The Kinetics and Mechanism of the Hydrolysis of 2,3-(Phenylmethylenedioxy)benzoic Acid (*OO'*-Benzylidene-2,3-dihydroxybenzoic Acid)

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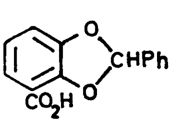
The hydrolysis of *OO'*-benzylidene-2,3-dihydroxybenzoic acid is considerably faster than that of *OO'*-benzylidene-3,4-dihydroxybenzoic acid and *OO'*-benzylidenecatechol. The pH-rate profile is of the form: $k_{obs} = k_1/(1 + K_a/10^{-pH})$. The high rate is associated with the k_1-term which probably arises from intramolecular general-acid catalysis. This kinetic parameters of this reaction are compared with those for the formally analogous intermolecularly general-acid catalysed hydrolysis of benzylidenecatechol. *OO'*-Benzylidene-2,3-dihydroxybenzoic acid is not intramolecularly hydrogen bonded in dilute solutions in carbon tetrachloride.

It has been shown that *o*-carboxyphenyl acetals and glycosides are hydrolysed at enhanced rates as a result of either intramolecular general-acid catalysis or electrostatic stabilisation of the transition state for the specific-acid-catalysed hydrolysis of the ionised form.[1-6] Mechanisms in which the carboxy-group acts as an intramolecular nucleophilic catalyst have been excluded for the hydrolysis of *o*-methoxymethoxybenzoic acid,[2,3] and we now provide additional evidence against the occurrence of such mechanisms. Intramolecular nucleophilic attack by the carboxy-group on the acetal-carbon atom of *OO'*-benzylidene-2,3-dihydroxybenzoic acid (I) is not possible and yet the kinetics of its hydrolysis are very similar to those for other *o*-carboxyphenyl acetals. The variation of k_{obs} with pH at 55° follows equation (1) with $k_1 = 4{\cdot}98 \times 10^{-3}$ s^{-1}, $k_2 = 8{\cdot}11 \times 10^{-3}$ l mol^{-1} s^{-1} and $K_a = 1{\cdot}11 \times 10^{-4}$ mol l^{-1} (Table 1).

$$k_{obs}[\text{Total substrate}] = k_1[\text{un-ionised form}] + k_2[\text{un-ionised form}] \times 10^{-pH} \quad (1)$$

The least-squares fit of the experimental data does not define the value of k_2 accurately as it only makes a minor contribution to the total rate in the pH range studied and a more accurate value is obtained from the values of k_{obs} in 0·10 and 1·00M-hydrochloric acid, $7{\cdot}40 \times 10^{-3}$ l mol^{-1} s^{-1}. This is the second-order constant for the hydronium-ion catalysed hydrolysis of the un-ionised form and it is slightly larger than the second-order constants for the hydronium-ion catalysed hydrolysis of *OO'*-benzylidenecatechol (II) and *OO'*-benzylidene-3,4-dihydroxybenzoic acid (III) which have values $6{\cdot}56 \times 10^{-3}$ and $2{\cdot}02 \times 10^{-3}$ l mol^{-1} s^{-1} respectively at 55°.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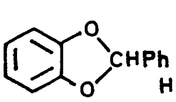
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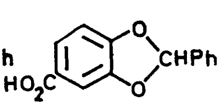
(III)

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[2] B. Capon and M. C. Smith, *Chem. Comm.*, 1965, 523.

[3] B. Capon, M. C. Smith, E. Anderson, R. H. Dahm, and G. H. Sankey, *J. Chem. Soc.* (*B*), 1969, 1038.

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[5] D. Piszkiewicz and T. C. Bruice, *J. Amer. Chem. Soc.*, 1968, **90**, 2156.

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If the term k_1 arose from a hydronium-ion-catalysed hydrolysis of the ionised form, the second-order constant for this process, $k_2^*(= k_1/K_a)$, would be 44·9 l mol^{-1} s^{-1} which is 6000 times greater than k_2. The corresponding factor for 2-carboxyphenyl β-D-glucoside is 1000 and for 2-methoxymethoxybenzoic acid 250.[3] The intramolecular catalysis or electrostatic stabilisation occurring in the hydrolysis of *OO'*-benzylidene-2,3-dihydroxybenzoic acid (I) is therefore more effective than found in the hydrolyses of these other compounds. Possibly this is connected with the fact that the hydrolysis of *OO'*-benzylidenecatechol (II)[7] and *OO'*-benzylidene-3,4-dihydroxybenzoic acid (III) (Table 3) are themselves intermolecularly general-acid catalysed. Opening of the benzodioxolan ring is sensitive to general-acid catalysis and hence it would not be surprising if intramolecular catalysis were more effective than in reactions of those classes of compounds which do not react with intermolecular general-acid catalysis.

TABLE 1

The kinetics of hydrolysis of benzylidene-2,3-dihydroxybenzoic acid at 55·0° (I = 0·10M)

Buffer	pH	10^3k_{obs}(s^{-1})	10^3k_{calc}(s^{-1}) [a]
1·00-M HCl	—	12·0	—
0·10-M HCl	1·29	5·39, 5·38	5·38
0·01-M HCl	2·21	4·87, 4·99	4·94
$ClCH_2CO_2H$	2·63	4·70, 4·75	4·71
,,	3·07	4·14, 4·60	4·41
HCO_2H	3·34	4·00, 4·10	4·00
,,	3·65	3·31, 3·35	3·33
,,	3·88	2·86, 3·00	2·71
,,	4·05	2·24, 2·30	2·21
CH_3CO_2H	4·45	1·28	1·21
,,	5·05	0·248, 0·300	0·37
,,	5·31	0·182, 0·179	0·21
,,	5·35	0·154, 0·161	0·19
$HO_2CCH_2CO_2H$	5·83	0·0529	0·065

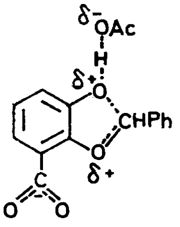
[a] Calculated from the expression $k_{calc} = k_1/(1 + K_a/10^{-pH}) + k_2 \times 10^{-pH}/(1 + K_a/10^{-pH})$ with $k_1 = 4·98 \times 10^{-3}$ s^{-1} (s.d. = 1·9%), $k_2 = 8·11 \times 10^{-3}$ l mol^{-1} s^{-1} (s.d. 45%), and $K_a = 1·11 \times 10^{-4}$ mol l^{-1} (s.d. 5·8%). The value of k_2 is not well defined as it only makes a small contribution to the total rate in the pH range studied. K_a was determined independently as $1·05 \times 10^{-4}$ mol l^{-1}.

There is no detectable buffer catalysis in the hydrolysis of *OO'*-benzylidene-2,3-dihydroxybenzoic acid (I) in acetate buffer pH 4·08 (Table 2) and this may be further indication that the high rate results from intramolecular catalysis rather than a hydronium ion-catalysed reaction of the ionised form. Clearly intramolecular general-acid catalysis are mutually exclusive and hence intermolecular catalysis would not be expected if the reaction involved intramolecular general-acid catalysis. On the other hand an intermolecularly general-acid catalysed hydrolysis of the ionised form is formally possible with transition state (IV) or (V). If the k_1 term in the rate law arises from a specific-acid catalysed hydrolysis of the ionised form the electrostatic stabilisation provided by the carboxylate group in the transition state (VI) or (VII) must be much greater than in the transition state (IV) or (V).

TABLE 2

Test for buffer catalysis in the hydrolysis of benzylidene-2,3-dihydroxybenzoic acid at 55·0° (I = 0·50M)

[AcOH]	[AcO$^-$]	pH	10^3k_{obs}(s^{-1})
0·080	0·020	4·09	1·85
0·160	0·040	4·07	1·83
0·240	0·060	4·08	1·87
0·320	0·080	4·07	1·83
0·400	0·100	4·09	1·95



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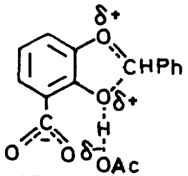

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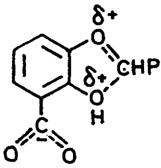

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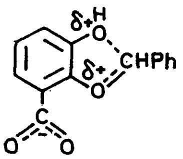

(VII)

The hydrolysis of *OO'*-benzylidene-3,4-dihydroxybenzoic acid (III) shows buffer catalysis (Table 3) and the rate constants extrapolated to zero buffer concentration level off at high pH values (Table 4) indicating a water-catalysed or spontaneous hydrolysis similar to

TABLE 3

The kinetics of hydrolysis of benzylidene-3,4-dihydroxybenzoic acid in acetate and formate buffers at 55·0° (I = 0·50M) [a]

pH 3·07 [HCO_2Na] = [HCO_2H]/5

[HCO_2H] (M)	0·083	0·168	0·249
10^5k_{obs} (s^{-1})	2·04	2·38	2·68
10^5k_{calc} (s^{-1})	2·05	2·37	2·69

Slope = $3·86 \times 10^{-5}$ l mol^{-1} s^{-1}, s.d. 3·6%. Intercept = $1·73 \times 10^{-5}$ s^{-1}, s.d. 1·4%. r = 0·999

pH 4·06 [AcONa] = [AcOH]/4

[AcOH] (M)	0·080	0·160	0·240	0·320
10^5k_{obs} (s^{-1})	1·13	1·24	1·32	1·42
10^5k_{calc} (s^{-1})	1·14	1·23	1·33	1·42

Slope = $1·19 \times 10^{-5}$ l mol^{-1} s^{-1}, s.d. 4·1%. Intercept = $1·04 \times 10^{-5}$ s^{-1}, s.d. 1·01%, r = 0·998

[a] Ionic strength maintained constant with sodium chloride.

TABLE 4

The pH-dependence of the rate of hydrolysis of benzylidene-3,4-dihydroxybenzoic acid at 55·0° (I = 0·50M)

Buffer	pH	10^5k_{obs} or 10^5k_{int} (s^{-1})
1·00M-HCl [a]	0·08	198, 196
0·10M-HCl	1·17	15·9, 15·6
0·010M-HCl	2·11	2·94, 2·95
Formate	3·08	1·72
Acetate	4·06	1·04

[a] I = 1·00 M.

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[7] B. Capon and M. I. Page, preceding paper.

that found with benzylidenecatechol.[7] At pH 3·0 k_{obs} for the hydrolysis of *OO'*-benzylidene-2,3-dihydroxybenzoic acid is *ca.* 300 times greater than for the 3,4-isomer.

TABLE 5

Solvent isotope effect for the hydrolysis of benzylidene-2,3-dihydroxybenzoic acid at 55·0° (I = 0·10M)

Medium	pH or pD [a]	10^3k_{obs}	$k(H_2O)/k(D_2O)$ [b]
0·0103M-HCl	2·11	5·20, 5·21	1·28
0·0103M-DCl	2·02	4·08, 4·07, 4·10	

[a] Meter reading +0·40. [b] Under these conditions the term in k_1 contributes more than 98% to the total rate.

As the hydrolysis of *OO'*-benzylidenecatechol is itself intermolecularly general-acid catalysed[7] it is possible to compare the hydrolysis of *OO'*-benzylidene-2,3-dihydroxybenzoic acid (I) with an apparently analogous intermolecular reaction. The ratio of k_1 to the second-order constant for the hydrolysis of *OO'*-benzylidenecatechol catalysed by a hypothetical acid of pK_a 4·1 is *ca.* 100 mol l^{-1}. The intramolecular catalysis provided by the carboxy-group of *OO'*-benzylidene-2,3-dihydroxybenzoic acid is therefore equivalent to intermolecular catalysis by an acid of the same pK_a at a concentration 100 mol l^{-1}. The solvent isotope for the intramolecularly-catalysed reaction is $k(H_2O)/k(D_2O)$ = 1·28 (Table 5) which is similar to that for the acetic-acid catalysed hydrolysis of benzylidenecatechol, $k(AcOH)/k(AcOD)$ = 1·4—1·5.[7] The entropy of activation for the formic-acid catalysed hydrolysis of benzylidenecatechol (II) is −34·8 cal deg^{-1} mol^{-1} at 65° (standard state 1M) whereas that for hydrolysis of *OO'*-benzylidene-2,3-dihydroxybenzoic acid is −12·8 cal deg^{-1} mol^{-1} at 65°. The much more negative entropy of activation for the intermolecular reaction must arise mainly from the loss of three degrees of translational freedom and three degrees of rotational freedom on formation of the transition state. It has long been recognised[8,9] that bimolecular reactions in the gas phase are disfavoured relative to analogous unimolecular reactions through loss of these degrees of freedom on formation of the transition state but as has recently been pointed out this is also important for reactions in solution.[9,10] The enthalpy of activation of the intramolecular reaction is *ca.* 4 kcal mol^{-1} greater than for the intermolecular reaction. Possibly there is some difficulty in achieving the best geometry for proton transfer in the intramolecular reaction. If so it is interesting that the isotope effects are so similar for the two reactions.

TABLE 6

The temperature-dependence of the rate of hydrolysis of *OO'*-benzylidene-2,3-dihydroxybenzoic acid in 0·01M-hydrochloric acid (I = 0·05M) [a,b]

Temperature (°C)	65·20	55·12	45·61	35·06	25·44
10^4k_{obs} (s^{-1})	124, 123, 124	5·23, 5·25, 5·19	2·01, 2·02, 1·99	7·67, 7·70, 7·69	2·73, 2·76, 2·76

[a] Under these conditions less than 1% of the reaction arises from the k_2-term of equation (1) at 55°. [b] The logarithms of k_{obs} were plotted against the reaprocals of the absolute temperature to yield a value for E_a = 19,165 cal deg^{-1} mol^{-1} (s.d. 0·61%) from which the following values of the activation parameters were calculated $\Delta H^{\ddagger}$ = 18,493 cal mol^{-1} (s.d. 120 cal mol^{-1}) $\Delta S^{\ddagger}$ = −12·83 cal deg^{-1} mol^{-1} (s.d. 0·30 cal deg^{-1} mol^{-1}) at 65·20°.

TABLE 7

Hydrogen-bonding studies on *OO'*-benzylidene-2,3-dihydroxybenzoic acid and related compounds by i.r. spectroscopy

Compound	Solvent	Concentration (M)	$\gamma_{C=O}$ (cm^{-1})	γ_{HO} (cm^{-1})
OO'-Benzylidene-2,3-dihydroxybenzoic acid	CCl_4	0·084	1697, 1740 (sh. 1763)	3533 (sh. 3510)
		0·003	*a*	
OO'-Benzylidene-2,3-dihydroxybenzoic acid	$CHCl_3$	0·016	1700, 1735	3520 (asymm.)
		0·003	*a*	
OO'-Methylene-2,3-dihydroxybenzoic acid	CCl_4	satd. <0·002M	1705, 1736	3540
OO'-Benzylidene-3,4-dihydroxybenzoic acid	CCl_4	satd.	1742, 1695	3551
OO'-Benzylidene-3,4-dihydroxybenzoic acid	$CHCl_3$	0·015	1730, 1693	3529
		0·003	*a*	
o-Methoxybenzoic acid	CCl_4	0·003	1710(w), 1750(s)	3366(s), 3533(w)

[a] Intensity of monomer peak at high wave numbers increase relative to that at low wave numbers on dilution.

In contrast to 2-methoxymethoxybenzoic acid[3] *OO'*-benzylidene-2,3-dihydroxybenzoic acid is not intramolecularly hydrogen bonded in carbon tetrachloride or chloroform solution. The i.r. spectra of dilute solutions show maxima only at 3533 and 3520 cm^{-1} characteristic of non-bonded hydroxy-group. Similar behaviour is shown by *OO'*-methylene-2,3-dihydroxybenzoic acid (see Table 7). The failure of these compounds to form intramolecular hydrogen bonds may be because of an unfavourable geometry or because the oxygens of the benzodioxolan ring are less basic than those of *o*-methoxymethoxybenzoic acid and *o*-methoxybenzoic acid. If the latter is correct the high sensitivity of *OO'*-benzylidenecatechol to general acid catalysis (α = 0·49)[7] may be associated with the low basicity of the oxygens.[11]

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[8] *Cf.* A. A. Frost and R. G. Pearson, 'Kinetics and Mechanisms,' John Wiley, New York, 2nd edn., 1961, pp. 92—93; K. Wiberg, 'Physical Organic Chemistry,' John Wiley, New York, 1964, p. 221.

[9] B. Capon, Essays in Chemistry, in the press (submitted June, 1970); B. Capon, *J. Chem. Soc.* (*B*), 1971, 1207.

[10] M. I. Page and W. P. Jencks, *Proc. Nat. Acad. Sci.*, 1971, **68**, 1678.

[11] *Cf.* E. Anderson and B. Capon, *J. Chem. Soc.* (*B*), 1969, 1033.

EXPERIMENTAL

2,3-(*Phenylmethylenedioxy*)*benzoic Acid* (*OO'-Benzylidene-2,3-dihydroxybenzoic Acid*).—A solution of methyl 2,4-hydroxybenzoate (m.p. 79—80°, 20 mmol) and benzylidene chloride (29 mmol) in pyridine (20 ml) was heated under reflux for 12 h in an atmosphere of nitrogen. The pyridine was evaporated and the residue was taken up in methylene chloride; the solution was washed with water, dilute hydrochloric acid, sodium hydroxide, and water. The methylene chloride was evaporated under reduced pressure and the residue was distilled using a diffusion pump (bath temperature 180°); yield 60% (Found: C, 70·4; H, 4·6. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%); δ (CCl_4) 3·95 (s, 3), 6·85 (m, 2), 7·0 (s, 1), and 7·38 p.p.m. (m, 6). The methyl ester was hydrolysed by shaking it with 2 equivalents of 0·1M-sodium hydroxide for 2 weeks at room temperature. Unchanged material was extracted with chloroform and the aqueous phase was carefully acidified to pH 3 with ice-cold 0·1M-hydrochloric acid in the presence of chloroform. The aqueous phase was extracted three more times with chloroform and the combined extracts were washed with water, dried, and evaporated. The residue was recrystallised twice from benzene, m.p. 179—181·5° (Found: C, 62·3; H, 4·1. $C_{14}H_{10}O_4$ requires C, 69·4; H, 4·2%). The n.m.r. spectrum in [$^2H_6$]dimethyl sulphoxide consists of a singlet at δ 7·33 p.p.m. (acetal proton) and a broad singlet at δ 7·55 p.p.m. (phenyl proton) which are overlapped by a multiplet arising from the other aromatic protons; mass spec. parent 242, 241, 198, 197, and 165.

3,4-(*Phenylmethylenedioxy*)*benzoic Acid* (OO'-*Benzylidene-3,4-dihydroxybenzoic Acid*).—Methyl 3,4-dihydroxybenzoic acid (m.p. 133°) was allowed to react with benzylidene chloride as described for the 2,3-derivative to give methyl *OO'*-benzylidene-3,4-dihydroxybenzoate; yield 40% (Found: C, 70·5; H, 4·55%); δ (CCl_4) 3·77 (s, 3), 6·73 (d, *J* 8·5 Hz, 1), 6·95 (s, 1), and 7·4 p.p.m. (m, 7). This ester (1·4 mol) was dissolved in dimethyl sulphoxide (50 ml), sodium hydroxide (35 mmol) in water (10 ml) was added to the mixture which was then shaken for 12h at room temperature. The solution was carefully acidified with dilute hydrochloric acid and extracted with chloroform. The residue obtained after evaporation was recrystallised twice from benzene; m.p. 179·5—181° (mixed m.p. with 2,3-compound *ca.* 160°) (Found: C, 69·3; H, 4·14); δ 7·10 (d, *J* 8 Hz, 1), 7·37 (s, 1), and 7·58 p.p.m. (m, 8).

Kinetic Measurements.—These were carried out as described in the preceding paper.[7] The variation of k_{obs} with pH for the hydrolysis of *OO'*-benzylidene-2,3-dihydroxybenzoic acid was fitted to equation (1) using the form of this equation given in Table 1 by a generalised least-squares method.[12,13] The standard deviations were calculated by the method of Deming,[12] *i.e.* using σ_{ext} rather than that of Wentworth [13] using σ_0.

Hydrogen Bonding Studies.—I.r. measurements were carried out on a Unicam SP 100 spectrophotometer. We thank Mrs. F. Lawrie for these measurements.

We thank the S.R.C. for a studentship.

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[12] W. E. Deming, 'Statistical Adjustment of Data,' Dover Publications, Inc., New York, 1964.

[13] W. E. Wentworth, *J. Chem. Educ.*, 1965, **42**, 96, 162.