# Intramolecular Catalysis of Sulphate Diester Hydrolysis by One and Two Carboxy Groups. The Hydrolysis of Aryl 2-Carboxyphenyl Sulphates

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The hydrolysis of aryl 2-carboxyphenyl (salicyl) sulphates is subject to efficient nucleophilic catalysis by the neighbouring carboxylate group. The intermediate cyclic acyl sulphate can be trapped with hydroxylamine. The reaction of disalicyl sulphate is further catalysed by the second carboxy group, acting, rather inefficiently, as a general acid.

Relatively little is known about the chemistry of sulphate diesters.[1] Reactivity at sulphur is substantially lower than at the phosphorus centre of phosphate triesters. (5-Membered cyclic compounds show very large—*ca.* $10^7$-fold—increases in reactivity in both cases.[2]) On the other hand, sulphate ester oxygen is the better leaving group, so that dialkyl or alkyl aryl sulphates react under most conditions as alkylating agents.[3]

As a result, attack at sulphur by nucleophiles other than hydroxide is generally too slow to measure for acyclic diesters. Even hydroperoxide anion attacks methyl 4-nitrophenyl sulphate at the methyl carbon;[4] and the observed catalysis of the hydrolysis of catechol sulphate by imidazoles almost certainly involves a general base, rather than a nucleophilic mechanism.[5]

In this situation, the simplest way to assess mechanism and reactivity in nucleophilic substitution at sulphur is to study an intramolecular reaction. The neighbouring carboxy is a highly efficient nucleophile towards the phosphorus centre of phosphate di- and tri-esters[6,7] so we prepared a series of diaryl sulphates (**1**), (**2**) containing one and two carboxy groups, in the expectation that their hydrolysis will be subject to intramolecular nucleophilic catalysis.

## Results

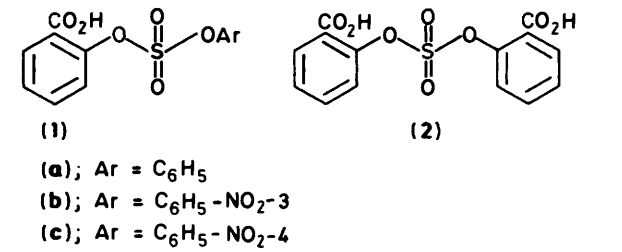
Aryl 2-carboxyphenyl sulphates were prepared from the corresponding aryl sulphuryl chlorides and benzyl salicylate. Debenzylation of the product [the mono- or di-benzyl ester of (**1**) or (**2**)] could not be achieved by hydrogenolysis, but the benzyl group was readily removed using iodotrimethylsilane.[8] This procedure gave the trimethylsilyl ester, which is itself rapidly hydrolysed on mild aqueous work-up. The bis-(2-carboxyphenyl) ester (**2**) was prepared in the same way. The apparently simpler direct route from sulphuryl chloride gave only low yields of protected diester.

Hydrolysis reactions were followed by monitoring the release of phenol or phenolate at 60 °C in aqueous buffers maintained at an ionic strength of 1.0M. Reactions of aryl 2-carboxyphenyl sulphates followed good first-order kinetics for at least two half-lives, and showed no catalysis by buffer constituents. For the hydrolysis of disalicyl sulphate (**2**), the first-order plots were no longer linear below pH 7, as the rate of release of a second equivalent of salicylate from salicyl sulphate becomes comparable with the initial step. These results were fitted successfully to a model for consecutive first-order reactions of the type:

$$A \xrightarrow{k_1} B + C$$

$$B \xrightarrow{k_2} C + D$$

Rate constants, $k_2$, for the hydrolysis of salicyl sulphate were obtainable by extrapolation of the data of Benkovic.[9]



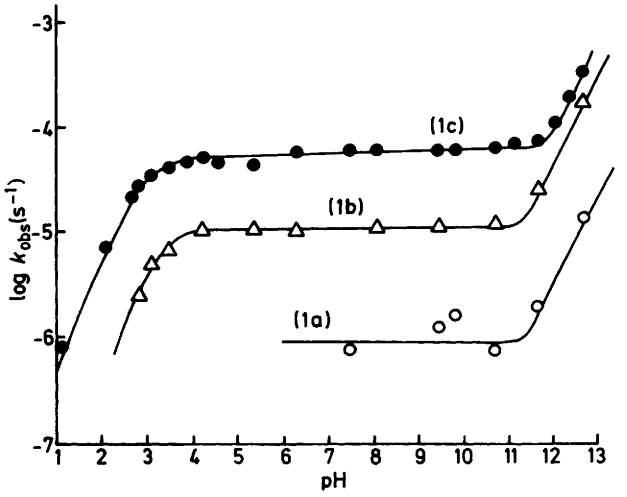




**Figure 1.** pH–Rate profiles for the hydrolysis of three aryl 2-carboxyphenyl sulphates (**1a**—**c**) at 60 °C and ionic strength 1.0M. The curves are calculated from the rate constants given in Table 1

Nucleophilic displacement on sulphur by carboxylate oxygen will lead to an acyl sulphate intermediate. To test for the presence of an acylating agent the hydrolysis of 4-nitrophenyl 2-carboxyphenyl sulphate (**1c**) was carried out in the presence of hydroxylamine buffer at pH 5.8.[6,7] Addition of aliquots to a solution of $FeCl_3$–$Hg(NO_3)_2$ gave increasing intensities of the expected characteristic ferric hydroxamate absorption ($\lambda_{max.}$ 530 nm).

Products were identified by their u.v. spectra as the phenol and salicyl sulphate. The further hydrolysis of salicyl sulphate interfered only in the case of the symmetrical diester (**2**). Salicylic acid was not a product (<2%) of the hydrolysis of phenyl salicyl sulphate (**1a**), as estimated by Trinder's method.[10]

Data for the hydrolysis of the three aryl salicyl sulphates (**1**) are presented graphically (Figure 1), and derived rate constants are given in Table 1. The apparent $pK_a$ for the 4-nitrophenyl ester (**1c**), for which the largest set of data was obtained, was

3.02, and values for the other esters were not significantly different.

The pH-rate profile for the first step of the hydrolysis of disalicyl sulphate (**2**) is presented in Figure 2, and the full set of data, including rate constants for the second step, the hydrolysis of salicyl sulphate, in Table 2.

## Discussion

The pH–rate profiles (Figure 1) for the hydrolysis of esters (**1b**) and (**1c**) follow the ionisation of the carboxy group (p$K$ 3.02), and the pH-independent reaction of the anion extends to pH 11. Since ionisation of $CO_2H$ can only make these compounds less electrophilic, this is clear evidence that the reaction is catalysed by the carboxylate group. The high efficiency of catalysis—neighbouring $CO_2^-$ is as efficient as 0.01M hydroxide—suggests that the group is involved as a nucleophile,[11] and all the kinetic evidence is consistent with this interpretation. The entropy of activation for the pH-independent reaction is almost zero for the reaction of (**1c**) and the rate is not significantly slower in $D_2O$ (Table 1).

It is not possible to measure the rate acceleration involved, because the hydrolysis of diphenyl sulphate is too slow to measure near neutrality. [If it is assumed that the acceleration is comparable to that associated with catalysis by carboxylate in the hydrolysis of phosphate di- or tri-esters (*ca.* $10^7$)[6,7] then the

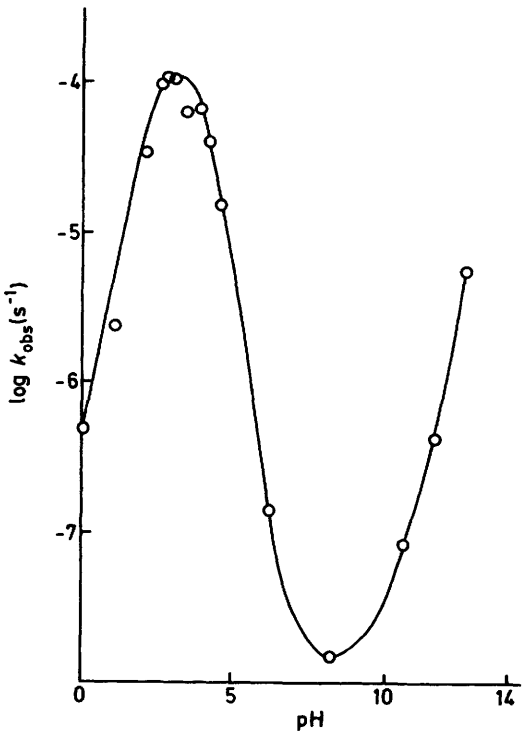



**Figure 2.** pH-Rate profile for the hydrolysis of disalicyl sulphate (**2**), at 60 °C and ionic strength 1.0M. Derived rate constants, using p$K_a$s of 2.72 and 3.32, are: $k_{monoanion}$ 2.20 ± 0.16 × $10^{-4}$ $s^{-1}$ (in $D_2O$ 2.45 × $10^{-4}$); $k_{dianion}$ 1.31 ± 0.04 × $10^{-8}$ $s^{-1}$; $k_{OH}$ (dianion) 5 ± 1 × $10^{-6}$ $dm^3$ $mol^{-1}$ $s^{-1}$

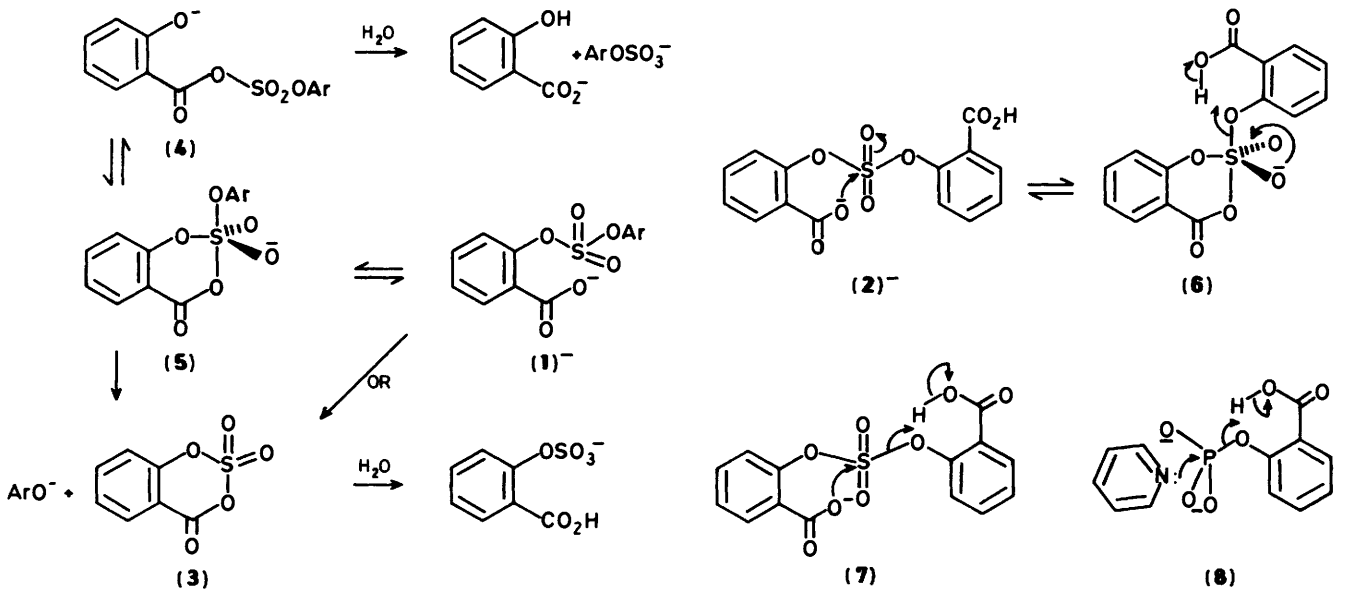
**Table 1.** Derived rate constants for the hydrolysis of aryl 2-carboxyphenyl sulphates in water at 60 °C, ionic strength 1.0M

| Ester | p$K_a$ | $k_o$ | $k_{OH^-}$ |
|---|---|---|---|
| (**1a**) | 3.02 | 9.74 ± 3.0 × $10^{-7}$ | 1.2 ± 0.1 × $10^{-5}$ |
| (**1b**) | 3.02 | 1.05 ± 0.03 × $10^{-5}$ | 1.55 ± 0.07 × $10^{-4}$ |
| (**1c**) | 3.02 | 5.86 ± 0.28 × $10^{-5}$ | 2.69 ± 0.01 × $10^{-4}$ |
| (**1c**) in $D_2O$ | | 5.82 ± 0.05 × $10^{-5}$ | |

**Table 2.** Rate constants ($k_1$) for the hydrolysis of bis-(2-carboxyphenyl) sulphate (**2**), in water at 60 °C and ionic strength 1.0M

| Buffer (M) | | pH | $k_1$ ($s^{-1}$) | $k_2$[a] ($s^{-1}$) |
|---|---|---|---|---|
| HCl | (1.0) | | 4.98 ± 0.11 × $10^{-7}$ | 3.25 × $10^{-3}$ |
| HCl | (0.1) | 1.12 | 2.42 ± 0.36 × $10^{-6}$ | 4.49 × $10^{-4}$ |
| HCl | (0.01) | 2.11 | 3.54 ± 0.93 × $10^{-5}$ | 1.66 × $10^{-4}$ |
| HCl | (0.003) | 2.68 | 1.01 ± 0.10 × $10^{-4}$ | 1.35 × $10^{-4}$ |
| HCl | (0.001) | 3.08 | 1.07 ± 0.06 × $10^{-4}$ | 1.15 × $10^{-4}$ |
| 20% FB[b] Formate | (1.0) | 2.81 | 1.10 ± 0.12 × $10^{-4}$ | 1.29 × $10^{-4}$ |
| 50% FB Formate | (1.0) | 3.47 | 8.06 ± 0.76 × $10^{-5}$ | 8.82 × $10^{-5}$ |
| (65 °C) | (1.0) | | 8.31 ± 0.15 × $10^{-5}$ | 1.61 × $10^{-4}$ |
| (70 °C) | (1.0) | | 1.38 ± 0.50 × $10^{-4}$ | 2.91 × $10^{-4}$ |
| (75 °C) | (1.0) | | 2.31 ± 0.54 × $10^{-4}$ | 5.41 × $10^{-4}$ |
| (80 °C)[c] | (1.0) | | 5.33 ± 0.46 × $10^{-4}$ | 8.93 × $10^{-4}$ |
| 80% FB Formate | (1.0) | 4.23 | 4.04 ± 0.70 × $10^{-5}$ | 3.17 × $10^{-5}$ |
| 20% FB Acetate | (1.0) | 3.88 | 6.84 ± 1.00 × $10^{-5}$ | 5.54 × $10^{-5}$ |
| 50% FB Acetate | (1.0) | 4.57 | 1.59 ± 0.21 × $10^{-5}$ | 1.65 × $10^{-5}$ |
| 50% FB Phosphate | (0.5) | 6.29 | 1.44 ± 0.04 × $10^{-7}$ | 3.57 × $10^{-7}$ |
| 80% FB Tris | (0.05) | 8.30 | 1.54 ± 0.05 × $10^{-8}$ | |
| NaOH | (0.01) | 10.70 | 4.95 ± 0.05 × $10^{-8}$ | |
| NaOH | (0.1) | 11.65 | 4.38 ± 0.18 × $10^{-7}$ | |
| NaOH | (1.0) | | 5.82 ± 0.03 × $10^{-6}$ | |
| | | pD[d] | | |
| DCl in $D_2O$ | (0.009) | 2.53 | 2.15 ± 0.70 × $10^{-5}$ | 1.29 × $10^{-4}$ |
| DCl in $D_2O$ | (0.003) | 2.62 | 2.71 ± 0.08 × $10^{-5}$ | 1.26 × $10^{-4}$ |
| DCl in $D_2O$ | (0.001) | 3.16 | 8.49 ± 0.49 × $10^{-5}$ | 1.10 × $10^{-4}$ |
| 50% FB Formate[e] ($D_2O$) | (1.0) | 3.91 | 7.80 ± 0.53 × $10^{-5}$ | 7.73 × $10^{-5}$ |

[a] Rate constant for the hydrolysis of salicyl sulphate. [b] FB = Free Base. [c] $\Delta H^{\ddagger}$ = 112 ± 2 kJ $mol^{-1}$ (26.9 ± 0.4 kcal $mol^{-1}$), $\Delta S^{\ddagger}$ 10 ± 10 J $mol^{-1}$ $K^{-1}$ (2.4 ± 2.4 cal $K^{-1}$ $mol^{-1}$) for the monoanion reaction. [d] Meter reading +0.40 (P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, 1960, **64**, 188). [e] $k_{H_2O}/k_{D_2O}$ = 0.90 for the hydrolysis of the monoanion.



rate constant for the hydrolysis of diphenyl sulphate at pH 5 is expected to be $< 10^{-12}$ s$^{-1}$ at 60 °C.] The effective molarity[11] of the carboxylate group cannot be measured for the same reason. Not surprisingly, no catalysis by formate buffer was detectable.

The nucleophilic mechanism requires at least one, acyl sulphate, intermediate. This could be the cyclic mixed anhydride (**3**) or the open-chain derivative (**4**), and evidence that the carboxylate group becomes an acylating agent in the course of the reaction was obtained by carrying out the hydrolysis in the presence of hydroxylamine. Increasing concentrations of hydroxamic acid, detected by the characteristic ferric hydroxamate absorption at 530 nm, were formed as the reaction proceeded.

The further hydrolysis of (**3**) and (**4**) would produce salicyl sulphate or salicylic acid, respectively. No significant amounts of salicylate could be detected on hydrolysis of phenyl salicyl sulphate, for which the route *via* (**4**) would be most favourable. We conclude that the hydrolyses of (**1a**, **b**, and **c**) proceed through the common intermediate (**3**). This could be formed by a concerted, 'in-line' displacement,[12] or by way of a penta-co-ordinate intermediate (**5**).[13] The evidence available does not permit a distinction: both mechanisms would involve significant amounts of S–OAr bond breaking in the rate-determining transition state, and we find $\beta_{LG}$ (the slope of the plot of log $k_{hyd}$ *versus* p$K_a$ of ArOH) to be −0.63 ($r$ 0.999) for the carboxylate-catalysed reactions of (**1a**—**c**), consistent with this. [For comparison, $\beta_{LG}$ for the hydroxide reaction is −0.50 ($r$ 0.961).]

If the S–OAr bond is breaking in the rate-determining transition state, it should be subject to intramolecular general acid catalysis, particularly if the leaving group is salicylate.[11,14] We therefore prepared the symmetrical disalicyl sulphate (**2**). This is a stable, crystalline compound, unlike the highly reactive phosphate analogue,[14] and its hydrolysis was followed at 60 °C, as for esters (**1a**—**c**). The bell-shaped pH–rate profile (Figure 2) from pH 0—7 confirms that both carboxy groups are involved in catalysis, one as the neutral, $CO_2H$ group, and the other in the ionised form.

The rate constant for the hydrolysis of the monoanion of (**2**) is $2.2 \times 10^{-4}$ s$^{-1}$ (Table 2). This is 26 times faster than expected from the Brönsted (leaving group) for compounds (**1a**—**c**), for the displacement of a leaving group of p$K_a$ 8.52,[14] confirming that the second, $CO_2H$, group plays an active role in the reaction. This can only reasonably be the expected general acid catalysis, though the solvent deuterium isotope effect, $k_{H_2O}/k_{D_2O}$ = 0.9, is insignificant (*cf.* $k_{H_2O}/k_{D_2O}$ = 1.2 for the hydrolysis of salicyl sulphate[9] and 0.96 for that of salicyl phosphate,[15] both of which are thought to involve similar general acid catalysis by $CO_2H$).[16,17]

The hydrolysis of (**2**) thus involves catalysis by both carboxy groups. We interpreted our similar observations with disalicyl phosphate in terms of a two-step mechanism involving a pentacovalent intermediate. In the sulphate case this becomes (**6**).

However, there is no compelling evidence that the two steps are not concerted, as in (**7**): intramolecular general acid catalysis by $CO_2H$ of nucleophilic attack by substituted pyridines (**8**) has been observed for the dianion of salicyl phosphate,[16] which certainly reacts by a concerted mechanism. In that case catalysis is highly efficient: the rate enhancement of the reaction with pyridine was estimated as *ca.* $10^8$-fold,[16] compared with the figure of 26 ascribed to catalysis by $CO_2H$ of the S–O bond cleavage of (**6**) or (**7**). This enormous difference presumably reflects the different amounts of bond breaking in the two systems, as discussed for the similar case of disalicyl phosphate.[14] Efficient intramolecular general acid catalysis in the salicylate system depends on a high degree of bond breaking, generating a substantial negative charge on the leaving group oxygen.[16] This is expected to be absent in the transition state for the breakdown of a pentacovalent intermediate, (**6**), and also in that for the closely related concerted process (**7**).

The rate constants for the reactions of our series of sulphate esters may be compared with those for the same reactions of the corresponding phosphate esters.[6,7,14] Intramolecular nucleophilic attack by $CO_2^-$ in aryl salicyl sulphates is 20—1 000 times slower than the same reaction of the corresponding phosphate diester anions. The factor is larger for better leaving groups, reflecting the much greater sensitivity to the leaving group for the reaction in the phosphate series.[6] If the comparison is made between neutral compounds, using the data for aryl phenyl salicyl phosphate triesters,[7] the factor is some 100 times larger (750—$10^5$).

Attack by hydroxide on phosphate diester anions is retarded by coulombic repulsion.[6] Consequently $k_{OH}$ values are more closely comparable for disalicyl sulphate dianion and disalicyl phosphate (trianion). (The effect of *ortho*-$CO_2^-$ on the rate of hydroxide attack is relatively small: compared with diphenyl sulphate,[2] phenyl salicyl and disalicyl sulphate are hydrolysed 2.5 and 6 times more slowly in NaOH).

## Experimental

*2-Benzyloxycarbonylphenyl Phenyl Sulphate.*—Phenol (2.0 g, 21 mmol) and pyridine (3.36 g, 43 mmol) were added dropwise to sulphuryl chloride (2.5 ml, 31 mmol) in dry diethyl ether at below −50 °C. The mixture was then allowed to warm to room temperature and stirred for a further 5 h. The solution of crude phenyl sulphuryl chloride was then transferred directly to a THF solution containing the sodium salt of benzyl salicylate (21mM) at below −50 °C. This was allowed to warm to room temperature and was then stirred for a further 19 h. The mixture was centrifuged and the liquid decanted off. The remaining solid (sodium chloride and sodium hydride) was washed twice with dry diethyl ether. The three solvent fractions were combined and evaporated to dryness. The remaining residue was purified by chromatography on silica gel [eluant light petroleum (40—60 °C)] to give the diester (22.6 g, 32%) as a pale yellow oil, $\nu_{max.}(CCl_4)$ 1 740 (C=O), 1 610 (Ar), 1 380, and 1 180 $cm^{-1}$ (sulphate); $\delta(CCl_4)$ 8.0—6.8 (14 H, m, Ar) and 5.2 (2 H, s, $ArCH_2$) [Found (e.i.); $M^+$, 384.066 85. $C_{20}H_{16}O_6S$ requires 384.0668].

The following were prepared in a similar manner.

*2-Benzyloxycarbonylphenyl 3-nitrophenyl sulphate*, white platelets, m.p. 59—61 °C (from $CCl_4$); $\nu_{max.}(CCl_4)$ 1 740 (C=O), 1 610 (Ar), 1 530 ($CNO_2$), 1 480 (Ar), 1 350, and 1 180 $cm^{-1}$ (sulphate); $\delta(CCl_4)$ 8.00—6.8 (13 H, m, Ar) and 5.2 (2 H, s, $ArCH_2$) [Found (e.i.): $(M - 1)^+$, 428.0460. $C_{20}H_{14}NO_8S$ requires 428.0440. C.i.: $(M + NH_4)^+$, 449].

*2-Benzyloxycarbonylphenyl 4-nitrophenyl sulphate*, pale yellow platelets, m.p. 108—110 °C (from $CCl_4$); $\nu_{max.}(CCl_4)$ 1 730 (C=O), 1 600 (Ar), 1 530 ($CNO_2$), 1 490 (Ar), 1 350, and 1 180 $cm^{-1}$ (sulphate); $\delta(CCl_4)$ 8.0—6.8 (13 H, m, Ar) and 5.2 (2 H, s, $ArCH_2$) [Found (e.i.): $(M - 1)^+$, 428.0425. $C_{20}H_{14}NO_8S$ requires 428.0440].

*Bis-(2-benzyloxycarbonylphenyl) sulphate*, white amorphous powder, m.p. 76—78 °C (from $CCl_4$); $\nu_{max.}(CCl_4)$ 1 730 (C=O), 1 610 (Ar), 1 480 (Ar), 1 380, and 1 180 $cm^{-1}$ (sulphate); $\delta(CCl_4)$ 8.0—6.8 (22 H, m, Ar) and 5.2 (4 H, s, $ArCH_2$) [Found (e.i.): $(M + 1)^+$, 519].

*2-Carboxyphenyl Phenyl Sulphate.*—Iodotrimethylsilane (Aldrich) (50 μl, 9.3 mmol) was added to a solution of dichloromethane containing 2-benzyloxycarbonylphenyl phenyl sulphate (0.123 g, 0.3mM) and the mixture was stirred for one h. The solution was washed with dilute hydrochloric acid and evaporated to dryness. The crude residue was recrystallised from tetrachloromethane to give 2-carboxyphenyl phenyl sulphate (83 mg, 95%) as white needles, m.p. 110—112 °C; $\nu_{max.}(CHCl_3)$ 3 500—2 500 ($CO_2H$), 1 710 (C=O), 1 610 (Ar), 1 490 (Ar), 1 350, and 1 180 $cm^{-1}$ (sulphate); $\delta(CDCl_3)$ 10.1 (1 H, br s, OH) and 8.0—6.5 (9 H, m, Ar) [Found: C, 52.8; H, 3.3. $C_{13}H_{10}O_6S$ requires C, 53.0; H, 3.4%. E.i.: $(M - OH)^+$, 277.0173. $C_{13}H_9O_5S$ requires 277.0171. C.i.: $(M + NH_4)^+$, 312; f.a.b.: $(M - 1)^-$, 293].

The following were prepared in the same manner.

*2-Carboxyphenyl 3-nitrophenyl sulphate*, white needles, m.p. 124—125 °C (from $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 500—2 500 ($CO_2H$), 1 710 (C=O), 1 610 (Ar), 1 530 ($CNO_2$), 1 350, and 1 180 $cm^{-1}$ (sulphate); $\delta(CD_3OD)$ 8.0—6.5 (m, Ar) [Found (e.i.): $(M - OH)^+$, 322.0020. $C_{13}H_8NO_7S$ requires 322.0020. C.i.: $(M + NH_4)^+$, 357].

*2-Carboxyphenyl 4-nitrophenyl sulphate*, pale yellow needles, m.p. 140—142 °C (from acetone–diethyl ether); $\nu_{max.}(CHCl_3)$ 3 500—2 500 ($CO_2H$), 1 710 (C=O), 1 600 (Ar), 1 530 ($CNO_2$), 1 500 (Ar), 1 350, and 1 180 $cm^{-1}$ (sulphate); $\delta(CD_3OD)$ 8.0—6.5 (m, Ar) [Found (e.i.): $(M - OH)^+$, 322.0041. $C_{13}H_8NO_7S$ requires 322.0022. C.i.: $(M + NH_4)^+$, 357; f.a.b.: $(M - 1)^-$, 338.

*Bis-(2-carboxyphenyl) sulphate* (disalicyl sulphate), white needles, m.p. >230 °C (from acetone–diethyl ether); $\nu_{max.}$ ($CHCl_3$) 3 500—2 500 ($CO_2H$), 1 690 (C=O), 1 610 (Ar), 1 370, and 1 180 $cm^{-1}$ (sulphate); $\delta(CD_3OD)$ 8.0—6.5 (m, Ar) [Found (e.i.): $(M - O_2H_2)$, 304. F.a.b.: $(M - 1)^-$, 337] (Found: C, 49.5; H, 3.2. $C_{14}H_{10}O_6S$ requires C, 49.7; H, 3.0%).

*Kinetic Methods.*—Reactions were followed in the thermostatted cell compartments of a Zeiss PMQ 3 or Gilford 2600 spectrophotometer, at 213 or 278 nm (**1a**), 380 or 350 nm (**1b**), 400 or 320 nm (**1c**), and 298.5 nm (the isosbestic point for salicylic acid and its anion) for (**2**). Runs were started by injecting a few μl of a stock solution of diester in dioxane into the preheated aqueous buffer solution, made up to an ionic strength of 1.0M with KCl. The pH of each solution was measured using an EIL 7050 pH meter fitted with a Russell CMJ 78 combination glass/reference electrode.

For the reactions of (**2**) below pH 7, which departed from first-order kinetics, results were computer fitted (method of least-squares) to a model for consecutive first-order reactions of the type:

$$A \xrightarrow{k_1} B + C$$

$$B \xrightarrow{k_2} C + D$$

where $[C] = 2[A_o] - [A_o][(2k_2 - k_1)e^{-k_1 t} - k_1 e^{-k_2 t}]/(k_2 - k_1)$ is the concentration of salicylic acid produced. Rate constants $k_2$ for the hydrolysis of salicyl sulphate were obtained by extrapolation, to 60 °C, of the data of Benkovic.[9]

*Hydroxylamine Trapping Experiment.*—4-Nitrophenyl 2-carboxyphenyl sulphate (20 mg) was dissolved in 4 ml of freshly prepared hydroxylamine buffer (0.40M; pH 5.8) at 60 °C. Aliquots (400 ml) were added to a cuvette containing $FeCl_3$ (0.25M), $Hg(NO_3)_2$ (0.25M), and HCl (0.12M). The characteristic absorption of ferric hydroxamate at 530 nm was observed in each case, its intensity increasing as reaction proceeded.

*Product Analysis.*—At high pH, where salicyl sulphate is stable, the initial products of hydrolysis of (**1a**) could be phenol and salicyl sulphate or phenyl sulphate and salicylic acid. Salicylic acid formed was estimated by the method of Trinder.[10] Phenyl 2-carboxyphenyl sulphate (5 mg) was dissolved in 0.05M TRIS buffer (pH 8.3, 1 ml) and aliquots (40 μl) added to 200 ml of the ferric chloride solution described above. The absorbance at 540 nm was measured, and compared with that of standard solutions of salicylate. Less than 2% of the theoretical amount of salicylic acid was produced on complete hydrolysis of (**1a**).

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