Kinetics of Iodination of *para*-Substituted Phenols

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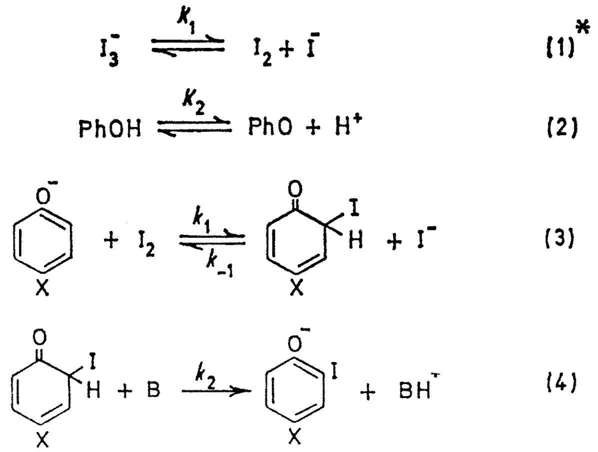
The correlation of log k for the iodination of *para*-substituted phenols with $\sigma_m + a\Delta\sigma_p^-$ is much better than that with σ_m alone. Limited conjugation between substituent and oxygen in the activated complex has been suggested as the reason for this. The catalytic influence of various bases on the iodination velocity has been studied and the Brønsted coefficient is very small, *ca.* 0·2. The reaction of iodine with phenolate ion becomes rate-determining when the concentration of iodide ion is low.

RECENTLY we studied the kinetics of coupling of *para*-substituted phenolate ions with diazotized sulphanilic acid.[1] Although aromatic diazonium salts are only moderately reactive, the estimated value of the Hammett reaction constant, ρ, is smaller than in most electrophilic substitutions of the benzene ring.[2] The small reaction constant is a consequence of the high reactivity of the phenolate anion compared with benzene. Further we found that the substituents with $-M$ effect are much more deactivating than expected from their σ_m constants.[3] We consider that this extra deactivation is due to the conjugation between the $-M$ substituent and oxygen being strongly diminished in the transition state. Very good linear correlation was found between log k and $(\sigma_m + a\Delta\sigma_p^-)$, where $a\Delta\sigma_p^-$ expresses the change in resonance energy.

The aim of the present work is to verify our conclusions for iodination. The mechanism of the iodination of phenols [(1)—(4)] was suggested by Grovenstein *et al.*[4,5] who studied the reaction kinetics of the iodination of phenol and *p*-nitrophenol. The iodination rate is given by equation (5) where $[I_2]$ and [PhOH] are the total concentrations of iodine and phenol respectively.



$$v = \frac{k_1k_2K_1K_2[I_2][PhOH][B]}{k_{-1}[I^-](K_1 + [I^-])(K_2 + [H^+])} = \frac{kK_1K_2[I_2][PhOH]}{[I^-](K_1 + [I^-])(K_2 + [H^+])} \quad (5)$$

Mayberry[7] studied quantitatively the influence of *ortho*-substituents in *p*-cresol on the rate of iodination. Among the substituents investigated the nitro-group had a $-M$ effect, but no large deactivating effect was noticed. This might be due to a poor correlation caused by the *ortho*-relation of the substituent to the oxygen.

EXPERIMENTAL

Commercial *p*-fluorophenol, *p*-cresol, *p*-t-butylphenol, and *p*-nitrophenol were purified by distillation (*p*-F, *p*-Me) or crystallization. The other *para*-substituted phenols were prepared by standard methods and distilled (*p*-Cl, *p*-Br) or recrystallized (*p*-Ac, *p*-CN, *p*-SO_2Me) from suitable solvents.

Dissociation constants of *para*-substituted phenols were determined spectrophotometrically[8] at 20 °C and ionic strength 0·5 (KCl). Borax and phosphate buffers were used. pH was measured on a Radiometer Kopenhagen PHM 4c pH-meter.

Kinetic Measurements.—All measurements were carried out at 20 °C and ionic strength 0·5 (KCl). Phosphate and acetate buffers were used. To 90 ml of a thermostatted aqueous solution of *para*-substituted phenol (5×10^{-4}—2×10^{-3}M), buffer, and KCl, 10 ml of aqueous 5×10^{-4}M-iodine in excess of KI were added at once. After mixing, a part of the solution was rapidly transferred to the quartz cell in the thermostatted cell compartment of a Unicam SP 800 spectrophotometer, and the change of optical density of I_3^- with time was measured at 350 nm. The residual optical density was practically zero in most cases. *p*-Acetyl- and *p*-nitrophenol absorb strongly at 350 nm. For *p*-acetylphenol the measurement was carried out at 380 nm and the residual optical density was subtracted from each reading. For *p*-nitrophenol, the decrease of iodine concentration was followed by titration with 0·01M-aqueous sodium thiosulphate according to the procedure

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* $K_1 = 1{\cdot}15 \times 10^{-3}$ at 20 °C as calculated from literature data.[6]

[1] I. Dobáš, V. Štěrba, and M. Večeřa, *Chem. and Ind.*, 1968, 1814.

[2] R. O. C. Norman and R. Taylor, 'Electrophilic Substitution in Benzenoid Compounds,' Elsevier, Amsterdam, 1965, p. 288.

[3] I. Dobáš, V. Štěrba, and M. Večeřa, *Coll. Czech. Chem. Comm.*, 1969, **34**, 3746.

[4] E. Grovenstein and D. C. Kilby, *J. Amer. Chem. Soc.*, 1957, **79**, 2972.

[5] E. Grovenstein and S. Aprahamian, *J. Amer. Chem. Soc.*, 1962, **84**, 212.

[6] M. Davies and E. Gwynne, *J. Amer. Chem. Soc.*, 1952, **74**, 2748.

[7] W. E. Mayberry, *Biochemistry*, 1967, **6**, 1320.

[8] E. P. Serjeant and A. Albert, 'Ionisation Constants of Acids and Bases,' Wiley, London, 1962.

described by Mayberry[7] for iodination of 4-methyl-2-nitrophenol. The pH of the kinetic solutions was measured on a Seibold GTB pH-meter.

RESULTS

In all experiments the concentration of phenol was at least ten times that of iodine to suppress the consecutive iodination of monoiodo-derivative. Under these conditions the reaction rate was determined by use of the first-order kinetic equation (6). Rate constant k_{obs} was determined

$$v = k_{\text{obs}}[I_2] \qquad (6)$$

graphically from the plot of logarithm of the optical density against time. From equations (5) and (6) we obtain relation (7).

$$k = \frac{k_{\text{obs}}(K_1 + [I^-])(K_2 + [H^+])[I^-]}{K_1K_2[\text{PhOH}]} = \frac{k_1k_2[B]}{k_{-1}} \qquad (7)$$

The rate constant, k, comprises the concentration of bases and therefore all the experiments intended to evaluate the influence of substitutents were carried out at constant buffer concentration. In order to verify the dependence of k_{obs} on $[I^-]$ as given in equation (7) and, thereby, the decomposition of intermediate as rate-determining step, all phenols were measured at two different $[I^-]$ (Table 1). The first-order dependence of k_{obs} on phenol concentration was confirmed in all cases investigated.

The pK_a of four p-substituted phenols was determined at 20 °C and ionic strength 0·5, and compared with thermodynamic values at 25 °C (Table 2). The differences between these two series of pK_a values are nearly constant, the mean being 0·21. This value was added to other thermodynamic pK_a values and used in computing log K.

TABLE 1

Kinetic measurements of iodination of *para*-substituted phenols at 20 °C

No.	Substituted phenol	pK_a	10^2[KI] / M	10^3[PhOH] / M	10^2k_{obs} / min^{-1}	$10^{-3}k$ / l mol^{-1} min^{-1}
1	*p*-Chlorophenol	9·63	1·5	2·0	4·79	2·30
			1·5	1·0	2·50	2·40
			3·0	2·0	1·27	2·35
2	*p*-Bromophenol	9·55 [a] *	1·5	2·0	5·79	2·32
			1·5	1·0	2·94	2·36
			3·0	2·0	1·69	2·61
3	*p*-Fluorophenol	10·02 [b] *	1·5	2·0	3·29	3·89
			1·5	1·0	1·57	3·72
4	*p*-Cresol	10·45	3·0	1·0	6·94	166
			3·0	0·5	3·40	163
			1·5	1·0	28·0	178
5	*p*-t-Butylphenol	10·44 [c]	3·0	1·0	9·40	226
			1·5	1·0	34·3	213
			1·5	0·5	16·9	210
6	*p*-Methylsulphonylphenol	8·05	1·5	4·0	2·60	0·0179
			3·0	4·0	0·778	0·0207
			1·5	2·0	1·31	0·0180
7	*p*-Cyanophenol	8·16 [d]	3·0	4·0	0·674	0·0298
			1·5	4·0	2·46	0·0235
8	*p*-Acetylphenol	8·26 [a] *	1·5	4·0	24·4	0·263
			3·0	4·0	5·88	0·245
			1·5	2·0	9·44	0·204
9	*p*-Nitrophenol	7·39	1·5	10·0	1·95	0·00150
			3·0	10·0	0·503	0·00149

* The pK_a value has been corrected for temperature and ionic strength used.

[a] F. G. Bordwell and G. D. Cooper, *J. Amer. Chem. Soc.*, 1953, **74**, 1058. [b] C. M. Jutson and M. Kilpatrick, *J. Amer. Chem. Soc.*, 1949, **71**, 3110. [c] L. A. Cohen and W. M. Jones, *J. Amer. Chem. Soc.*, 1963, **85**, 3397. [d] G. Wheland, R. M. Brownell, and E. C. Mayo, *J. Amer. Chem. Soc.*, 1948, **70**, 2492.

The relation between log k and $(\sigma_m + a\Delta\sigma_p^-)$ for a equal to unity is shown in the Figure and expressed by equation (8). The correlation of log k with σ_m is much poorer (9).

$$\log k = 4{\cdot}92 - 3{\cdot}83(\sigma_m + \sigma_p^- - \sigma_p); \quad r = 0{\cdot}993; \quad s = \pm 0{\cdot}178 \qquad (8)$$

$$\log k = 4{\cdot}94 - 5{\cdot}66\sigma_m; \quad r = 0{\cdot}952; \quad s = \pm 0{\cdot}69 \qquad (9)$$

TABLE 2

Dissociation constants of *para*-substituted phenols

Compound	pK_a (20 °C)	pK_a (25 °C)	ΔpK_a
p-Cresol	10·45 ± 0·05	10·26 [a]	0·19
p-Chlorophenol	9·63 ± 0·05	9·42 [b]	0·21
p-Methylsulphonylphenol	8·05 ± 0·07	7·83 [b]	0·22
p-Nitrophenol	7·39 ± 0·06	7·15 [c]	0·24

[a] A. J. Biggs, *Trans. Faraday Soc.*, 1956, **52**, 35. [b] Ref. *c* of Table 1. [c] R. H. Robinson and A. J. Biggs, *Trans. Faraday Soc.*, 1955, **51**, 901.

The catalytic effect of bases was studied in iodination of p-cresol and equation (10) was used for evaluation of base catalysis in acetate buffer, and equations (11) and (12) for that catalysis in phosphate buffer. The experi-

$$k_{\text{obs}}[H^+] = \left(k_0 + \sum_0^i k_{B_i}[B_i]\right)\frac{K_1K_2[\text{PhOH}]}{[I^-](K_1 + [I^-])} = k_0' + \sum_0^i k'_{B_i}[B_i] \qquad (10)$$

$$k_{\text{obs}}[H^+] = k_0' + [A]\left(k_A' + \frac{k_B}{a}\right); \quad a = [A]/[B] = [HPO_4^{2-}]/[H_2PO_4^-] \qquad (11)$$

$$k_{\text{obs}}[H^+] = k'' + k_B''[B]; \quad k'' = k_0' + k_A'[A] \qquad (12)$$

TABLE 3

The influence of base concentration on the iodination rate constant of *p*-cresol at 20 °C

No.	10^2[Na_2HPO_4] M	10^2[KH_2PO_4] M	10^2[AcONa] M	pH	10^2k_{obs} min^{-1}	10^9k_{obs}[H^+] min^{-1}
1	2·0	2·0		6·66	2·82	6·17
2	4·0	2·0		6·98	6·94	7·29
3	6·0	2·0		7·16	13·8	9·55
4	8·0	2·0		7·30	21·5	10·8
5	10·0	2·0		7·43	35·6	13·2
6	12·0	2·0		7·51	46·3	14·3
7	2·0	4·0		6·35	1·46	6·54
8	2·0	8·0		6·01	0·697	6·82
9	2·0	12·0		5·80	0·477	7·56
10	4·0	8·0		6·33	1·93	9·02
11	8·0	16·0		6·31	2·53	13·9
12	3·0	1·0		7·13	9·13	6·77
13	6·0	2·0		7·16	13·53	9·36
14	12·0	4·0		7·19	21·9	14·1
15			4·5	5·61	1·654	40·8
16			9·0	5·66	2·30	50·3
17			18·0	5·65	3·35	75·0
18			27·0	5·64	4·31	98·8
19			36·0	5·62	5·10	122·4

The concentrations were 3×10^{-2}M-KI and 1×10^{-3}M *p*-cresol in phosphate buffers and $1{\cdot}5 \times 10^{-2}$M-KI and 2×10^{-3}M *p*-cresol in acetate buffers.

mental conditions and results are in Tables 3 and 4, respectively.

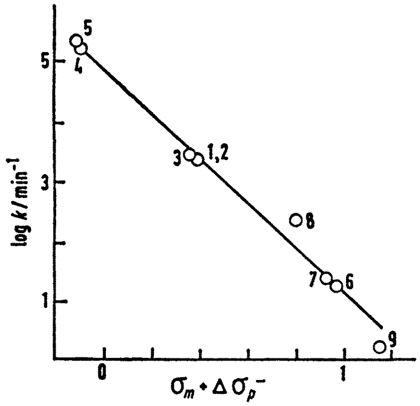
TABLE 4

Constants for base-catalysed iodination of *p*-cresol

Base	10^8k_B/min^{-1}	r_{xy}	$10^{-5}k_B$ l mol^{-1} min^{-1}
Na_2HPO_4	8·48 ± 0·425	0·995	19·4
KH_2PO_4	1·30 ± 0·174	0·982	2·98
AcONa	26·2 ± 0·613	0·9997	7·75
H_2O [a]	0·415		0·950
H_2O [b]	2·93 ± 0·136		0·869

[a] Measured in phosphate buffers. [b] Measured in acetate buffers.

The formation of intermediate should become the rate-determining step at sufficiently low concentrations of I^-. This change in mechanism was found by Grovenstein and Aprahamian [5] in the iodination of *p*-nitrophenol carried out at low pH values, where the kinetics were complicated by the iodination of the undissociated phenol. We have studied the dependence of k_{obs} on concentration of I^- in iodination of *p*-cresol and *p*-sulphonylmethylphenol in acetate buffer at constant acetate anion concentration. Equation (13), derived from equations (1)—(4) by means of the steady-state approximation, was used for evaluation of k_1. The results are in Table 5.



Correlation between rate constant, *k*, for iodination of substituted phenols and $\delta_m + \Delta\delta_p^-$

$$\frac{K_1[\mathrm{PhOH}]}{k_{obs}(K_2 + [\mathrm{H}^+])} \cdot \frac{K_1}{K_1 + [\mathrm{I}^-]} = \frac{k_{-1}[\mathrm{I}^-]}{k_1 \Sigma k_2 [\mathrm{B}]} + \frac{1}{k_1} \quad (13)$$

TABLE 5

Variation of rate of iodination of *p*-cresol and *p*-methylsulphonylphenol with concentration of potassium iodide

PhOH	10^3[PhOH] M	10^3[KI] M	$10^3k'$ min^{-1}	$\frac{K_2[\mathrm{PhOH}]K_1}{k_{obs}(K_2 + [\mathrm{H}^+])(K_1 + [\mathrm{I}^-])}$
p-Cresol [a]	4	30	14·95	0·1460
	4	15	59·30	0·0710
	4	10	125·0	0·0489
	4	5	442·0	0·0251
	1	2	466·0	0·0116
	1	1	1310·0	0·0060
	1	0·5	294·0 [b]	0·0035
	1	0·25	574·0 [b]	0·0021
p-Methylsulphonylphenol [a]	4	10	5·88	260
	4	5	21·16	131
	4	2	90·10	60
	4	1	226·0	35
	2	0·5	252·4	20
	4	0·25	1013·0	12

[a] The buffer used was 4×10^{-2}M-AcOH and $3{\cdot}6 \times 10^{-1}$M-AcONa (pH 5·62). [b] $3{\cdot}6 \times 10^{-1}$M-AcOH, pH 4·62.

DISCUSSION

As in coupling, a very good correlation was obtained between log k and $(\sigma_m + a\Delta\sigma_p^-)$ in the iodination of *para*-substituted phenols, although the latter reaction differed both in the charge of reagent being studied and rate-determining step. Similar behaviour of $-M$ substituents in both reaction series strongly suggests that an important factor is the loss of resonance energy owing to the limited conjugation between these substituents and oxygen in transition state. The difference of resonance energy between phenol and phenolate ion is proportional to $2{\cdot}23\Delta\sigma_p^-$, where 2·23 is the value of the reaction constant of dissociation of substituted phenols.[9] In iodination the change in resonance energy is similarly proportional to $-3{\cdot}83\Delta\sigma_p^-$. The greater value in the latter case is probably caused by the smaller conjugation of substituent with oxygen in the transition state as compared with the undissociated phenol. The value of the reaction constant in iodination is comparable with that found in the coupling of substituted phenols with diazonium salts. This is in spite of the fact that the rate-determining step in the former reaction is the decomposition of the intermediate. The value of the reaction constant, ρ, should probably not change significantly if the formation of intermediate were the rate-determining step. This appears to be correct as the ratio $k_{1,\mathrm{Me}} : k_{1,\mathrm{SO_2Me}}$ is almost the same as the corresponding ratio of k constants when the decomposition of the intermediate is the rate-determining step. From the results, it follows that iodine is about two powers of ten more reactive to *para*-substituted phenols than *p*-nitrobenzenediazonium chloride.

The difference in catalytic activities of various bases is rather small (Table 4). The value of β calculated from Brønsted relation is *ca.* 0·2. This indicates that the transition state and the intermediate have closely similar structures. This is in agreement with the large decrease of resonance energy deduced from the relation of log k against $(\sigma_m + a\Delta\sigma_p^-)$ because conjugation between substituent and oxygen in the intermediate is almost absent.

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[9] A. J. Biggs and R. A. Robinson, *J. Chem. Soc.*, 1961, **69**, 388.