Intramolecular Nucleophilic Assistance in the Reactions of *OO'*-Benzylidenecatechols

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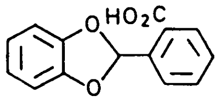
3-(2-Hydroxyphenoxy)phthalide is an intermediate in the hydrolysis of *OO'*-(2-carboxybenzylidene)catechol in aqueous buffers of pH 2·9—5. This reaction is general acid catalysed by carboxylic acids and also occurs spontaneously in a reaction which probably involves water as a general acid catalyst. The catalytic constants for the reactions catalysed by acetic and formic acids are similar to those of the analogously catalysed hydrolyses of *OO'*-(4-carboxybenzylidene)catechol. but the catalytic constant for the spontaneous reaction is *ca.* 30 times greater than that for spontaneous hydrolysis of the latter compound. This is attributed to nucleophilic assistance in reaction of *OO'*-(2-carboxybenzylidene)catechol. In the pH range 2—5. 2.3-*OO'*-(2-carboxybenzylidene)-2,3-dihydroxybenzoic acid is converted into 3-(3-carboxy-2-hydroxyphenoxy)phthalide. The pH-rate profile is bell-shaped but at the maximum the reaction occurs only *ca.* three times faster than the hydrolysis of 2.3-*OO'*-(4-carboxybenzylidene)-2.3-dihydroxybenzoic acid. The neighbouring carboxylate group of the aldehyde moiety of this acid does not provide appreciable anchimeric assistance in the intramolecularly catalysed opening of the dioxolan ring.

ALTHOUGH several examples of nucleophilic assistance to fission of an acetal or glycosidic bond have been reported[1-4] the occurrence of nucleophilic assistance concerted with general acid catalysis has been less well established.[5] In view of the sensitivity of the *OO'*-benzylidenecatechol system to both inter- and intramolecular catalysis[6,7] we have investigated the hydrolysis of acetals (I) and (IV) both of which have a carboxy-group suitably situated to carry out nucleophilic attack on the acetal carbon atom. The initial products of such attacks would be the acylals (II) and (V) and these are prepared easily by sublimation of (I) and (IV).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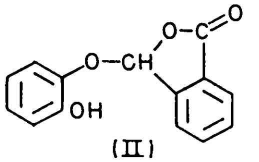
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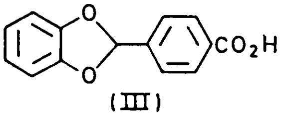
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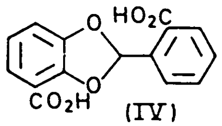
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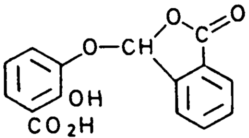
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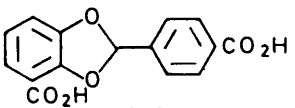
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RESULTS AND DISCUSSION

OO'-(2-Carboxybenzylidene)catechol (I).—The kinetics of hydrolysis of this compound were studied spectrophotometrically at 65° in buffers of ionic strength 0·5M. At pH 2·9, 3·4, and 4·0 reaction proceeds *via* the acylal (II) which is hydrolysed more slowly than it is formed under these conditions. This was shown by repetitively scanning the u.v. spectrum of the reaction mixture. Also at pH 3·55 the reaction mixture was extracted before hydrolysis was complete and the presence of the acylal (II) was shown by its characteristic bands in the i.r. spectrum (see Experimental section). At pH 4·9 the change in u.v. spectrum again shows the intermediacy of the acylal (II) but the rate of disappearance of the acetal (I) is similar to the rate of hydrolysis of the acylal. The final spectra of the acylal and acetal hydrolyses corresponds exactly to that of the expected products, catechol and phthalaldehydic acid, under all these conditions. At pH 5·7 and 7·3 and in 0·1M-sodium hydroxide the acylal is hydrolysed too rapidly for it to be detected in the hydrolysis of the acetal if it were an intermediate. Under these conditions the hydrolysis products are unstable, but the final spectra of the acylal and acetal reaction solutions correspond to this changed spectrum of the products. In 0·1 and 1·0M-hydrochloric acid the spectra of the acylal (II) and the hydrolysis products are similar but there is no evidence for the acylal (II) being an intermediate in the hydrolysis of the acetal (I). Under these conditions the rate constant for the hydrolysis of the acylal (II) is similar to or smaller than that of the acetal (I) and hence the acylal should have been detectable if it had been in intermediate. The spectrum of the acylal always changed smoothly into that of the products and there was no evidence for formation of the acetal.

The pH dependence of the rate constant for the hydrolysis of the acylal (II) is given in Table 1. In acetate buffers of constant buffer ratio and ionic strength there is a small increase in rate with increasing concentration of acetic acid (*ca.* 10% on going from 0·1 to 0·5M) but this probably arises from the small change in pH. From the pH dependence of k_{obs} it therefore seems that the reaction is specific hydronium and hydroxide ion catalysed with possibly a slow

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[1] B. Capon and D. Thacker, *J. Amer. Chem. Soc.*, 1965, **87**, 4199; *J. Chem. Soc.* (*B*), 1967, 1322.

[2] J. C. Speck, D. J. Rynbrandt, and I. H. Kocheva, *J. Amer. Chem. Soc.*, 1965. **87**, 4979.

[3] D. Piszkiewicz and T. C. Bruice, *J. Amer. Chem. Soc.*, 1967, **89**. 6237: 1968, **90**, 5844.

[4] E. Anderson and B. Capon, *J.C.S. Perkin II*, 1972, 515.

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

[6] B. Capon and M. I. Page, *J.C.S. Perkin II*, 1972, 522.

[7] B. Capon, M. I. Page, and G. H. Sankey, *J.C.S. Perkin II*, 1972, 529.

spontaneous hydrolysis. Intramolecular general base catalysis by the ionised phenolic hydroxy-group is also a possibility. The specific hydroxide ion catalysed hydrolysis probably proceeds with attack on the carbonyl carbon but the mechanism of the acid-catalysed reaction is uncertain. It has been pointed out recently that the mechanism of the acid catalysed hydrolysis of acylals ' is a delicate function of substrate structure '.[8]

TABLE 1

The variation of k_{obs} with pH for the hydrolysis of 3-(2-hydroxyphenoxy)phthalide at 65·0° (I = 0·50M)

Buffer	pH	$10^4k_{obs}/s^{-1}$	$10^4k_{calc}/s^{-1}$ [a]
1·0M-HCl		5·8	
0·10M-HCl	1·11	1·07	1·06
Chloroacetate	2·74	0·120	0·122
Formate	3·53	0·105	0·124
Acetate	4·08	0·249	0·184
Acetate	4·59	0·651	0·427
Acetate	5·14	1·42	1·09
Acetate	5·64	3·42	3·23
Phosphate	6·05	7·79	8·20
Phosphate	6·48	21·0	21·9
Phosphate	7·05	66·7	74·0
Borate	7·85	447	511

[a] Calculated from the expression $k_{obs} = k_H 10^{-pH} + k_{H_2O} + k_{OH}\ 10^{pK_w-pH}$ where $k_H = 1{\cdot}24 \times 10^{-3}$, $k_{H_2O} = 9{\cdot}59 \times 10^{-6}\ s^{-1}$, and $k_{OH} = 5{\cdot}82 \times 10^3\ l\ mol^{-1}\ s^{-1}$ and $pK_w = 12{\cdot}9023$. It is clear from the poorness of the fit that the value of k_{H_2O} is not very accurate but the fit obtained when this term was omitted was considerably worse.

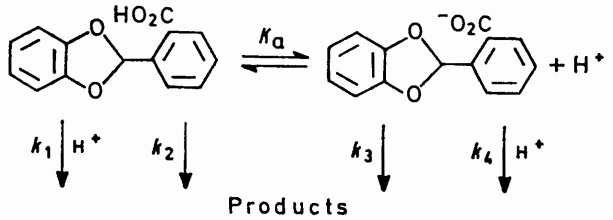
The pH dependence of the rate constant for disappearance of *OO'*-(2-carboxybenzylidene)catechol (I) is given in Table 2. The reaction is general acid catalysed and the values quoted for buffer solutions were obtained by extrapolation to zero buffer concentration. At pH 1·11—3·10 the reaction was followed at 290 nm at which wavelength the extinction coefficients of the acylal (II) and the products were identical. Between pH 3·4 and 4·4 the spectrum of the products changes as the phthalaldehydic acid dissociates and the acylal (II) and the products no longer have the same extinction coefficient at 290 nm. Under these conditions the extinction coefficients of the acylal (II) and *OO'*-(2-carboxybenzylidene)catechol (I) are significantly different (by *ca.* 20%) at 288 nm and the reaction was followed at this wavelength. The reaction was followed for less than 1·5 half-lives to avoid any complication from the subsequent hydrolysis of the acylal. Above pH 5 the hydrolysis of the acylal is faster than the disappearance of *OO'*-(2-carboxybenzylidene)catechol and the rate constants were also obtained from constant wavelength scans at 288 nm. The first-order constants calculated after 1·5 and 4·5 half-lives were identical.

TABLE 2

The variation of k_{obs} and k_0 with pH for the hydrolysis of *OO'*-(2-carboxybenzylidene)catechol at 65° (I = 0·50M)

Buffer	pH	10^5k_{obs} or k_0/s^{-1}	$10^5k_{calc}/s^{-1}$ [a]
1·0M-HCl		11·3 [b]	
0·10M-HCl	1·11	9·99 [b]	9·96
0·010M-HCl	2·11	1·50 [b]	1·59
Chloroacetate	2·13	1·62	1·56
Formate	2·74	1·59	1·53
Formate	3·10	2·34	2·32
Formate	3·53	3·90	4·05
Acetate	4·08	6·61	6·65
Acetate	4·63	8·52	8·26
Acetate	5·15	12·3	8·85
Acetate	5·70	14·0	9·06
Phosphate	5·50	9·15	9·13
Phosphate	7·26	7·35	9·14
Carbonate	9·66	8·27	9·15

[a] Calculated from $k_{calc} = (k_1\ 10^{-pH} + k_2' + k_3K_a/10^{-pH})/(K_a/10^{-pH} + 1)$ with $k_1 = 1{\cdot}23 \times 10^{-3}\ l\ mol^{-1}\ s^{-1}$; k_2' $4{\cdot}38 \times 10^{-6}\ s^{-1}$, $k_3 = 9{\cdot}15 \times 10^{-5}\ s^{-1}$, $K_a = 2{\cdot}09 \times 10^{-4}\ mol^{-1}\ l^{-1}$.
[b] Value of k_{obs}.



SCHEME 1

The values of k_{obs} for the reactions in buffers increased with increasing buffer concentration and values of k_0 were obtained by extrapolation to zero buffer concentration. The variation of k_0 with pH was analysed according to Scheme 1 to yield equation (1) where the term k_2' includes the rate constants for the kinetically equivalent spontaneous hydrolysis of the form with un-ionised carboxy-group as shown in equation (2). The variation of k_0 with pH for the hydrolysis of *OO'*-

$$k_0 = (k_1 \times 10^{-pH} + k_2' + k_3 \times K_a/10^{-pH})/(K_a/10^{-pH} + 1) \quad (1)$$

$$k_2' = k_2 + k_4 \times K_a \quad (2)$$

(4-carboxybenzylidene)catechol (III) appears to follow equation (1) as well (*cf.* Table 3). The difference in reactivity between the forms with the carboxy-group ionised and un-ionised is not as large as that found with the *ortho*-isomer and must arise from the difference in the substituent effects of the 4-carboxylate and 4-carboxy-group. As the results were not very extensive they were not analysed in detail. It appears that the rate constant for the hydronium ion catalysed hydrolysis of

TABLE 3

The variation of k_{obs} and k_0 with pH for the hydrolysis of *OO'*-(4-carboxybenzylidene)catechol at 65·0° (I = 0·50M)

Buffer	pH	10^6k_{obs} or k_0/s^{-1}
1·0M-HCl		722 [a]
0·10M-HCl	1·11	55·9 [a]
0·010M-HCl	2·11	8·20 [a]
Formic acid	2·71	2·90
Formic acid	3·10	2·54
Formic acid	3·54	3·47
Acetic acid	4·60	3·48
Phosphate	7·30	2·28

[a] Value of k_{obs}.

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[8] D P. Weeks and G. W. Zuorick, *J. Amer. Chem. Soc.*, 1969, **91**, 477.

the un-ionised form of (III) (k_1) is *ca.* $5{\cdot}3 \times 10^{-4}$ l mol^{-1} s^{-1} and that for the spontaneous hydrolysis of the ionised form *ca.* 3×10^{-6} s^{-1}.

The value of K_a from the pH–rate profile for the hydrolysis of *OO'*-(2-carboxybenzylidene)catechol (I) is $2{\cdot}09 \times 10^{-4}$ mol l^{-1} which is of the order of magnitude expected for an acid of this structure (K_a for *o*-toluic acid is $1{\cdot}235 \times 10^{-4}$ mol l^{-1} at 25°).[9] The value of k_1 the second-order constant for the hydronium ion catalysed hydrolysis of the un-ionised form is $1{\cdot}23 \times 10^{-3}$ l mol^{-1} s^{-1} at 65° compared to $8{\cdot}93 \times 10^{-3}$ l mol^{-1} s^{-1} for the hydrolysis of benzylidenecatechol and $5{\cdot}3 \times 10^{-4}$ l mol^{-1} s^{-1} for the hydrolysis of the un-ionised form of *OO'*-(4-carboxybenzylidene)catechol (III). Clearly the carboxy-group exerts a rate-decreasing effect on this reaction as would be expected from its electron-withdrawing effect. The value of k_2' is $4{\cdot}38 \times 10^{-6}$ s^{-1}: this is equal to $k_2 + k_4K_a$ and there is no rigorous way of separating these. The rate constant, k_3, for the spontaneous hydrolysis of the form with the carboxy-group ionised is $9{\cdot}15 \times 10^{-5}$ s^{-1}. This is *ca.* 30 times greater than the rate constant for the hydrolysis of the ionised form of *OO'*-(4-carboxybenzylidene)catechol (III) ($2{\cdot}76 \times 10^{-6}$ s^{-1}) and 25 times greater than that for the spontaneous hydrolysis of benzylidenecatechol ($3{\cdot}66 \times 10^{-6}$ s^{-1}).[6] Since the hydrolysis of the anion of *OO'*-(2-carboxybenzylidene)catechol (I) proceeds *via* the acylal (II) the simplest explanation of the enhanced rate is that the carboxylate group provides nucleophilic assistance, although an electrostatic effect cannot be conclusively ruled out.

The catalytic constants for the hydrolysis of *OO'*-(2-carboxybenzylidene)catechol (I) catalysed by carboxylic acids are given in Table 4. These include terms for the hydrolysis of the ionised and un-ionised forms which have not been separated. As would be expected from the greater electron-withdrawing power of the carboxy compared to the carboxylate group the catalytic constant for catalysis by formic acid increases with increasing pH. The values are only 2—3 times greater than the analogous constants for the hydrolysis of *OO'*-(4-carboxybenzylidene)catechol (III) (Table 5) and hence it seems unlikely that the carboxylic acid catalysed hydrolysis of either the ionised or un-ionised form of *OO'*-(2-carboxybenzylidene)catechol (I) is enhanced significantly relative to that of its *para*-isomer (III). Therefore the only reaction of *OO'*-(2-carboxybenzylidene)catechol whose rate is enhanced is the water catalysed or spontaneous conversion of the anion into the acylal (II). Also it is not certain if carboxylic acid catalysed hydrolysis of (I) proceeds *via* the acylal (II) since this comprises only 20—30% of the total reaction. Although it was shown that most of the reaction proceeded *via* the acylal it is possible that this minor portion did not.

TABLE 4

Catalytic constants for the general acid catalysed hydrolysis of *OO'*-(2-carboxybenzylidene)catechol at 65·0° (I = 0·50M)

Acid	pH	10^5k_{HA}/s^{-1} [a]
Chloroacetic	2·17	1·50
Formic	2·74	1·59
Formic	3·10	2·00
Formic	3·53	3·10
Acetic	4·08	2·00

[a] Not corrected for the ionisation of the *OO'*-(2-carboxybenzylidene)catechol.

TABLE 5

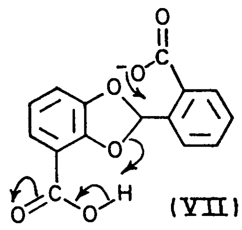
Catalytic constants for the general acid catalysed hydrolysis of *OO'*-(4-carboxybenzylidene)catechol at 65·0° (I = 0·50M)

Acid	pH	10^5k_{HA}/s^{-1} [a]
Formic	2·71	0·90
Formic	3·10	1·1
Formic	3·53	1·3
Acetic	4·60	0·89

[a] Not corrected for the ionisation of the *OO'*-(2-carboxybenzylidene)catechol.

Nucleophilic catalysis is needed only when the general acid catalyst is very weak and the leaving group is a poor one. This implies that the α value for the non-nucleophilically assisted reaction is greater than for the nucleophilically assisted reaction. If the α value is taken as a measure of the degree of proton transfer it then follows from Hammond's postulate that the acetal oxygen to which proton transfer is occurring is more basic in the transition state for the nucleophilically assisted reaction than in that for the non-nucleophilically assisted reaction. Therefore *if these arguments are correct* there must be a greater degree of carbon–oxygen bond breaking in the former than in the latter.

2,3-*OO'*-(2-*Carboxybenzylidene*)-2,3-*dihydroxybenzoic Acid* (IV).—This acetal was studied because it was thought that there was a possibility of the monoionic form reacting with the bifunctional catalysis as symbolised by (VII). The change in u.v. spectrum with time of solutions of this acetal at pH 2—5 and at 55° indicates that the initial product is the acylal (V) which is only hydrolysed slowly under these conditions. This was confirmed for the reaction in formate buffer of pH 3·8 by isolating the acylal in 90% yield after 18 half-lives (see Experimental section). The reaction showed no buffer catalysis and the dependence of k_{obs} on pH is given in Table 6.



(VII)

The most noticeable feature of the pH–rate profile (see Figure) is the bell-shape between pHs 1·11 and

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[9] See G. Kortum, W. Vogel, and K. Andrusson, ' Dissociation Constants of Organic Acids in Aqueous Solution,' Butterworths, London, 1961, p. 354.

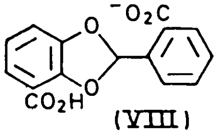
5·68 with a maximum at pH 3·8. This suggests that one of the monionic forms is more reactive than the dianionic or un-ionised forms. However it seems unlikely that this high reactivity can arise from bifunctional catalysis as the shape of the pH–rate profile for the hydrolysis of the *para*-isomer (VI) is similar (see Figure) and at the maximum the *ortho*-isomer (IV) reacts only three times faster (Tables 6 and 7). It seems reasonable to suppose that the reactive monoanionic species are (VIII) and (IX). These would be more reactive than the dianionic species because they can react with intramolecular general acid catalysis[7] and more reactive than the un-ionised species because of the poorer electron-withdrawing ability of the carboxylate group ($\sigma_p = 0{\cdot}00$) compared to the carboxy-group ($\sigma_p = 0{\cdot}45$). The pH dependences of k_{obs} were analysed according to Scheme 2 where it is assumed that the ionisation constant of each carboxy-group is independent of the state of ionisation of the other. The rate of reaction, cyclisation for the *ortho*-isomer, and hydro-

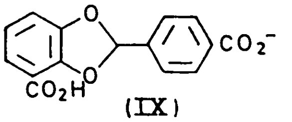
TABLE 6

The variation of k_{obs} with pH for the isomerisation of 2,3-*OO′*-(2-carboxybenzylidene)-2 3-dihydroxybenzoic acid at 55·0° (I = 0·10M)

Buffer	pH	$10^4k_{obs}/s^{-1}$	$10^4k_{calc}/s^{-1}$ [a]
5·021M-HClO$_4$ [b]		94·7	
2·995M-HClO$_4$ [b]		24·6	
2·000M-HClO$_4$ [b]		12·6	
1·00M-HCl [b]		4·90	
0·10M-HCl	1·11	3·23	3·27
0·01M-HCl	2·11	4·93	4·87
Chloroacetate	2·72	9·54	9·17
Formate	3·10	14·1	14·1
Formate	3·32	17·0	17·2
Formate	3·59	19·4	19·6
Acetate	3·84	19·7	19·9
Acetate	4·06	18·1	18·3
Acetate	4·23	15·9	17·4
Acetate	4·47	11·9	12·3
Acetate	4·71	9·2	8·6
Acetate	5·08	3·75	4·34
Acetate	5·68	1·56	1·21

[a] Calculated from $k_{calc} = (k_1 \times 10^{-pH} + k_2 + k_3K_4/10^{-pH})/[1 + K_4/10^{-pH} + K_5/10^{-pH} + K_4K_5/(10^{-pH})^2]$ with $k_1 = 0$, $k_2 = 3{\cdot}08 \times 10^{-4}$ s^{-1}, $k_3 = 3{\cdot}61 \times 10^{-3}$ s^{-1}, $K_4 = 4{\cdot}57 \times 10^{-4}$ mol l^{-1}, $K_5 = 6{\cdot}62 \times 10^{-5}$ mol l^{-1}. [b] Ionic strength equal to the molarity of the acid.


(VIII)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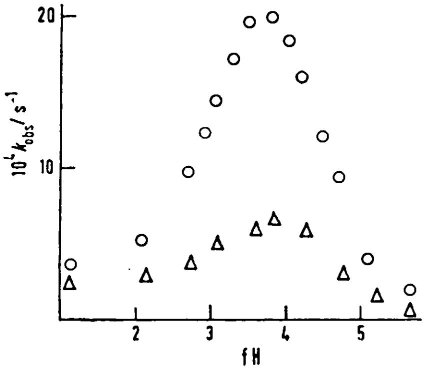


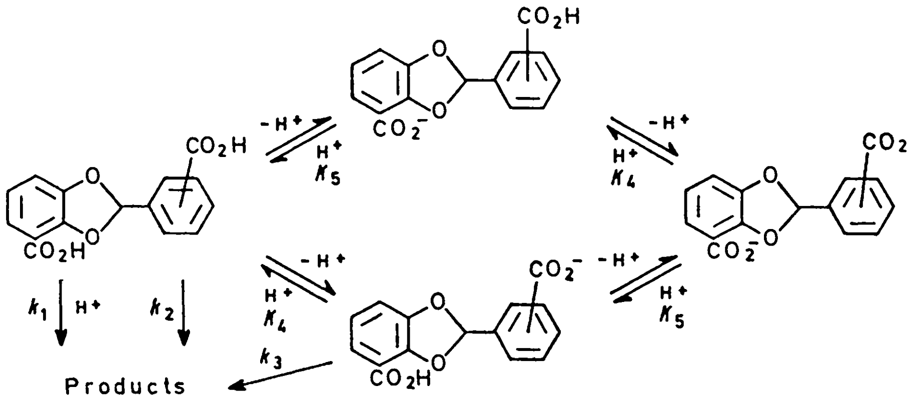
Plot of k_{obs} against pH for the isomerisation of 2,3-*OO′*-(2-carboxybenzylidene)-2,3-dihydroxybenzoic acid (IV) (○) and for the hydrolysis of 2,3-*OO′*-(4-carboxybenzylidene)-2,3-dihydroxybenzoic acid (VI) (△) at 55° (I = 0·10M)

TABLE 7

The variation of k_{obs} with pH for the hydrolysis of 2,3-*OO′*-(4-carboxybenzylidene)-2,3-dihydroxybenzoic acid at 55·0° (I = 0·10M)

Buffer	pH	$10^4k_{obs}/s^{-1}$	$10^4k_{calc}/s^{-1}$ [a]
5·021M-HClO$_4$ [b]		86·7	
1·00M-HCl [b]		4·36	
0·10M-HCl	1·11	2·54	2·49
0·01M-HCl	2·11	2·71	2·61
Chloroacetate	2·72	3·73	3·90
Formate	3·10	5·05	5·37
Formate	3·59	5·90	6·91
Acetate	3·84	6·49	6·82
Acetate	4·27	5·61	5·12
Acetate	4·70	2·91	2·81
Acetate	5·21	1·25	1·07
Acetate	5·68	0·294	0·387

[a] Calculated from $k_{calc} = (k_1 \times 10^{-pH} + k_2 + k_3K_4/10^{-pH})/[1 + K_4/10^{-pH} + K_5/10^{-pH} + K_4K_5/(10^{-pH})^2]$ with $k_1 = 0$, $k_2 = 2{\cdot}45 \times 10^{-4}$ s^{-1}, $k_3 = 1{\cdot}65 \times 10^{-3}$ s^{-1}, $K_4 = 2{\cdot}12 \times 10^{-4}$ mol l^{-1}, $K_5 = 9{\cdot}41 \times 10^{-5}$ mol l^{-1}. [b] Ionic strength equal to the molarity of the acid.



SCHEME 2

lysis for the *para*-isomer, is then given by equation (3) which on replacement of the concentrations by the ionisation constants and the pH reduces to equation (4). The values of k_{calc} in Tables 6 and 7 were calculated from

$$\text{Rate} = k_1[\text{AH}] \times 10^{-\text{pH}} + k_2[\text{AH}] + k_3[\text{A}^-] \quad (3)$$

$$k_{\text{obs}} = (k_1 \times 10^{-\text{pH}} + k_2 + k_3K_4/10)^{-\text{pH}}/ [1 + K_4/10^{-\text{pH}} + K_5/10^{-\text{pH}} + K_4K_5/(10^{-\text{pH}})^2] \quad (4)$$

this equation and the given values of k_1, k_2, K_1, and K_2. In the pH region 1·11—5·68 the term $k_1 \times 10^{-\text{pH}}$ is not sufficiently large to make a significant contribution to the total rate. The value of k_3 for the *ortho*-isomer (IV) is only just over twice that for the *para*-isomer. Therefore the ionised carboxy-group can provide little anchimeric assistance in the cyclisation of the *ortho*-isomer and probably it captures the carbonium ion in a fast product-forming step. This reaction therefore provides another example of the absence of nucleophilic assistance when the leaving group is good. As pointed out elsewhere [10-12] the driving force for the rapid hydrolyses of *o*-carboxyphenyl acetals is probably that the leaving group is a stabilised salicyl-type anion. There should therefore be less carbon–oxygen bond breaking in the transition state for ionisation of acetal (IV) than in that for the water catalysed ionisation of acetal (I). The incipient carbonium ion will therefore be less electrophilic and there will be less need for nucleophilic participation.

A similar observation has been reported by Bruice and Piszkiewicz in their study of the hydrolysis of *o*-nitrophenyl 2-acetamido-2-deoxy-β-D-glucoside, *o*-carboxyphenyl-β-D-glucoside, and *o*-carboxyphenyl 2-acetamido-2-deoxy-β-D-glucoside. It was reported that the effects of the neighbouring carboxy- and acetamido-groups found with the first two of these compounds were not additive in the hydrolysis of the last one and the lack of efficiency of the bifunctional catalysis was explained in terms of the unfavourable entropy of bringing the catalytic groups together.[5] Unfortunately the data used in the three-point Arrhenius plots do not support their arguments. Recalculation of the results for the last of the above compounds, taking the highest and medium, and then the medium and lowest temperature give entropies of activation differing by 16 cal K^{-1} mol^{-1} and enthalpies of activation differing by 5·3 kcal mol^{-1}. The authors were trying to explain differences in the entropies of activation of 6 cal K^{-1} mol^{-1}. An explanation similar to that given in the last paragraph seems more reasonable.

Recently Anderson and Fife showed that the pH–rate profile for the hydrolysis of benzaldehyde disalicyl acetal is bell-shaped but concluded that ' any participation by the carboxylate anion can be giving only a relatively small increase in the rate constant '.[13] This compound and 2,3-*OO′*-(2-carboxybenzylidene)-2,3-dihydroxybenzoic acid therefore appear to behave similarly.

EXPERIMENTAL

OO′-(2-*Carboxybenzylidene*)*catechol* (I).—Methyl α,α-dibromo-*o*-toluate, m.p. 52—53° (0·17 mol), was allowed to react with catechol (0·19 mol) in refluxing pyridine under nitrogen for 12 h. The pyridine was evaporated *in vacuo* and the residue dissolved in methylene chloride. This solution was washed with dilute acid, dilute sodium hydroxide, and water and the methylene chloride evaporated. The product was recrystallised from benzene–methanol to yield an unidentified lactone (m.p. 300°, $\nu_{\text{C=O}}$ 1780 cm^{-1}). The mother liquors were evaporated and the residue was chromatographed on a silica column eluting with ether. The resulting ester was dissolved in dioxan, an equal volume of 1M-sodium hydroxide was added and the mixture was shaken for 4 days at room temperature. The solution was acidified and extracted with chloroform. The *product* obtained after evaporation of the chloroform was recrystallised twice from methanol and four times from benzene (Found: C, 69·1; H, 4·3. $C_{14}H_{10}O_4$ requires C, 69·4; H, 4·2%), $\nu_{\text{max.}}$ (KBr) 3300—2400, 1693, 1579, 1480, 1268, 1231, and 1020 cm^{-1}, δ ($CD_3{\cdot}CO{\cdot}CD_3$) 6·97 (s, 4H), 7·80 (m, 4H), and 7·97 p.p.m. (s, 1H), *m*/*e* 242 (M^+), 197, 134, 110, and 105.

3-(2-*Hydroxyphenoxy*)*phthalide* (II).—This was prepared by subliming *OO′*-(2-carboxybenzylidene)catechol (I), m.p. 145—146·5° (Found: C, 69·5; H, 4·25%), $\nu_{\text{max.}}$ (KBr) 3390, 1760, 1597, 1515, 1380, 1288, 1235, 1120, 1055, and 935 cm^{-1}, δ ($CD_3{\cdot}SO{\cdot}CD_3$) 6·95—7·10 (m, 4H) and 7·88 p.p.m. (m, 5H), *m*/*e* 242 (M^+), 196, 181, 133, 141, and 109.

OO′-(4-*Carboxybenzylidene*)*catechol* (III).—Methyl α,α-dibromo-*p*-toluate, m.p. 68—69°, was allowed to react with catechol as described for the *ortho*-isomer. The resulting OO′-(4-*methoxycarbonylbenzylidene*)*catechol* (30%) was recrystallised twice from methanol, m.p. 80·5—81·5° (Found: C, 70·5; H, 4·8. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%), δ ($CDCl_3$) 3·86 (s, 3H), 6·81 (m, 4H), 7·59, and 8·08 p.p.m. (apparent doublets with *J* 8·5 Hz, 4H), $\nu_{\text{max.}}$ (Nujol) 1713, 1489, 1088, and 1020 cm^{-1}. The ester was hydrolysed to *OO′*-(4-carboxybenzylidene)catechol (III) as described for the *ortho*-isomer and recrystallised twice from benzene, m.p. 198—199° (Found: C, 69·5; H, 4·2%). δ ($CD_3{\cdot}SO{\cdot}CD_3$) 6·95 (m, 4H), 7·27 (s, 1H), 7·70, and 8·12 p.p.m. (apparent doublets with *J* 8·5 Hz), $\nu_{\text{max.}}$ 3400—2500, 1681, 1628, 1582, 1240, 1042, and 1022 cm^{-1}.

2,3-OO′-(2-*Carboxybenzylidene*)-2,3-*dihydroxybenzoic Acid* (IV).—Methyl α,α-dibromo-*o*-toluate was allowed to react with methyl 2,3-dihydroxybenzoate as described for the reaction of catechol. The resulting oil was recrystallised from ether to yield an unidentified lactone ($\nu_{\text{C=O}}$ 1780 and 1720 cm^{-1}). The mother liquors were evaporated and chromatographed on a silica column, eluting with ether, to yield a product which was still a mixture of two compounds (t.l.c.). This was recrystallised from methanol to yield *methyl* 2,3-OO′-(2-*methoxycarbonylbenzylidene*)-2,3-*dihydroxybenzoate* (15%), m.p. 94—95° (Found: C, 64·7; H, 4·7. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%), δ ($CDCl_3$) 3·90 (s, 3H), 3·95 (s, 3H), 6·90 (m, 3H), 7·75 (m, 5H), and 8·04 p.p.m. (s, 1H). This was hydrolysed as described for the other esters to yield a *product* (80%) which was recrystallised

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[10] B. Capon, E. Anderson, N. S. Anderson, R. H. Dahm, and M. C. Smith, *J. Chem. Soc.* (*B*), 1971, 1963.

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

[12] B. Capon, *Essays in Chemistry*, 1972, **3**, 127.

[13] E. Anderson and T. H. Fife, *Chem. Comm.*, 1971, 1470.

twice from methanol (Found: C, 63·1; H, 3·5. $C_{15}H_{10}O_6$ requires C, 62·9; H, 3·5%), $\nu_{max.}$ (KBr) 3300—2200, 1683, 1630, 1578, 1467, 1415, 1300, 1243, 1053, and 1025 cm^{-1}, *m/e* 286 (M^+), 242, 197, 154, 133, 105, 77, and 44.

3-(3-*Carboxy*-2-*hydroxyphenoxy*)*phthalide* (V).—This was prepared by subliming 2,3-*OO′*-(2-carboxybenzylidene)-2,3-dihydroxybenzoic acid at 120° and 0·5 mmHg, m.p. 226—227° (Found: C, 62·8; H, 3·5%), $\nu_{max.}$ (KBr) 3300—2500, 1790, 1660, 1615, 1463, 1445, 1372, 1245, 1063, 1040, and 965 cm^{-1}. The mass spectrum was identical with that of the diacid (IV). It was confirmed that this compound was not the corresponding 2-carboxy-6-hydroxyphenoxyphthalide by determining the approximate pK_a spectrophotometrically (*ca.* 3) and testing with ferric chloride solution when a blue colour was obtained. The compound is therefore a substituted salicylic acid and must be the 3-carboxy-2-hydroxyphenoxy-compound.

2,3-OO′-(4-*Carboxybenzylidene*)-2,3-*dihydroxybenzoic Acid.*—Methyl α,α-dibromo-*p*-toluate and methyl 2,3-dihydroxybenzoate were allowed to react in the usual way. The product was chromatographed on a silica column, eluting with diethyl ether–light petroleum (b.p. 40—60°) (1 : 1) and recrystallised three times from methanol to give *methyl* 2,3-OO′-(4-*methoxycarbonylbenzylidene*)-2 3-*dihydroxybenzoate* (20%), m.p. 108—109° (Found: C, 65·0; H, 4·5%), δ ($CDCl_3$) 3·91 (s, 3H), 3·93 (s, 3H), 7·0 (m, 2H), 7·10 (s, 1H), 7·42 (q, *J* 8·2 and 2·8 Hz, 4H), 7·60 and 8·04 p.p.m. (apparent doublets, *J* 8·8 Hz, 4H), $\nu_{max.}$ (Nujol) 1720, 1292, 1240, 1200, and 1025 cm^{-1}. The ester groups were saponified in aqueous dioxan and the *product* (60%) was recrystallised twice from ethanol (Found: C, 63·1; H, 3·6%), δ ($CD_3{\cdot}SO{\cdot}CD_3$) 7·2 (m, 3H), 7·40 (s, 1H), 7·70 and 8·07 p.p.m. (apparent doublets, *J* 8·8 Hz, 4H), $\nu_{max.}$ (Nujol) 3400—2600, 1699, 1303, 1252, 1040, and 1020 cm^{-1}.

Isolation of 3-(3-*Carboxy*-2-*hydroxyphenoxy*)*phthalide from* 2,3-OO′-(2-*Carboxybenzylidene*)-2 3-*dihydroxybenzoic Acid in an Aqueous Buffer.*—2,3-*OO′*-(2-Carboxybenzylidene)-2,3-dihydroxybenzoic acid (IV) (3 mg) dissolved in dioxan (1 ml) was added to formate buffer (50 ml), pH 3·8, at 55° and left for 90 min (18 half-lives). The mixture was cooled in ice, acidified with ice-cold hydrochloric acid to pH 0, and extracted five times with ether (100 ml). The combined extracts were washed with water, dried, and evaporated to yield 3-(3-carboxy-2-hydroxyphenoxy)phthalide (V) (2·7 mg, 89%), m.p. 228—230°, mixed m.p. with authentic (V) 226—227°, m.p. of (V) 226—227°, m.p. of equimolar mixture of phthalaldehydic acid and 2,3-dihydroxybenzoic acid, 91—96°. The i.r. spectrum (KBr) was identical to that of an authentic sample with characteristic peaks at 1790, 1660, 1445, 1040, and 965 cm^{-1}. An equimolar mixture of phthalaldehydic acid and 2,3-dihydroxybenzoic acid has no absorption at these frequencies. T.l.c. on silica and polyamide powder showed only one spot with R_F identical to that of (V). The u.v. spectrum was also identical to that of (V).

Demonstration that 3-(2-*Hydroxyphenoxy*)*phthalide is an Intermediate in the Hydrolysis of* OO′-(2-*Carboxybenzylidene*)-*catechol.*—*OO′*-(2-Carboxybenzylidene)catechol (I) (4·4 mg) dissolved in dioxan (1 ml) was added to formate buffer (50 ml), pH 3·55, at 65° and left for 5 h (*ca.* 2 half-lives). The mixture was cooled in ice, acidified with ice-cold hydrochloric acid to pH 1, and extracted five times with ether (100 ml). The combined extracts were washed with water, dried, and evaporated to yield a product (4·3 mg) whose i.r. spectrum (KBr) showed peaks at 1760, 1380, and 935 cm^{-1} characteristic of 3-(2-hydroxyphenoxy)phthalide (II). Neither an equimolar mixture of phthalaldehydic acid nor (I) absorb at these frequencies. Continuous scanning of the u.v. spectrum of the hydrolysing acetal (I) showed that the acylal (II) was an intermediate. At pH 3·4 and at 65° the extinction coefficient of the acylal (II) and the hydrolysis products are similar at 284 nm and that of the acetal (I) is different, whereas at 257 nm that of the acylal (II) and acetal (I) are similar and that of the reaction products is different. The absorbance at 284 nm changes by 50% of that expected for complete reaction in 4 h, but at 257 nm the change corresponds to less than 5% hydrolysis. When the absorbance at 257 nm is followed there is a long induction period followed by the expected change for hydrolysis. Similar results were obtained at pH 2·9, 4·0, and 4·9. At pH 4·0 the absorbance changes by 17% of that expected for complete reaction at 286 nm but only by 1·5% of that expected for complete hydrolysis at 257 nm. At 274 nm the absorbance first decreases and then increases. All these observations indicate that under the specified conditions the acylal (II) is an intermediate in the hydrolysis of the acetal (I).

Kinetic Measurements.—Rate constants were determined as previously described.[6] The values of k_{obs} for the reactions of (I) and (III) were plotted against buffer concentration to yield the values of k_0 and k_{cat} given in Tables 2—5. The values of k_{obs} or k_0 were fitted to the equations of the pH–rate profile by an iterative procedure to find a minimum in the sum of the squares of the residuals: $\Sigma(k_0{}^i - k_{calc}{}^i)^2/k_0{}^i$. When the results for the dicarboxy-compound were fitted to equation (4) the fit was not improved significantly by including the k_1 term. Presumably it does not make an appreciable contribution. (<10%) to k_{obs} at the pH values studied. Several other simplifying assumptions were also made in this analysis. These were that the dissociation constant of each carboxy-group was independent of the state of ionisation of the other and that the hydrolyses of the other monoionised form and of the di-ionised form do not make significant contributions. Although these are reasonable they may lead to small errors in the derived constants.

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