Intramolecular Catalysis. Part 5.[1] The Intramolecular Cannizzaro Reaction of *o*-Phthalaldehyde and [α,α′-$^2H_2$]-*o*-Phthalaldehyde

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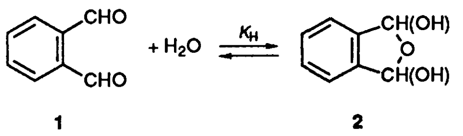
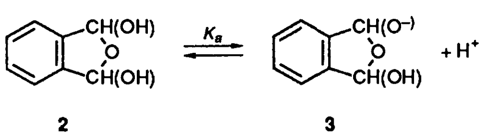
o-Phthalaldehyde, as well as the α,α′-dideuterio isomer, has been shown to undergo a Cannizzaro reaction in water containing base, while partially hydrated and ionised. The reaction of the monoanion of the hydrate is intramolecular and of the first order in the monoanion of the hydrate, and either first or zero order in the base. The rate coefficients have been measured at several temperatures and activation paramaters evaluated. The kinetic isotope effect, k_H/k_D, for the first and second order processes were found to be *ca.* 1.9 and 1.8, respectively. The alkaline hydrolysis of the corresponding lactone, phthalide, has also been studied under the same conditions. The evidence for the intramolecular Cannizzaro reaction indicates a mechanistic pathway involving rate-determining hydride transfer from the chain tautomers of both monoanion and dianion of the hydrate.

In our previous study[1] of an intramolecular Cannizzaro reaction, the disproportionation of 2,2′-biphenyldicarbaldehyde has been studied. The latter dialdehyde is not significantly hydrated in aqueous solution. However, *o*-phthalaldehyde (**1**) is extensively hydrated to form a cyclic monohydrate (**2**) in aqueous solution,[2,3] as in Scheme 1 below. The hydrate is a weak acid, ionising as in Scheme 2 below, and its acidity has been measured.[2,3]

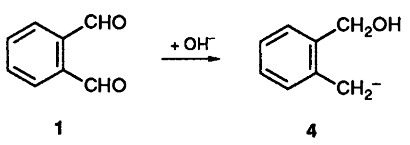


Scheme 1.



Scheme 2.

For some time *o*-phthalaldehyde has been known to undergo a Cannizzaro reaction, as in Scheme 3 below.[4] Some preliminary kinetic studies of this reaction have been made.[5] The mechanism of the intramolecular Cannizzaro reaction of phenylglyoxal, a keto aldehyde, has been investigated in some detail.[6–9] Such reactions can be considered as models for enzymic catalysis, such as those involved in reductases and glyoxalases. However, an important facet of the present and previous studies[1] is their ability to measure quantitatively the advantages of, and factors contributing to, intramolecular catalysis.



Scheme 3.

In the present study, we have made a comprehensive investigation of the Cannizzaro reaction of *o*-phthalaldehyde. The rate coefficients for the reaction, activation parameters, kinetic solvent isotope and isotope effects have been determined, and labelling studies have been carried out. The alkaline hydrolysis of a possible intermediate, phthalide, has also been investigated.

Experimental

Materials.—*o*-Phthalaldehyde was purified as described previously.[2] [α,α′-$^2H_2$]-*o*-Phthalaldehyde was prepared by the method of Barton *et al.*[10] by the reduction of *N,N,N′,N′*-tetramethylphthalamide with $LiAlD_4$. Phthalide and *o*-hydroxymethylbenzoic acid were obtained commercially and recrystallised from water to have m.p.s in good agreement with literature values. Other materials and solvents were prepared as described previously.[11]

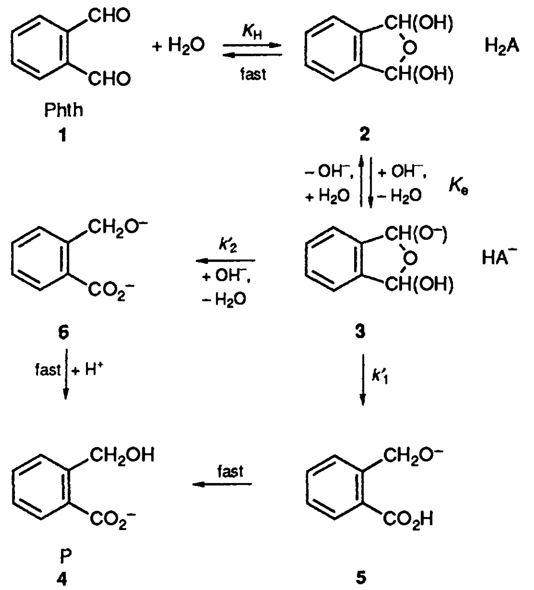
Kinetic Procedure.—The same procedures were followed as when making measurements of the hydration and ionisation.[2] The reactions were followed using a Unicam SP8000 spectrophotometer and the cell temperature was controlled to ± 0.05 °C by means of a Churchill thermocirculator. The Cannizzaro reaction was monitored at 265 nm and the alkaline hydrolysis at 324 nm. The substrate concentrations were about 5×10^{-5} mol dm^{-3}. Both reactions gave, as the product, the anion of *o*-hydroxymethylbenzoic acid quantitatively. This was confirmed by spectral comparison of the products of the two reactions with *o*-hydroxymethylbenzoic acid under identical basic conditions. The lactone, phthalide, was also isolated from the Cannizzaro reaction or re-isolated from the alkaline hydrolysis in quantitative yield after acidification to pH 1 and standing for 4 h at 25 °C. Studies of the Cannizzaro reaction of *o*-phthalaldehyde in D_2O and [α,α′-$^2H_2$]-*o*-phthalaldehyde in water gave phthalide which showed no significant incorporation of the solvent isotope. Both the Cannizzaro and alkaline hydrolysis reactions were first-order in substrate. The absorbance after ten half-lives was assumed to be the final reading and the rate plots were linear to 80% reaction. The first-order rate coefficients were determined from the slopes which were calculated by a least-squares method. The alkaline hydrolysis of the lactone was also first-order in hydroxide anion, with the base concentration being in the range 1×10^{-3}–1×10^{-1} mol dm^{-3}. The reaction of *o*-phthalaldehyde involves hydration and ionisation, as well as the Cannizzaro reaction

Table 1. Equilibrium constants for hydration (K_H) and for ionisation (K_e) of *o*-phthalaldehyde in water (μ = 1.0 mol dm^{-3}) (extrapolated from data in ref. 2)[a]

T/°C	K_H	K_e/dm^3 mol^{-1}
55.0	1.26	92.1
60.0	1.01	88.9
70.0	0.670	83.2
75.0	0.550 (0.797)[b]	80.6 (73.5)[b]

[a] See the text. [b] $pK_a^D - pK_a^H$ equals 0.04 and K_H/K_D equals 0.69 at 25 °C.

itself. The rates of the Cannizzaro reaction were measured at 55.0, 60.0, 70.0 and 75.0 °C. At these temperatures the rates of reaction were conveniently rapid at hydroxide anion concentrations of 0.2 mol dm^{-3} and below. This avoided any uncertain activity corrections for high concentrations of base. The reactions were conducted at constant ionic strength (μ = 1.0 mol dm^{-3}), using sodium chloride to maintain the ionic strength. In Table 1 are shown the equilibrium constants for hydration, K_H, and for ionisation, K_e, extrapolated from the results in our previous study.[2] The pK_a and K_H for [α,α'-$^2H_2$]-*o*-phthalaldehyde were determined in the same manner as that described previously for the unlabelled dialdehyde.[2]



Scheme 4.

A purely kinetic scheme is shown in Scheme 4. The equilibrium constant for hydration, K_H, for *o*-phthalaldehyde is defined by eqn. (1)

$$K_H = [\text{Hydrate}]/[\text{Aldehyde}] \quad \text{or } [H_2A]/[\text{Phth}] \qquad (1)$$

The hydrate of *o*-phthalaldehyde can ionise in base as shown below (neglecting solvation and assuming the second ionisation is negligible under the conditions) in eqn. (2).

$$H_2A \rightleftharpoons H^+ + HA^- \qquad (2)$$

$$pK_a = pH + \log[H_2A]/[HA^-] \qquad (3)$$

$$pH = pK_w - pOH \qquad (4)$$

Eqns. (3) and (4) are obeyed up to a pOH of *ca.* 10, when eqn. (5)

$$pH = pK_w - pOH + \log f^{\pm} \qquad (5)$$

is required using the activity coefficient $f^{\pm}$.[12] The measurements in this study were made at a constant ionic strength (μ = 1.0 mol dm^{-3}). An equilibrium constant, K_e, for the ionisation of the hydrate can be defined in eqn. (6) below to give eqn. (7).

$$H_2A + OH^- \overset{K_e}{\rightleftharpoons} HA^- + H_2O \qquad (6)$$

Using eqn. (7) for K_e, eqn. (8) can be obtained by substitution.

$$K_e = [HA^-]/[H_2A][OH^-] \qquad (7)$$

$$K_e = K_a/K_w \qquad (8)$$

The rate of appearance of product is given by eqn. (9).

$$\frac{\partial P}{\partial t} = k_1[HA^-] + k_2[HA^-][OH^-] = [HA^-](k_1 + k_2[OH^-]) \qquad (9)$$

The total *o*-phthalaldehyde, $[\text{Phth}]_T$, is given by eqn. (10), which can be converted into the eqn. (11).

$$[\text{Phth}]_T = [\text{Phth}] + [H_2A] + [HA^-] \qquad (10)$$

$$[\text{Phth}]_T = \frac{[H_2A]}{K_H} + \frac{[HA^-]}{K_e[OH^-]} + [HA^-] = \frac{[HA^-](1 + K_H + K_HK_e[OH^-])}{K_HK_e[OH^-]} \qquad (11)$$

The rate of disappearance of total *o*-phthalaldehyde is equal to the rate of appearance of product as shown in eqn. (12).

$$\frac{\partial P}{\partial t} = \frac{-\partial[\text{Phth}]_T}{\partial t} \qquad (12)$$

Combining eqns. (9), (11) and (12) gives eqn. (13). This reduces to the expression for k_{obs} as shown in eqn. (14) below. The fraction, f, can be defined as in eqn. (15) and is given in eqn. (16) below.

$$-\frac{1}{[\text{Phth}]_T}\cdot\frac{\partial[\text{Phth}]_T}{\partial t} = \frac{K_HK_e[OH^-]}{1 + K_H + K_HK_e[OH^-]}(k_1 + k_2[OH^-]) \qquad (13)$$

$$k_{obs} = \frac{K_HK_e[OH^-]}{1 + K_H + K_HK_e[OH^-]}\cdot(k_1 + k_2[OH^-]) \qquad (14)$$

$$k_{obs} = f(k_1 + k_2[OH^-]) \qquad (15)$$

$$f = \frac{K_HK_e[OH^-]}{1 + K_H + K_HK_e[OH^-]} \qquad (16)$$

Extrapolated values of K_H and K_e are shown in Table 1 for the temperatures at which the kinetic studies were made. Eqn. (17) was fitted by a standard least-squares treatment giving an

$$k_{obs}/f = k_1 + k_2[OH^-] \qquad (17)$$

intercept equal to k_1 and slope equal to k_2. Table 2 shows a typical set of results for the rate coefficients at 70.0 °C in water at constant ionic strength (μ = 1.0 mol dm^{-3}). Eqn. (18) was

Table 2. Rate coefficients (k_{obs}) for the Cannizzaro reaction of *o*-phthalaldehyde at 70.0 °C in water (μ = 1.0)[a]

$[OH^-]$/mol dm^{-3}	$k_{obs}/10^{-4}$ s^{-1}	f	$(k_{obs}/f)/10^{-4}$ s^{-1}
0.01	1.07	0.213	5.03
0.02	2.96	0.351	8.42
0.035	6.51	0.487	13.4
0.05	10.0	0.575	17.5
0.1	24.6	0.730	33.7
0.2	42.3	0.844	50.1

[a] Values of k_{obs} are reproducible to within ±4%.

Table 3. Rate coefficients (k_1 and k_2) for the Cannizzaro reaction of *o*-phthalaldehyde in water at constant ionic strength (μ = 1.0 mol dm^{-3}).[a]

T/°C	$k_1/10^{-4}$ s^{-1}	$k_2/10^{-3}$ dm^3 mol^{-1} s^{-1}
55.0	1.66 (±0.32)	5.76 (±0.08)
60.0	2.38 (±0.30)	9.87 (±0.30)
70.0	5.89 (±0.21)	23.1 (±2.0)
75.0	7.51 (±0.20)	35.6 (±2.0)
[75.0	3.90 (±0.16)	19.7 (±0.8)][b]

[a] Standard deviations are shown in parentheses using the six concentrations of base shown in Table 2. [b] [α,α'-$^2H_2$]-*o*-Phthalaldehyde.

Table 4. Rate coefficients (k_2) for the alkaline hydrolysis of phthalide in water at constant ionic strength (μ = 1.0 mol dm^{-3}).[a]

T/°C	k_2/dm^3 mol^{-1} s^{-1}
25.0	0.176
35.0	0.345
45.0	0.646
55.0	1.22

[a] Rate coefficients are reproducible to within ±3%.

Table 5. Activation parameters for the intramolecular Cannizzaro reaction of *o*-phthalaldehyde in water at 30.0 °C at constant ionic strength (μ = 1.0 mol dm^{-3}).[a]

	$\Delta H^‡$/kcal mol^{-1} [c]	$\Delta S^‡$/cal mol^{-1} K^{-1} [c]
k_1	17 200 (±1100)	−24 (±3)
k_2	19 800 (±500)	−9 (±2)
[k_2	19 900 (±200)	−22 (±1)][b]

[a] Standard deviations are shown in parentheses. [b] Alkaline hydrolysis of phthalide. [c] 1 cal = 4.184 J.

obtained from these results, with a correlation coefficient of 0.987 and the uncertainties shown in parentheses.

$$k_{obs}/f = 5.89\,(\pm 0.21) + 23.1\,(\pm 2.0)[OH^-] \qquad (18)$$

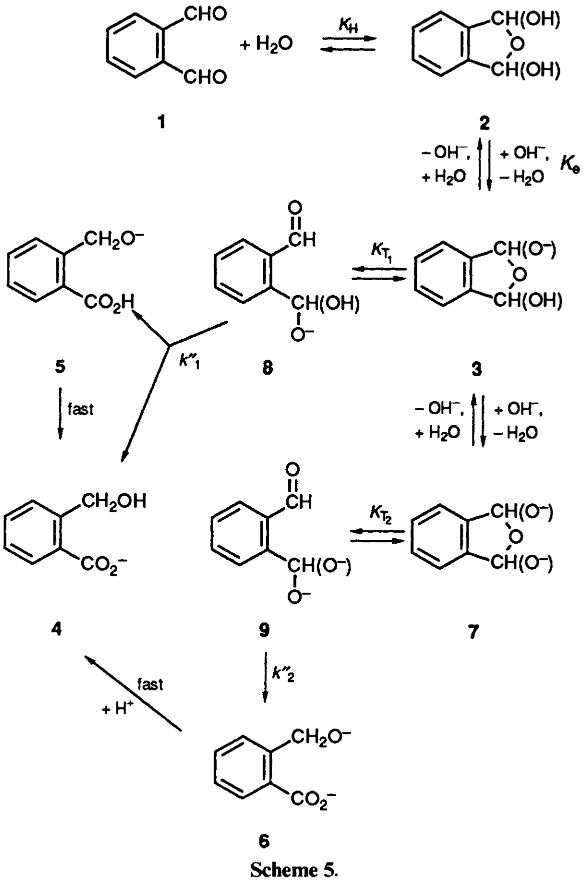
The values of k_1 and k_2 in water are shown in Table 3 for 55.0, 60.0, 70.0 and 75.0 °C. The rate coefficients for the alkaline hydrolysis of phthalide under the same conditions are shown in Table 4 for 25.0, 35.0, 45.0 and 55.0 °C. Table 5 shows the activation parameters for both reactions at 30.0 °C.

Results and Discussion

The product of the Cannizzaro reaction of *o*-phthalaldehyde is the anion of *o*-hydroxymethylbenzoic acid **4**. The reaction has been shown to be completely intramolecular by conducting the reaction of the dialdehyde in D_2O and the [α,α'-$^2H_2$] dialdehyde in H_2O to give no significant incorporation of the solvent isotope in the product. The reaction is first order in substrate (as the anion) and either zero or first order in base. Thus two routes to product exist, *i.e.* through the monoanion and the dianion. The kinetic isotope effect, k_H/k_D, for k_1 is *ca.* 1.9 and for k_2 *ca.* 1.8. Not only are these values similar to each other, but they are close to the values observed for other Cannizzaro reactions, both intramolecular[1,15] and intermolecular.[14,15] This ratio appears to be comparatively insensitive to the nature of the Cannizzaro reaction in terms of molecularity, *i.e.* uni or bi, inter or intra. While these values are similar to those found in other hydride transfer reactions[16] when corrected for a reverse contribution from secondary effects,[1] those predicted by theoretical studies are larger.[17]

The effect of the order in base and the activation parameters do have interesting implications for the Cannizzaro reaction of *o*-phthalaldehyde. At low base concentrations, the process described by k_1 predominates (at 75 °C and 0.01 mol dm^{-3} base, nearly 70%); while at high base concentrations of reaction, the process described by k_2 predominates (at 75 °C and 0.2 mol dm^{-3} base *ca.* 90% reaction). As the temperature decreases, the importance of the process described by k_2 decreases. This balance between k_1 and k_2, which will vary from substrate to substrate and from intermolecular to intramolecular reaction, gives rise to the observed switches in kinetic dependence on base observed for the Cannizzaro reaction.[18]

The activation parameters for the process described by k_1 are indicative of a bimolecular reaction and $\Delta S^‡$ value of −24 cal mol^{-1} K^{-1} denotes a molecule of water involved intimately in the transition state. Those for the reaction described by k_2 are sensible for a bimolecular process. Both the latter processes are separate here from the ionisation and hydration. They cannot be compared directly with those for the reaction of 2,2′-



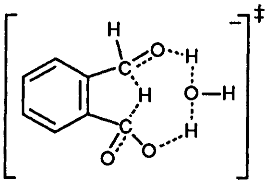
Scheme 5.

biphenyldicarbaldehyde[1] which is termolecular. However, it is possible to compare the latter to the k_2 process, if the hydration and ionisation process are allowed for in calculating the overall entropy and enthalpy terms. Unfortunately, the uncertainties are then rather large.

Lactone Hydrolysis.—The rate coefficients for the alkaline hydrolysis of phthalide are shown in Table 4 and compare closely to those previously measured in water,[19] as do the activation parameters shown in Table 5. Phthalide is more rapidly hydrolysed by base than the ε-lactone of 2′-(hydroxymethyl)biphenyl-2-carboxylic acid by a factor of *ca.* two at 25 °C, allowing for the solvent difference.[1,20] The relationship between ring-size and reactivity in lactones,[21] as well as in the related pseudo-esters,[22] is more complex than was originally believed.[23]

The important conclusion from the study of the hydrolysis of phthalide is that, if the lactone were formed as an intermediate in the Cannizzaro reaction under study, it would not accumulate and could not be directly determined. However, our other studies,[1,13] using direct determinations, and those of Swain *et al.*,[18] using isotope dilution, indicate that these types of intermediate do not occur in closely related reactions.

Proposed Mechanism for the Intramolecular Cannizzaro Reaction.—The suggested mechanistic pathway for the intramolecular Cannizzaro reaction of *o*-phthalaldehyde is shown in Scheme 2. The obvious drive for hydride transfer in the chain monoanion **8** and dianion **9** makes reaction *via* these tautomers more attractive. Both the suggested transition states, **10** and **11** for the rate determining steps k_1 and k_2, respectively, involve five-membered rings which will be 'strained.'



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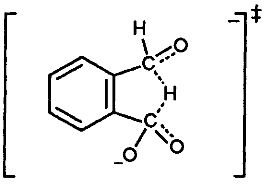

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Paper 0/01353F
Received 29*th March* 1990
Accepted 15*th August* 1990