Hydrolysis of Phthalic and 3,6-Dimethylphthalic Anhydrides

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Phthalic and 3,6-dimethylphthalic anhydrides give flat pH profiles for hydrolysis in aqueous solution over the range from 4M-hydrochloric acid to pH 5·2. The addition of electrolytes or 1,4-dioxan has the expected rate-retarding effect and 3,6-dimethylphthalic anhydride is slightly more sensitive to such changes than phthalic anhydride. The results of a study of the variation of equilibrium constant for the 3,6-dimethylphthalic anhydride–diacid equilibrium with temperature are reported and the activation parameters for the forward and reverse reactions and for the hydrolysis of phthalic anhydride are given. These values are consistent with a mechanism suggested for the hydrolysis of these anhydrides. At 25° phthalic anhydride is hydrolysed nearly eight times faster than the 3,6-dimethyl compound.

HYDROLYSIS of phthalic and 3,6-dimethylphthalic anhydrides and the effect of temperature, acid concentration, and added electrolytes or dioxan on the rate have been studied as part of an investigation of the trifluoroethyl,[1] diphenylmethyl, and α-phenylanisyl monoesters of the corresponding acids and of a series of substituted phthalanilic and 3,6-dimethylphthalanilic acids.[2]

Eberson [3] has reported that 3,6-dimethylphthalic anhydride is in equilibrium with the diacid in aqueous solution and that the equilibrium mixture contains 32% of anhydride at 61·5°. This equilibrium was examined as part of this study and the hydrolysis of phthalic anhydride was investigated to determine the effect of dimethyl substitution on the rate.

EXPERIMENTAL

Materials.—Phthalic anhydride (B.D.H. reagent grade) was recrystallised twice from chloroform and stored in a vacuum desiccator before use. 3,6-Dimethylphthalic anhydride was prepared by dehydrating the 2,5-dimethylfuran–maleic anhydride Diels–Alder adduct with 90% sulphuric acid at 0—10 °C.[4] The product was recrystallised three times from 2 : 2 : 5 (v/v) chloroform–ethyl acetate–petroleum (b.p. 60—80°); yield 76%; m.p. 142·5—143·5° (lit.,[4] 142—143°).

2,5-Dimethylfuran was prepared from hexane-2,5-dione. Three methods of dehydration were examined: refluxing the dione (28·5 g, 0·25 mole) for 1 h with phosphorus pentoxide (4 g) or anhydrous zinc chloride (2 g) gave yields of 60 and 46%, respectively, and passing the dione vapour in a stream of nitrogen over heated alumina resulted in 59% conversion and a virtually quantitative yield. The products, which were collected in glass traps cooled in ice–salt or solid CO_2–methanol, were separated by distillation through a silvered, vacuum-jacketed column packed with Fenske helices and equipped with a partial take-off head. The fraction boiling at 93—95° was collected (2,5-dimethylfuran; lit.,[5] b.p. 94°; n^{20} 1·4376, lit.,[5] 1·4363). The residue, mainly unchanged dione (b.p. 191—194°), was recycled. This vapour-phase reaction with alumina or heating under reflux with phosphorus pentoxide were the most convenient methods.

3,6-Dimethylphthalic acid, m.p. 144—148° (decomp.) [lit.,[6] 145° (decomp.); lit.,[3] 145—150° (decomp.)]; equiv. wt. 97·6 (calc. for $C_{10}H_{10}O_4$: 97·1), was prepared by a published method.[3]

Kinetics.—The acids used for the kinetic experiments were prepared from B.D.H. volumetric standard solutions. Salts were of AnalaR grade and were used without further purification. All water was either degassed double-distilled or was taken from an ion-exchange column. B.D.H. spectroscopic grade dioxan was used without further purification and was stored, preferably under nitrogen, at *ca.* 5°.

The hydrolysis of phthalic and 3,6-dimethylphthalic anhydrides was followed by adding 1 drop of a stock solution of the anhydride in 1,4-dioxan to a 10 mm stoppered spectroscopy cell containing the reaction medium at the required temperature and following the decrease in optical density at 300 and 322 nm, respectively, with a Beckman DU spectrometer. The quartz cell was heated in a steel cell-holder through which water was circulated from a thermostatic bath controlled to within ±0·02°.

First-order rate constants were determined graphically from integrated first-order equation plots of log ($OD_t - OD_\infty$) against time (t), or were evaluated by Guggenheim's method.[7] The 3,6-dimethylphthalic anhydride–diacid equilibrium was approached from either direction. Standard solutions of the anhydrides or the diacid in dioxan, for molecular extinction coefficient determinations, were prepared by direct weighing. The values obtained agreed well with those found by extrapolating the optical density to zero time in the hydrolysis experiments. The composition of the equilibrium mixture, and hence the equilibrium constant, was calculated from the optical density of standard solutions of the 3,6-dimethylphthalic anhydride–diacid equilibrium mixture in 0·01M- and 0·1M-hydrochloric acid. The pH values of sodium acetate–acetic acid buffers in aqueous dioxan were calculated by using the published pK_a value of acetic acid in 20% dioxan.[8]

RESULTS AND DISCUSSION

Both phthalic and 3,6-dimethylphthalic anhydrides gave flat pH profiles for hydrolysis in sodium acetate–acetic acid buffers in 20% dioxan or over the complete range from 4M-hydrochloric acid to pure water or sodium acetate–hydrochloric acid buffers between pH 0·63 and 5·20 (see Table 1).

Added electrolytes or dioxan retarded the hydrolysis. The effect of sodium chloride or other electrolytes was small; thus added NaCl had a negligible influence on the rate at concentrations up to 1M. The hydrolysis of

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[1] M. D. Hawkins, following paper.

[2] M. D. Hawkins, unpublished results.

[3] L. Eberson, *Acta Chem. Scand.*, 1964, **18**, 2015.

[4] M. S. Newman and B. T. Lord, *J. Amer. Chem. Soc.*, 1944, **66**, 733.

[5] 'Handbook of Chemistry and Physics,' Chemical Rubber Co., Cleveland, Ohio, 51st edn., 1970—1971.

[6] M. Freund and K. Fleischer, *Annalen*, 1916, **411**, 14.

[7] E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

[8] H. S. Harned and G. L. Kazanjian, *J. Amer. Chem. Soc.*, 1936, **58**, 1912.

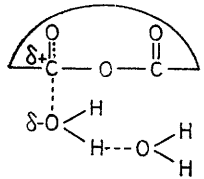
3,6-dimethylphthalic anhydride was more sensitive to added electrolytes: the effect of sodium perchlorate in aqueous 0·1M-hydrochloric acid, for example, is shown in Table 2. Plots of log k_{obs} against log c_{H_2O} for hydrolysis in aqueous dioxan are linear: the gradient for phthalic anhydride at 37°, for example, is 3·7 (±0·2) which indicates the high degree of hydration involved in the spontaneous hydrolysis [see (A)].

TABLE 1

Hydrolysis of phthalic and 3,6-dimethylphthalic anhydrides

	Phthalic anhydride T 28° $10^3 k_{obs}/s^{-1}$ †	3,6-Dimethylphthalic anhydride T 65·8° $10^3 (k_1 + k_{-1})/s^{-1}$ †
Sodium acetate (0·04M)–acetic acid buffers in 20% dioxan, pH 4·29—6·92; mean value	5·45	6·80
Hydrolysis in aqueous solution over range between 4M-HCl and sodium acetate–hydrochloric acid buffers from pH 0·63 to 5·2; mean value	21·6	18·7
Hydrolysis in ion-exchange-purified water		19·1

† Maximum standard deviation of rate constants for a minimum of twenty-one determinations was 3%.



(A)

The gradient of the corresponding log $(k_1 + k_{-1})$ *vs.* log c_{H_2O} plot for the hydrolysis of 3,6-dimethylphthalic anhydride at 65·8° is 3·5 (±0·08). Results at higher temperatures indicate that these gradients decrease with increasing temperature. These findings agree with the type of mechanism suggested by Batts and Gold for the hydrolysis of acetic anhydride.[9] Bell and Critchlow have reported reaction orders for water of this magnitude for the hydration of 1,3-dichloroacetone in aqueous dioxan.[10] These were interpreted qualitatively in a similar way in terms of the number of water molecules involved in the transition state and were consistent with the cyclic transition state proposed by Eigen.[11]

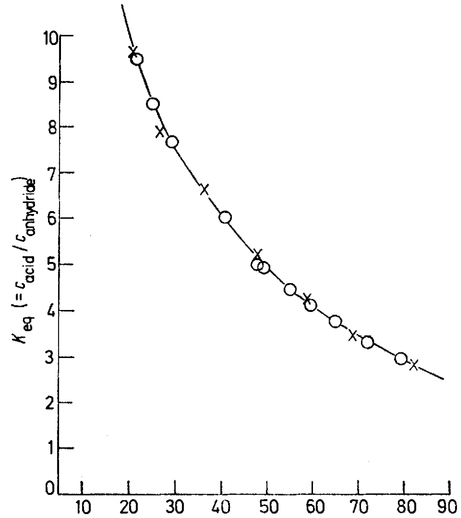
TABLE 2

Hydrolysis of 3,6-dimethylphthalic anhydride; effect of sodium perchlorate

$10^3 (k_1 + k_{-1})/s^{-1}$	$[NaClO_4]/M$
45·46	0
21·24	1·33
17·8	2·34
9·23	3·34
4·42	4·34

The entropy and enthalpy of activation for the hydrolysis of phthalic anhydride in aqueous 20% dioxan ($\Delta H^{\ddagger} = 61·9$ kJ mol^{-1}; $\Delta F^{\ddagger} = 86·6$ kJ mol^{-1}; $\Delta S^{\ddagger} = -82·4$ J mol^{-1} K^{-1}) agree well with the figures published by Bunton and his co-workers[12] for other carboxylic anhydrides which are hydrolysed by the same $A2$ mechanism as proposed for this compound.

3,6-Dimethylphthalic anhydride differs from phthalic anhydride in that it is in equilibrium with the diacid in aqueous solution. Presumably a similar equilibrium does exist in the case of phthalic anhydride (or any other carboxylic anhydride) but is too far over to the acid side to be detected spectrophotometrically. The study of such equilibria is important in the case of vicinal diacids because situations where the anhydride concentration is high, indicating a rapid cyclisation step, correspond to fast intramolecular catalysis. The proportions of 3,6-dimethylphthalic anhydride and diacid in the equilibrium mixture were determined spectrophotometrically by use of the value of the molecular extinction coefficient (3370) determined at 322 nm, which is the absorption maximum for the anhydride at a wavelength at which the diacid does not absorb. The variation of the equilibrium constant with temperature is shown in the Figure. The gradient of the straight line obtained by plotting log K_{eq} against $1/T$ gives a value of −16·78 kJ mol^{-1} for the enthalpy of reaction. There is some discrepancy between the equilibrium constant at 61·5° found in this work ($c_{acid}/c_{anhydride} = 3·96$ or *ca.* 20% anhydride) and the value of *ca.* 2 in 0·01M-hydrochloric acid, which is equivalent to about 32% anhydride in the equilibrium mixture, reported by



Hydrolysis of 3,6-dimethylphthalic anhydride; variation of equilibrium constant with temperature

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[9] B. D. Batts and V. Gold, *J. Chem. Soc.* (*A*), 1969, 984.

[10] R. P. Bell and J. E. Critchlow, *Proc. Roy. Soc.* (*A*), 1971, **325**, 35.

[11] M. Eigen, *Discuss. Faraday Soc.*, 1965, **39**, 7.

[12] C. A. Bunton, N. A. Fuller, S. G. Perry, and V. J. Shiner, *J. Chem. Soc.*, 1963, 2918.

Eberson.[3] This is apparently due to Eberson's erroneous value of the molecular extinction coefficient of the anhydride at 322 nm (ε 7000). His recently published corrected value of the equilibrium constant,[13] found by determining $(k_1 + k_{-1})$ spectrophotometrically and k_1 separately by the pH-stat method, agrees well with the value obtained in this work.

Results for the effect of temperature on $(k_1 + k_{-1})$ were used in conjunction with the equilibrium constants plotted in the Figure to calculate the separate rate constants for the forward and reverse reactions and the thermodynamic activation parameters for each (Table **3**).

TABLE 3

Hydrolysis of 3,6-dimethylphthalic anhydride; effect of temperature

T/°C	25·0	39·5	65·8
$10^3(k_1 + k_{-1})$/s^{-1}	1·127	3·666	18·74

Apparent $E_a = 57{\cdot}6$ kJ mol^{-1}; $\Delta H^{\ddagger} = 55{\cdot}1$ kJ mol^{-1}; $\Delta F^{\ddagger} = 90$ kJ mol^{-1}; $\Delta S^{\ddagger} = 116$ J mol^{-1} K^{-1}

$$\text{anhydride} + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{diacid}$$

	Forward reaction	Reverse reaction
T/°C	10^4k_1/s^{-1}	10^5k_{-1}/s^{-1}
25·0	10·09	11·8
39·5	31·4	52·2
65·8	147	400

Activation parameters at 25° from measured value of equilibrium constant at 25·0° = 8·55; $(k_1 + k_{-1}) = 1{\cdot}127 \times 10^{-3}$ s^{-1}.

	Forward reaction	Reverse reaction
$\Delta H^{\ddagger}$/kJ mol^{-1}	49·3	65·81
$\Delta F^{\ddagger}$/kJ mol^{-1}	90·16	95·48
$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}	−131	−98·86

Net changes for reaction at 25°:

$\Delta F = 90{\cdot}16 - 95{\cdot}48 = 5{\cdot}23$ kJ mol^{-1} or from $-RT\ln K_{eq}$ using the measured value of the equilibrium constant at 25°.

$\Delta H = 49{\cdot}3 - 65{\cdot}81 = -16{\cdot}51$ kJ mol^{-1} (*cf.* value from gradient of log K_{eq} *vs.* $1/T$ plot in the range 21—82·1°, $\Delta H = -16{\cdot}78$ kJ mol^{-1}).

$\Delta S = -131 - (-98{\cdot}86) = -32$ J mol^{-1} K^{-1}.

Comparison of the rate constant for the forward reaction ($1{\cdot}009 \times 10^{-3}$ s^{-1}) with the value for phthalic anhydride in aqueous solution at 25° ($7{\cdot}9 \times 10^{-3}$ s^{-1}; $E_a = 67$ kJ mol^{-1}) indicates that phthalic anhydride is hydrolysed nearly eight times faster than 3,6-dimethylphthalic anhydride. The slower hydrolysis of the latter compound has been attributed to steric hindrance to attack by the two methyl groups. However, although it is difficult to say how much of the difference is due to solvation and how much to the barrier to be surmounted at the reaction centre, the lower activation energy indicates that this is probably not so, and that the rate difference is partly due to the less favourable (more negative) entropy of reaction and to the effect of the two methyl groups in favouring the reverse or cyclisation step in the case of 3,6-dimethylphthalic anhydride. If an upper limit of, say, 0·5% is put on the proportion of anhydride in the phthalic anhydride–phthalic acid equilibrium mixture at 25°, the maximum rate of formation of the anhydride (diacid $\rightleftharpoons$ anhydride + H_2O) may be calculated from the equilibrium constant $K_{eq} = c_{\text{anhydride}}/c_{\text{diacid}} = 5 \times 10^{-3}$ and the observed first-order rate constant $(k_1 + k_{-1}) = 4{\cdot}20 \times 10^{-3}$ s^{-1}. The rate constant obtained ($2{\cdot}1 \times 10^{-5}$ s^{-1}) indicates that the ring closure step is at least six times faster in the case of 3,6-dimethylphthalic acid. Thus it appears that the driving force for the formation of the more stable anhydride in this latter compound is the relief of the steric strain caused by the two methyl groups in the anhydride as compared with the corresponding diacid.

Although the equilibrium constant value for phthalic acid is only approximate, it is of a similar magnitude to that found from the rate constant for the hydrolysis of phthalanilic acid[2] by using the log $k_{\text{succinanilic acid}}$–log K_{eq} graph published by Eberson and Welinder[13] to correlate the data for compounds which are hydrolysed by a similar cyclisation mechanism involving an anhydride–vicinal diacid equilibrium. The point plotted by using the rate constant for 3,6-dimethylphthalanilic acid[2] and the corresponding anhydride–diacid equilibrium constant also lies close to Eberson and Welinder's line.

[4/1463 *Received*, 17*th July*, 1974]

[13] L. Eberson and H. Welinder, *J. Amer. Chem. Soc.*, 1971, **93**, 5821.