.0° 25.0°, and 30.0° determined by the pH-stat method at pH 5.20. Titrating liquid: 0.1 N Na_2HPO_4

Anhydride	20.0°		25.0°		30.0°		E_a kcal/mole	lit. value	$-\Delta S\ddagger$, e.u.	lit. value
	k min^{-1}	lit. value	k min^{-1}	lit. value	k min^{-1}	lit. value				
Acetic	0.1149	0.114[8]	0.1577	0.160[1] 0.160[32] 0.153[8] 0.159[31]	0.209		10.6	10.5[8] 11[1]	36.8	35[1]
Succinic	0.1087	0.110[8]	0.1585	0.159[33] 0.161[1]	0.227		13.0	12.8[8] 13[1]	28.7	28[1]
Methylsuccinic	0.1512	0.151[8]	0.219	0.227[33]	0.302		12.2	12.0	30.7	
2,2-Dimethyl-succinic	0.1216		0.1704	0.175[33]	0.234		11.6		33.3	
dl-2,3-Dimet-hylsuccinic	0.168		0.237	0.254[33]	0.311		10.9		35.0	
meso-2,3-Dime-thylsuccinic	0.247		0.344	0.352[33]	0.459		10.9		34.0	
Trimethyl-succinic	0.1337		0.1830	0.180[33]	0.246		10.8		35.9	
Tetramethyl-succinic	0.01008		0.01396	0.0147[33] 0.0136[1]	0.0196		11.7	13.5[1]	37.7	32[1]
cis-Caronic	0.1257		0.1779		0.240		11.4		33.8	
Glutaric	0.1125	0.121[8]	0.1614	0.162[1] 0.162[32]	0.224		12.2	12.1[8]	31.5	
2-Methyl-glutaric	0.0832		0.1166		0.1607		11.6		33.9	
3-Methyl-glutaric	0.0726		0.1028		0.1406		11.7		34.0	
2,2-Dimethyl glutaric	0.0754		0.1041		0.1414		11.1		35.8	
3,3-Dimethyl-glutaric	0.00781	0.00842[8]	0.01161		0.01733		14.1	13.4[8]	30.3	
dl-2,4-Dime-thylglutaric	0.0949		0.1363		0.1814		11.4		34.4	
meso-2,4-Dime-thylglutaric	0.0482		0.0675		0.0957		12.1		33.4	
3-Methyl-3-et-hylglutaric	0.00641		0.00966		0.01444		14.3		29.8	
3,3-Diethyl-glutaric	0.00541		0.00814		0.01274		15.1		27.5	
3,3-Tetrame-thyleneglutaric	0.01030		0.01518		0.02315		14.3		29.0	

observations; in the conductometric method good first-order kinetics are obeyed in spite of the fact that the pH changes from an initially neutral solution to the pH of a solution of the completely hydrolyzed anhydride.[8] Also, the measured values of catalytic constants for the hydrogen ion catalyzed reaction show that hydrogen ion catalysis is negligible at pH values above 2.[8] All constants reported in this investigation were run at pH 5.20, unless otherwise stated.

The reproducibility of the rate constants was excellent; for succinic anhydride at 20.0° seven consecutive measurements gave the values 0.1084, 0.1088, 0.1077, 0.1092, 0.1095, 0.1078, and 0.1092 min^{-1} which gives a mean value of 0.1087 min^{-1} with a probable error of a single measurement of $\pm$ 0.0005, and a probable error of the mean value of $\pm$ 0.0002. The constants given in this paper are the mean values of three runs and the reproducibility is accordingly better than $\pm$ 1 %. This is sufficient to give activation energies and entropies with probable errors of $\pm$0.2 kcal/mole and $\pm$0.6 e.u., respectively.

Table 2 shows rate constants for the hydrolysis of a number of cyclic anhydrides in aqueous solution at 20.0, 25.0, and 30.0°, together with activation parameters at 25.0° Literature values are included and it is seen that the agreement generally is satisfactory, especially in those cases where several independent data are available. For the substituted glutaric anhydrides a somewhat different order or reactivity is found than Wheeler and Almeida[11] obtained in 1:5 dioxane-water (v/v). Their rate constants were measured by the conductometric method, and in the evaluation of the constants it was assumed that conductance is proportional to the concentration of the acid formed. This is, however, not correct since the relation between conductance and acid concentration is considerably more complicated; in fact, each acid requires a separate calibration procedure.[8] A preliminary check of rate constants for the hydrolysis of some glutaric anhydrides under the conditions employed by Wheeler and Almeida indicated that their values are too large by a factor (not constant) between 2 and 3, which explains some pecularities of their data, especially the low activation energies found for the 3,3-dialkylglutaric anhydrides.

DISCUSSION

Rate constant variations in the hydrolysis of cyclic anhydrides have previously been rationalized in terms of steric and polar effects. Thus Bruice and Pandit[10] employed a Taft type equation to evaluate steric parameters for the simultaneous hydrolysis and ethanolysis of a number of cyclic anhydrides in 28.5 % ethanol-water at 35.0°. The negative effect upon rate by alkyl substitution was attributed to steric hindrance to the approach of lyate species to the anhydride carbonyl group. A comparison of their data with those in Table 2. indicates that such a simple explanation is not feasible, since relative rates are considerably changed in aqueous solution at 25.0°, e.g. in the first case [10] the reactivity order is succinic > glutaric≈2,2-dimethylsuccinic anhydride, while in aqueous solution it is succinic ≈ glutaric<2,2-dimethylsuccinic. There are some other data in Table 2 which indicate that no simple explanation in terms of the usual effects of theoretical organic chemistry is possible. For example, the introduction of one, two, or three methyl groups in the succinic acid molecule produces a rate enhancement contrary to what would be expected from considerations based on the inductive effect of methyl groups on reactions of other carboxylic acid derivatives. The introduction of conformational strain as an explanatory factor is equally unsatisfactory, since tetramethylsuccinic anhydride, with two pairs of eclipsed methyl groups, would then be expected to show a higher rate than the unsubstituted compound.

A more detailed analysis of the activation parameters shows why an explanation of the reactivity orders is bound to fail and that discussions of these comparatively small rate variations must be conducted with great care. If we plot E_a against $\Delta S^{\ddagger}$ for the anhydride hydrolyses in Table 2 they fall distinctly into two groups, each satisfying an isokinetic relationship (Fig. 2).[34] The first group includes relatively fast hydrolyses (rate constants in the interval 0.0675-0.344 min^{-1} at 25.0°) and the other one more slowly hydrolyzing anhydrides (rate constants in the interval 0.00814—0.01518 min^{-1} at 25.0°), i.e. there is a factor of about 10 in difference between the rate constants of the two groups. Now one of the important features of an isokinetic relationship is that it can be expected to apply only to a series of reactions in which the structural change does not change the mechanism. Considerable changes in steric interactions in the transition state usually remove a reaction from the isokinetic line and may sometimes give a new isokinetic line, correlating reactions with the same degree of steric hindrance. This appears to be the case for the anhydrides listed in Table 2.

An isokinetic relationship may be represented by the equation[34]

$$\Delta H^{\ddagger} = \Delta H_0^{\ddagger} + \beta \, \Delta S^{\ddagger}$$

where $\Delta H_0^{\ddagger}$ is a constant with the value of $\Delta H^{\ddagger}$ corresponding to $\Delta S^{\ddagger} = 0$, and β is the slope of the isokinetic line, having the dimensions of absolute temperature. Combining the above equation with the usual expression for the free energy of activation $\Delta F^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$ gives:

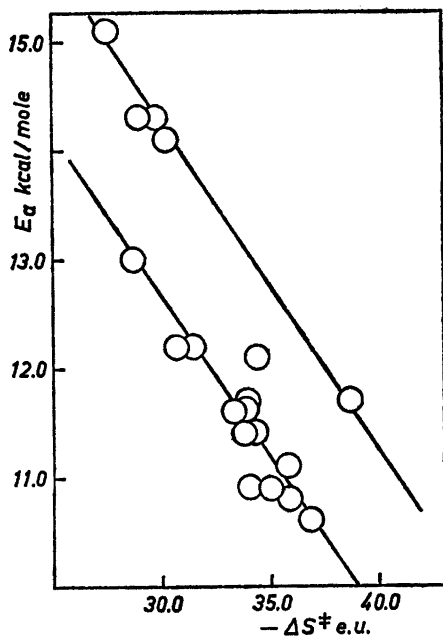$$\Delta F^{\ddagger} = \Delta H_0^{\ddagger} - (T-\beta)\Delta S^{\ddagger}$$

Fig. 2. Plot of activation energy *versus* activation entropy for the anhydrides listed in Table 2.

which means that all rate constants in a reaction series are the same, within the precision of the isokinetic relationship, at $T = \beta =$ the isokinetic temperature. For the two lines in Fig. 2 the β values are 290 and 320°K, respectively, *i.e.* very close to the experimental temperature. Working so close to the isokinetic temperature means that variations in rate constant within each group will be rather small and difficult or impossible to interpret in terms of inductive or steric effects.[34] As an example, it is not safe to conclude from the constancy of the hydrolysis rates of acetic, succinic and glutaric anhydride that ring strain does not have any effect upon reaction rate, since the constancy may be due to the trivial fact that the rate constants have been measured at a temperature very close to the isokinetic temperature.

Clearly, a more detailed discussion of anhydride solvolyses must await the accumulation of further data. At present the only safely founded conclusions appear to be that the difference in rate constants between the two groups of anhydrides in Figure 2 is due to steric hindrance, and that any interpretation of the variation within each group is not possible.

It may be noted that the hydroxide ion catalyzed ring opening of lactones[35] is rather insensitive to the introduction of methyl groups in the lactone ring. These reactions also obey an isokinetic relationship with a β value close to the experimental temperature.

EXPERIMENTAL

Materials. The cyclic anhydrides were prepared from the carefully purified dicarboxylic acids by treatment with an excess of acetyl chloride at reflux temperature. The final purification was achieved by distillation in the case of liquid anhydrides and recrystallization followed by sublimation in the case of solid anhydrides. The purity was checked by gas chromatography and titration with standard base and in all cases was better than 99.5 %. Acetic anhydride was of Merck *pro analysii* quality. Physical constants were in good agreement with literature values.

Kinetics. The kinetic measurements were carried out with the SBR2c titrigraph combined with the SBU1a syringe buret, and the TTT1a titrator from Radiometer, Copenhagen. The reaction vessel was equipped with a jacket, through which thermostated water from an ultrathermostat was circulated. The temperature constancy was better than $\pm 0.03°$. The volume of water used in a kinetic experiment was 20.0 ml and, after thermal equilibrium had been attained, the appropriate amount of anhydride dissolved in 100 μl of dioxane was added by means of a micropipet. In separate experiments it was established that the presence of 0.5 % dioxane in the reaction mixture had practically no effect upon reaction rate. The titrating liquid was 0.1 M Na_2HPO_4, and the reactions were run at pH 5.20. It was also established that a ten-fold variation in anhydride concentration had no effect upon reaction rate. Rate constants were evaluated graphically by the Guggenheim method and all values reported in Table 2 are mean values from at least three runs. The performance of the instrument was frequently checked by measurements on acetic anhydride, which always gave rate constants within the limits of error given above.

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