

**1016.** *Kinetics and Mechanisms of Aromatic Halogen Substitution. Part XVIII.*<sup>1</sup> *Conjugative Electron Release from the Hydroxyl Group, and the Bromination of Phenols.*

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The kinetics of bromination of phenol and a number of alkyl-phenols have been examined in acetic acid under conditions conducive to second-order reaction. The relative rates are discussed with reference to the additivity of substituent effects. Evidence for steric inhibition of resonance is discussed through comparison with the reactivity of anisole and its homologues. It is suggested that conjugative electron-release by the hydroxyl group can be augmented by a polarisability involving H-O non-bond resonance.

HYDROXYL, attached to an unsaturated system, is very powerfully electron-releasing; in certain circumstances it seems even more so than methoxyl. Attempts to establish this difference need careful kinetic control of the mechanism of the reaction, since the formation of a phenoxide ion from a phenol produces a substrate containing the still more powerfully electron-releasing O<sup>-</sup> group. There have, however, been several investigations free from this ambiguity. Robertson, de la Mare, and Swedlund<sup>2</sup> showed that phenol is brominated in acetic acid faster than is anisole, and the rate is not reduced by addition of sulphuric acid. Eaborn and Webster<sup>3</sup> showed that the proto-desilylation of substituted phenyltrimethylsilanes is markedly more accelerated by the hydroxyl than by the methoxyl group; the kinetic form precluded ionisation of hydroxyl. Deno and

<sup>1</sup> Part XVII, de la Mare, Johnson, and Lomas, *J.*, 1963, 5973.

<sup>2</sup> Robertson, de la Mare, and Swedlund, *J.*, 1953, 782.

<sup>3</sup> Eaborn, *J.*, 1956, 4858; Eaborn and Webster, *J.*, 1957, 4449.

co-workers<sup>4</sup> showed that the triarylmethanols were more ionised by the hydroxyl than by the methoxyl group; in this investigation the acidity was such as to preclude ionisation of the hydroxyl group. In accordance with these results, H. C. Brown and Okamoto<sup>5</sup> have estimated measures of the electron-releasing power, *viz.*,  $\sigma^+_{p-OH} = -0.92$ ;  $\sigma^+_{p-OMe} = -0.78$ ; this sequence implies that the hydroxyl group is expected to be more electron-releasing than methoxyl for reactions which show linear free-energy correlations with aromatic substitutions.

The reason for this difference has been uncertain. When the electron-releasing power of an OR-group is modified by changing R, it has been shown that inductive electron-withdrawal within R reduces the electron-releasing power of the oxygen, as measured for example by the relative rates of chlorination of aromatic ethers, ROAr, in acetic acid:<sup>6</sup>

R:	Pr <sup>i</sup>	Et	Me	<i>p</i> -Me·C <sub>6</sub> H <sub>4</sub> ·CH <sub>2</sub>	Ph·CH <sub>2</sub>	<i>p</i> -Cl·C <sub>6</sub> H <sub>4</sub> ·CH <sub>2</sub>	<i>p</i> -O <sub>2</sub> N·C <sub>6</sub> H <sub>4</sub> ·CH <sub>2</sub>
Rel. rate ...	440	199	100	95	68	41	14

On this basis, the methoxyl group should release electrons conjugatively more strongly than does the OH group. The Hammett  $\sigma_m$ -values (OH, +0.121; OMe, +0.115)<sup>7</sup> show that where conjugative effects are of minimal importance the methoxyl group is slightly less electron-withdrawing than the hydroxyl. The inductive influence of the methyl group as compared with hydrogen does not seem to be at all abnormal in this situation, and does not help in interpreting the relatively great electron-releasing power of the hydroxyl group.

Two other hypotheses require consideration. One is that the hydroxyl group has an advantage over the methoxyl group in being able to release electrons hyperconjugatively, or otherwise by no-bond resonance, as suggested by Robertson, de la Mare, and Swedlund.<sup>2</sup> It was supported by Eaborn,<sup>3</sup> who considered that the solvent assisted this effect through hydrogen-bonding. Analysis of this theory requires that the possible magnitude should be estimated of the effect considered in the alternative hypothesis, namely, that the methoxyl group is unable, when attached to the benzene ring, to exert its full electron-releasing power because the *ortho*-hydrogen atoms inhibit coplanarity.

In 1959 an attempt<sup>8</sup> was made to assess the relative importance of these two structural features by analysis of the relative rates of bromination of substituted phenols and anisoles. The crucial experimental data were of a preliminary nature, and suffered because the reactions were so fast that the kinetic form for bromination was not established to be identical for phenol and anisole. We have now tried to obtain more satisfactory experimental information, and have extended the measurements to other substituted phenols.

#### EXPERIMENTAL

Some of the materials and methods have been described.<sup>9</sup> The phenols were usually redistilled commercial specimens, and had the following properties: phenol, b. p. 182°/760 mm., m. p. 42°; *o*-cresol, b. p. 191—192°/760 mm., m. p. 30°; *p*-cresol, b. p. 202°/760 mm., m. p. 34°; 2,6-dimethylphenol, m. p. 47°; 2,4-dimethylphenol, b. p. 211°/760 mm.; 2-*t*-butylphenol, b. p. 101—103°/14 mm.; 4-*t*-butylphenol, b. p. 130°/20 mm., m. p. 97°; 2,4-di-*t*-butylphenol, b. p. 130°/15 mm., m. p. 57°; 2,6-di-*t*-butylphenol, recrystallised from aqueous ethanol, m. p. 36°. Anisole had b. p. 155°/766 mm.; 2-methylanisole, b. p. 171°/760 mm.; 2,6-dimethylanisole, b. p. 83—84°/25 mm. Lithium bromide was dried by heating in a current of dry nitrogen, then dissolved in acetic acid to give a stock solution whose concentration was determined by titration. Lithium perchlorate was dried similarly, weighed quickly, and dissolved in acetic acid. Solutions of sodium acetate were prepared by dissolving a known weight of sodium in acetic acid.

<sup>4</sup> Deno and Schriesheim, *J. Amer. Chem. Soc.*, 1955, **77**, 3051; Deno and Evans, *ibid.*, 1957, **79**, 5804.

<sup>5</sup> Brown and Okamoto, *J. Amer. Chem. Soc.*, 1958, **80**, 4979.

<sup>6</sup> Bradfield and Jones, *Trans. Faraday Soc.*, 1941, **37**, 726.

<sup>7</sup> McDaniel and Brown, *J. Org. Chem.*, 1958, **23**, 420.

<sup>8</sup> de la Mare, *Tetrahedron*, 1959, **5**, 107.

<sup>9</sup> Robertson, de la Mare, and Johnston, *J.*, 1943, 276.

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Deuteroacetic acid ( $\text{CH}_3\cdot\text{CO}_2\text{D}$ ) was prepared by allowing purified acetic anhydride to react with deuterium oxide. It was purified by careful fractional distillation; b. p.  $117^\circ/760$  mm.

The equilibrium constant for the formation of the tribromide ion in acetic acid containing 0.2M-lithium perchlorate was determined spectrophotometrically as described earlier.<sup>10</sup> The optical densities were determined at 3450—3800 Å in 1 cm. cells at  $25^\circ$  in a Unicam S.P. 500 spectrophotometer with control solutions containing lithium bromide and lithium perchlorate in the appropriate proportions. The total concentration of bromine was always  $5.31 \times 10^{-4}\text{M}$ . Table 1 gives the optical densities of the various solutions.

TABLE I.  
Optical densities (1 cm. cells,  $25^\circ$ ) of solutions of bromine containing lithium bromide and lithium perchlorate (total salt concentration, 0.2M).

Wavelength (Å)	Optical density, with concn. of lithium bromide:						K (mole l. <sup>-1</sup> )
	0.00 *	0.0016	0.0040	0.0080	0.0160	0.0400	
3450	0.025	0.219	0.382	0.563	0.728	0.860	0.0065
3500	0.036	0.183	0.316	0.449	0.578	0.672	0.0066
3550	0.044	0.156	0.262	0.372	0.490	0.543	0.0065
3600	0.052	0.143	0.230	0.320	0.410	0.467	0.0067
3700	0.070	0.143	0.212	0.280	0.348	0.397	0.0066

\* Mean of values obtained before and after the other measurements.

From these results the equilibrium constant  $K = [\text{Br}^-][\text{Br}_2]/[\text{Br}_3^-]$  can be obtained graphically<sup>10</sup> for each wavelength by plotting  $1/\{\epsilon^{\text{app}} - \epsilon\}$  against  $1/[\text{Br}^-]$ , where  $\epsilon^{\text{app}}$  is the apparent extinction coefficient of the same concentration of bromine in the absence of bromide ion. Since<sup>10</sup>

$$\frac{1}{(\epsilon^{\text{app}} - \epsilon_{\text{Br}_2})} = \frac{K}{(\epsilon_{\text{Br}_3^-} - \epsilon_{\text{Br}_2}) \cdot [\text{Br}^-]} + \frac{1}{(\epsilon_{\text{Br}_3^-} - \epsilon_1)}$$

where  $\epsilon_{\text{Br}_3^-}$  is the extinction coefficient of the tribromide ion, the plot should be linear, and from its slope and intercept can be calculated the equilibrium constant ( $K$ ) and the extinction coefficient of the tribromide ion. The values of  $K$  so derived (Table 1) vary very little with wavelength; the mean is 0.0066 mole l.<sup>-1</sup>. This is consistent with other values,<sup>10,11</sup> the known trend with solvent change being borne in mind:  $K = 0.0119$  in 70% acetic acid at  $20^\circ$ ; 0.0114 in 75% acetic acid at  $20^\circ$ ; 0.0109 in 80% acetic acid at  $20^\circ$ , 0.0068 in 90% acetic acid at  $24.8^\circ$ .

Kinetic measurements of rates of bromination were generally made conventionally.<sup>9</sup> The following is a typical example, for 0.00149M-phenol and 0.00146M-bromine with 0.244M-LiBr in acetic acid at  $25^\circ$ . Aliquot parts (5 ml.) were removed at intervals for titration with 0.0025N-sodium thiosulphate:

Time (min.)	0.00	3.40	7.12	11.73	14.82	19.28	23.78
Titre (ml.)	5.85	5.00	4.30	3.80	3.35	2.95	2.70

From the graph of percentage reaction ( $x$ ) against time ( $t$ ) the rate-coefficients for  $x = 20, 30, 40,$  and  $50\%$  reaction are 34, 33, 34, and 33, l. mole<sup>-1</sup> min.<sup>-1</sup> respectively. The following summarises, for phenol, the values at different concentrations of lithium bromide:

LiBr (M)	0	0.00875	0.0124	0.0165	0.0688	0.122	0.244
$k_2$ (l. mole <sup>-1</sup> min. <sup>-1</sup> )	360	157	123	104	48	39	34

Since the reactions without lithium bromide are very fast, and may have their kinetic forms slightly disturbed by the hydrogen bromide which is formed in the reaction, it was thought best to evaluate the rate-coefficients for reaction with molecular bromine by using results obtained at constant ionic strength with mixtures of lithium bromide and lithium perchlorate. The following is a typical kinetic run under these conditions, for phenol (0.00142M) and bromine (0.00152M) with 0.10M-LiBr and 0.10M-LiClO<sub>4</sub> in acetic acid at  $25^\circ$ :

Time (min.)	0	1.35	3.00	5.00	6.80	8.30	9.85
Titre (ml.)	6.10	5.40	4.75	4.15	3.75	3.50	3.20
$k_2$ (l. mole <sup>-1</sup> min. <sup>-1</sup> )	—	68	67	68	66	61	67

<sup>10</sup> Grovenstein and Henderson, *J. Amer. Chem. Soc.*, 1956, **78**, 569; Keefer and Andrews, *ibid.*, 1956, **78**, 3637.

<sup>11</sup> Bradfield, Davies, and Long, *J.*, 1949, 1389.

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The rate coefficients above were evaluated by using the formula:  $k_2 = 2.303\{\log_{10} [b(a-x)/a(b-x)]\}/t(a-b)$  where  $a$  and  $b$  are the initial concentrations of reactants, and  $x$  is the concentration of product formed at time  $t$ . Whenever, as in this case, the reaction was sufficiently slow, the time-zero was taken as that of the first aliquot part titrated, the initial concentration being appropriately adjusted. This procedure minimises systematic errors of timing; it cannot be used satisfactorily for very fast runs, for which the initial concentration of bromine was obtained by titration of the stock solution of this reagent. In many cases the initial concentrations of reagents were sufficiently close to allow use of the formula  $k_2 = x/a t(a-x)$ , where  $a$  is the concentration of both reagents. Under these circumstances we usually obtained the rate coefficients at  $x = 10, 20, 30, 40, 50\%$  reaction from smoothed curves of  $x$  against  $t$ .

In general, the rate coefficients were satisfactorily constant, and are quoted for 20–40% reaction, where the measurements are most accurate. There seemed to be a slight tendency for them to fall in the later stages of reaction; this may arise from slight disturbance resulting from the liberation of HBr.

Table 2 summarises the rate-measurements made in acetic acid at 25°, with various phenols

TABLE 2.

Measured rate-coefficients ( $k_2$ , l. mole<sup>-1</sup> min.<sup>-1</sup>), reagents both M/640 except where otherwise stated, and derived second-order rate coefficients ( $k$ ) for bromination of phenol, anisole, and related compounds in acetic acid at 25°.

Compound	LiBr(M): LiClO <sub>4</sub> (M):	$k_2$ (l. mole <sup>-1</sup> min. <sup>-1</sup> ) with added salts:						$k$ (l. mole <sup>-1</sup> min. <sup>-1</sup> ) (for total salt concentration 0.20M)
		0.20 0.00	0.15 0.05	0.10 0.10	0.05 0.15	0.00 0.20	0.00 0.00 <sup>a</sup>	
Anisole .....	0.34	0.53	0.92	2.0	34	3.4	12	
2-Methylanisole .....	2.2	3.4	5.5	12.1	118	22	50	
2,6-Dimethylanisole .....	—	—	—	—	1.8	0.43	—	
Phenol .....	32 <sup>b</sup>	43	65	122	—	360	1100	
Phenol in CH <sub>3</sub> ·CO <sub>2</sub> D .....	27	38	55	102	—	220	750	
2-Methylphenol .....	190 <sup>b</sup>	227	310	700	—	1165	5600	
4-Methylphenol .....	8.1	11.4	17.3	34	550	101	250	
2,6-Dimethylphenol <sup>c</sup> .....	230 <sup>b</sup>	296	398	550	—	1600	7500	
2,4-Dimethylphenol .....	22 <sup>b</sup>	30	39	84	970	326	670	
2-t-Butylphenol .....	280	350	—	965	—	1400	8250	
4-t-Butylphenol .....	11.0	15.2	20.5	50	—	120	340	
2,4-Di-t-butylphenol .....	49	—	—	200	—	830	1530	
2,6-Di-t-butylphenol .....	—	—	—	—	—	300 <sup>d</sup>	—	

<sup>a</sup> Values of  $k_2$  for  $x = 20\%$  reaction. <sup>b</sup> Interpolated from results at other concentrations of lithium bromide. <sup>c</sup> Initial concns., M/1280. <sup>d</sup> Initial concns., M/20,000; spectrophotometric rate of formation of dienone; see text.

and bromine at nearly equal concentrations, and lithium bromide and lithium perchlorate totalling 0.2M. Some representative values obtained without added salts are included also.

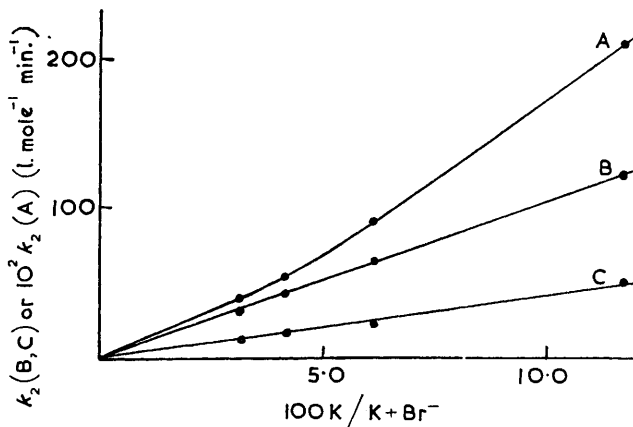
To obtain the true rate-coefficients for reaction of the aromatic compounds with molecular bromine, the procedure recommended by Berliner and Beckett<sup>12</sup> was adopted. The measured rate-coefficients,  $k_2$ , were plotted against  $K/(K + Br^-)$  where  $K$  is the equilibrium constant for the equilibrium  $Br_3^- \rightleftharpoons Br_2 + Br^-$ , determined for our solutions as 0.0066 mole l.<sup>-1</sup> (Table 1).

For the more rapidly reacting compounds, the plot was linear, a result which indicates that even with zero concentration of bromide ion the third-order reaction<sup>2</sup> (kinetic form,  $-d[Br_2]/dt = k[ArH][Br_2]^2$ ) made no significant contribution to the overall reaction. The rate-coefficients were then calculated from the slope of the graph of  $k_2$  against  $K/(K + Br^-)$  which in all cases went through the origin within experimental error. For anisole and its homologues, however, the plots were curved, showing that the third-order reaction was contributing significantly in the absence of bromide ion. The rates were then calculated from the initial slope. Typical plots are given in the Figure, and values of  $k$  in Table 2.

The *ortho*:*para*-ratio for the bromination of phenol was determined under conditions approximating to those of the kinetic measurements. Bromine (0.25 g.) in acetic acid (10 ml.) was added dropwise during 3–4 hr. to phenol (0.15 g.) in acetic acid (500 ml.). The reaction

<sup>12</sup> Berliner and Beckett, *J. Amer. Chem. Soc.*, 1957, **79**, 1425.

mixture was then added to water and extracted with ether. The ether extracts were washed first with a solution of sodium bicarbonate and then with a buffer solution, pH 6.4. The ether extract was then dried ( $\text{Na}_2\text{SO}_4$ ) and most of the ether was distilled off. Other experiments were carried out with higher concentrations of reactants. The recovery procedure was tested by using a mixture containing 2- (0.0241 g.) and 4-bromophenol (0.2191 g.). The recovered samples were dissolved in a little acetone and analysed by vapour-phase chromatography. A 6-ft. column packed with silicone fluid M.S. 550 (25% w/w) coated on Celite (80–100 mesh) and operated at  $160^\circ$  was used; nitrogen (1.3 l./hr.) was the carrier. The retention times of *o*- and *p*-bromophenol were 8 min. and 18 min., respectively. A calibration curve of peak-area against composition was constructed by using synthetic mixtures of 2- and 4-bromophenol. The results (% of 2-isomer) were as follows: synthetic mixture after recovery,  $9.5 \pm 0.3\%$  (actual composition, 9.9%); product from reaction in dilute solution, 5.0, 5.5,



Dependence of the rate on the bromide ion concentration for anisole (A), phenol (B), and 4-t-butylphenol (C).

6.3%; product from reaction in concentrated solution, 5.4%. It seems reasonable, therefore, to assess the isomer-ratio in the bromination of phenol under conditions conducive to the second-order kinetic form as being *ortho* : *para* = 5.5 : 94.5 ( $\frac{1}{2}o : p = 0.029$ ). Holleman and Rinkes<sup>13</sup> determined the amount of *p*-substitution in acetic acid at  $30^\circ$  as 87.5%; it is very probable that their method would have produced some dibromo-derivatives.

*Bromination of 2,6-Di-t-butylphenol.*—Ershov and Volod'kin<sup>14</sup> showed that bromination of 2,6-di-t-butylphenol can produce the product of substitution with prototropic rearrangement, 4-bromo-2,6-di-t-butylcyclohexa-2,5-dien-1-one (I). This has been confirmed. Equimolecular amounts of bromine and 2,6-di-t-butylphenol were mixed in 90% acetic acid, the mixture was poured quickly into aqueous potassium iodide, and aqueous sodium thiosulphate was added to remove iodine. The resulting solution was extracted several times with light petroleum (b. p.  $40$ – $60^\circ$ ). The petroleum solvent was then evaporated at room temperature, and the product was recrystallised from light petroleum, giving 4-bromo-2,6-di-t-butylcyclohexa-2,5-dien-1-one, m. p.  $69$ – $71^\circ$  (Found: C, 58.7; H, 7.3; O, 5.6; Br, 28.0. Calc. for  $\text{C}_{14}\text{H}_{21}\text{BrO}$ : C, 58.9; H, 7.4; O, 5.6; Br, 28.1%). Its infrared spectrum has strong characteristic bands at 1665 and 1640  $\text{cm}^{-1}$ . Its ultraviolet spectrum in cyclohexane has a peak with a maximum at 2520 Å ( $\epsilon = 13,400$ ).

When the bromination of 2,6-di-t-butylphenol is followed kinetically in acetic acid by using the customary technique, the building-up of the intermediate dienone (I) can be recognised since it reacts slowly with acidified potassium iodide solutions, so that after the end-point has apparently been reached, more iodine is liberated. The rate of formation of the intermediate can be followed spectrophotometrically. Thus 2,6-di-t-butylphenol (0.00005M)

<sup>13</sup> Holleman and Rinkes, *Rec. Trav. chim.*, 1911, **30**, 48.

<sup>14</sup> Ershov and Volod'kin, *Izvest. Akad. Nauk, Otdel. Chim. Nauk*, 1962, 730.

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and bromine (0.00005M) in acetic acid were mixed at 25° in a 1 cm. cell, and the optical density recorded at intervals was as follows:

Time (min.)	0.5	0.75	1.00	1.50	2.00	2.75	3.50
Optical density	0.040	0.048	0.050	0.056	0.060	0.065	0.070
Time (min.)	4.00	5.00	7.00	9.00	12.00	14.00	16.00
Optical density	0.070	0.082	0.095	0.103	0.112	0.135	0.145
Time (min.)	19.00	23.00	25.00	30.00	37.00	40.00	
Optical density	0.145	0.163	0.170	0.193	0.210	0.220	

From these data the initial rate of forming the dienone is  $k_2 = ca. 300 \text{ l. mole}^{-1} \text{ min.}^{-1}$ , and the velocity falls off as the reaction proceeds, showing that in acetic acid the dienone is probably slowly decomposed to give the final product of substitution.

It was shown also that the rate of formation of the dienone is made more rapid by adding water to the acetic acid solvent. In this, the reaction resembles the bromination of aromatic compounds generally,<sup>2</sup> and of phenol and anisole specifically.

Search was made for corresponding behaviour in the bromination of other phenols. For these compounds, the titration behaviour was quite normal, and clearly the dienone does not survive under the conditions of the estimation of bromine. For some compounds, however, such an intermediate can be detected spectrophotometrically. Thus with 2,6-dimethylphenol (0.000033M) and bromine (0.000033M) in acetic acid in 1 cm. cells at 25° the optical densities at intervals were as follows:

Time (min.)	0.5	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	12.0	15.0
Optical density	0.050	0.060	0.080	0.097	0.114	0.125	0.136	0.142	0.150	0.153	0.154	0.149

If the extinction coefficient of the dienone at 2520 Å is the same as that for the dienone from 2,6-di-*t*-butylphenol, and with  $t = 0.5$  min. as the first point, in order to minimise errors arising from residual absorption, the rate of change of optical density over the first 5% of reaction corresponds with a rate-coefficient  $k_2 = 1440 \text{ l. mole}^{-1} \text{ min.}^{-1}$ . This is in satisfactory agreement with that determined by titration at higher concentration (1600  $\text{l. mole}^{-1} \text{ min.}^{-1}$ ; see Table 2), and indicates that the rate-measurements made by bromine-titration are not in this sort of case vitiated by dienone formation. The build-up of dienone in the above experiment reaches at its maximum about 27% of the value expected for complete conversion; thereafter the optical density declines, showing that the decomposition of the dienone to give the product of substitution is relatively rapid. Further kinetic studies of these decompositions are in progress.

## DISCUSSION

*The Additivity Principle.*—The second-order rate-coefficients,  $k$ , for the bromination of phenol and its alkyl derivatives can be treated by the “additivity principle,” that is, by assuming that the influence of substituents is independent and additive in free energy of activation.<sup>15</sup> We have chosen to treat the *ortho* : *para* ratio for bromination of phenol as an unknown, for comparison with the experimental value, as also is the partial rate factor,  $f_m^{\text{Me}}$ , for activation by a *meta*-methyl group. We cannot determine from the present experiments the absolute partial rate factors, since the rate of bromination of benzene is too slow for direct measurement under these experimental conditions. The experimental values of  $k$  for bromination of phenol, 2-methylphenol, and 4-methylphenol, together with the requirements of the additivity principle and the fact that these reactions give substitution *ortho*- and *para*-, but not *meta*- to the hydroxyl group, lead to the equations:  $2f_p^{\text{OH}} + f_p^{\text{OH}} = 1100a$ ;  $f_o^{\text{OH}} \cdot f_m^{\text{Me}} + f_p^{\text{OH}} \cdot f_m^{\text{Me}} = 5600a$  and  $2f_p^{\text{OH}} \cdot f_m^{\text{Me}} = 250a$ , where  $a = 6/k_{\text{benzene}}$ . Solution of these gives two values which can be compared with experiment. The first is  $f_m^{\text{Me}} = 5.2$ . This agrees very well with independent estimates of the partial rate factor for bromination *meta*- to a methyl group, namely those given by Stock and Brown<sup>16</sup> for third-order bromination in acetic acid and in nitromethane (5.5, 4.7). The second is the value of  $f_o^{\text{OH}}/f_p^{\text{OH}} = 0.0228$ . This can be compared with the experimental

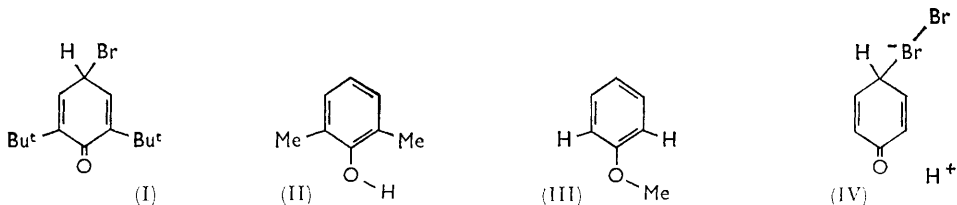
<sup>15</sup> de la Mare and Ridd, “Aromatic Substitution—Nitration and Halogenation,” Butterworths, London, 1958.

<sup>16</sup> Stock and Brown, in “Advances in Physical Organic Chemistry I,” ed. V. Gold, 1963, p. 35 ff.

$\frac{1}{2}$ ortho:para ratio for bromination of phenol as determined by vapour-phase chromatography (0.029). The agreement is quite satisfactory, in view of the experimental difficulties. Further test of the additivity principle can be made by calculating the rate of bromination of 2,4-dimethylphenol, which should be 650 l. mole<sup>-1</sup> min.<sup>-1</sup>. The experimental value is 670 l. mole<sup>-1</sup> min.<sup>-1</sup>.

A similar treatment can be applied to the t-butylphenols. From the above partial rate factors, the rate of bromination of 4-t-butylphenol allows us to derive  $f_m^{t-Bu} = 7.0$ . Stock and Brown's<sup>17</sup> experimental partial rate factor for third-order bromination directed by a meta-t-butyl group is 6.1, in satisfactory agreement. Extrapolation as before to 2-t-butylphenol gives an expected rate of 7620 (found, 8250); and for 2,4-di-t-butylphenol, 1190 (found, 1530). It can be seen that the additivity principle is obeyed relatively well in these systems, provided that not more than one substituent is located ortho- to the hydroxyl group.

**2,6-Dimethylphenol: Steric Inhibition of Resonance.**—One factor which is theoretically expected<sup>18</sup> to interfere with the application of the additivity principle is steric inhibition of resonance. Experimental illustration comes from the rates of chlorination of 2,6- and 2,N-disubstituted anilides, as we<sup>8,15,18</sup> and others<sup>19</sup> have discussed. For phenols, the effect is less important, but its magnitude can be estimated by calculating the expected rate of bromination of 2,6-dimethylphenol for comparison with experiment. From the results already given,  $k$  should be 28,490: the experimental value is 7500. So the reactivity of this compound is less than would be expected on the additivity principle by a factor of 3.8. We think that this is the most that can be attributed to steric inhibition of mesomerism arising from steric interaction between the hydroxyl group and an ortho-methyl substituent. This corresponds with a contribution to the free energy of activation of 0.8 kcal. mole<sup>-1</sup>. An effect of this magnitude seems not unreasonable: if the van der Waals radius of a methyl group is taken as 2.0 Å, and normal bond lengths and bond angles (as for example in 1,4-dimethoxybenzene<sup>20</sup>) are assumed, the non-bonding overlap for the planar conformation (II) is 0.7 Å. For comparison, the strain-energy of *cis*-, as compared with *trans*-but-2-ene, from their heats of hydrogenation,<sup>21</sup> is 1.0 kcal. mole<sup>-1</sup>, and on similar



assumptions *cis*-but-2-ene has a non-bonding overlap of 1.2 Å (Me-Me), whereas *trans*-but-2-ene has two of 0.5 Å (Me-H).

**Comparison of Phenol and Anisole: H-O No-bond Resonance.**—Steric inhibition of the rotation of the methoxyl group in anisole through the planar conformation (III) should be very similar to that for the hydroxyl group in 2,6-dimethylphenol (II). Geometrical calculation of the expected overlap shows that anisole should be slightly the more hindered if the Ar-O-R bond angle is less than 120° (the value in planar 1,4-dimethoxybenzene),<sup>20</sup> but any difference must clearly be very small. It seems unreasonable, therefore, to consider that the rate of bromination of anisole is reduced by steric inhibition of resonance by much more than in 2,6-dimethylphenol; that is, by much more than a factor of 3.8. Thus the conclusion reached in our preliminary study<sup>8</sup> is confirmed.

<sup>17</sup> Stock and Brown, *J. Amer. Chem. Soc.*, 1959, **81**, 5615.

<sup>18</sup> de la Mare and Hassan, *J.*, 1958, 1519.

<sup>19</sup> Baddeley, Holt, Smith, and Whittaker, *Nature*, 1951, **168**, 386; Baddeley, Smith, and Vickars, *J.*, 1956, 2455.

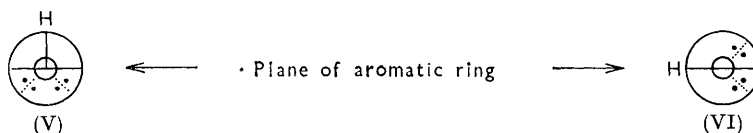
<sup>20</sup> Goodwin, Przybylska, and Robertson, *Acta Cryst.*, 1950, **3**, 279.

<sup>21</sup> Conant and Kistiakowsky, *Chem. Rev.*, 1937, **20**, 181.

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The reactivity of phenol in second-order bromination (kinetic form,  $-d[\text{Br}_2]/dt = k[\text{ArH}][\text{Br}_2]$ ) is, however, greater than that of anisole by a factor of 92. The inductive influence of the methyl group on the lone-pair electrons, and hence on the reactivity, ought, from the evidence already cited, to operate in the opposite direction, as we have argued above from theory and illustrated from experiment. So there remains an unexplained rate-discrepancy, involving a factor of at least  $92/4 = 23$ , between phenol and anisole; the hydroxyl group is more electron-releasing than the methoxyl group, by this amount, and by an effect which seems to be conjugative in origin, since it reaches the positions *ortho*- and *para*- to the hydroxyl group.

We thus have confirmed the experimental basis for the suggestion that the unexpectedly great electron-releasing power of the hydroxyl substituent should be ascribed to H-O hyperconjugation, through which the attainment of the transition state for electrophilic attack by bromine is facilitated by the contribution of structures, the limiting form of one of which, with bromine as the electrophil, would be formulated as structure (IV). This description of the transition-state stabilisation suffers from an important difficulty. Hyperconjugation from H-C bonds is now known\* to be subject to a steric requirement,<sup>22</sup> which in this case is that, for effective overlap between the pair of electrons involved in hyperconjugation and the double bond system with which this pair is hyperconjugated, the axis of the pair of electrons must have a resolved component perpendicular to the plane of the double bond system. In other words, for best hyperconjugative overlap of the pair of H-O bonding electrons, the geometry of the system must be as in structure (V); and for worst, and probably nearly zero, overlap, the geometry should be as in structure (VI).



In a preliminary discussion,<sup>8</sup> it was suggested that the transition state for bromination may not always occur in such a way that the conformation of the hydroxyl group is exactly that of structure (VI), with the H-O bond in the plane of the aromatic ring. Small rotations away from such a position would not greatly affect the lone-pair conjugation, particularly if steric hindrance to free rotation encourages some distortion of the bond-angles in the transition state. It seems probable, however, that the attainment of the transition state would occur in such a way as to allow conjugation to be maximised in the transition state (cf. ref. 1), and so we consider that this is unlikely to provide a complete interpretation of the observed rate-increase. There is, however, a feature of these structures to which attention does not yet seem to have been drawn. The no-bond canonical form (VII) contributes to the structure of the phenolic bond even when the electron-pair from the hyperconjugating bond is in the plane of the ring. The contribution from such a structure facilitates electron-release from the lone pair of electrons (as in Structure VIII, the arrows being neglected) which themselves are in a geometry which allows conjugation with the ring; for structures such as (VII) help to transfer charge from oxygen to hydrogen, and so reduce the restriction imposed by the nuclear charge of oxygen on its lone pairs of electrons. The extent to which lone-pair electron release can be increased by H-O charge-transfer as in (VII) will depend on how much electron-demand is put on the oxygen atom; the more positive this atom is required to become, the more charge will be transferred to hydrogen to allow further lone-pair electron-release. In situations of minimal electron-demand, the order of electron-release,

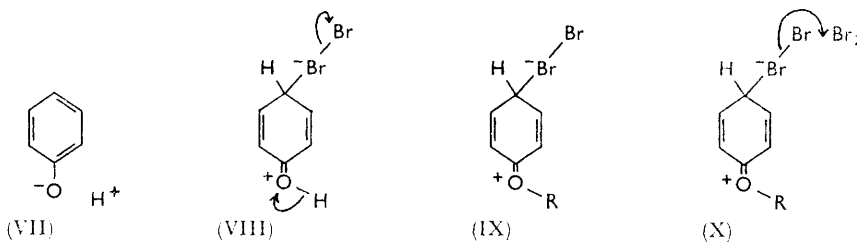
\* This difficulty was the subject of discussion at the Hyperconjugation Conference in 1958; at that time, no experimental evidence of the steric requirements of hyperconjugation was available.

<sup>22</sup> Shiner, *J. Amer. Chem. Soc.*, 1960, **82**, 2655; Shiner and Humphrey, *ibid.*, 1963, **85**, 2416.



5314 *de la Mare, el Dusouqui, Tillett, and Zeltner: Kinetics and*

MeO > HO, is seen, a result which shows that (VII) does not dominate under these conditions. It is only when the electron-demand is very high (as, for example, in the transition state for bromination) that the augmenting effect ascribable to this type of electron-release manifests itself clearly.



There may well be controversy concerning the classification of the structural influence under consideration. If the overall effect of the substituent is thought of, it is certainly of a conjugative character, since it is evoked by its very nature only at positions conjugated with the substituent. It certainly involves delocalisation of the electrons of the H-O group under the demand of the reagent. Perhaps the most generally acceptable classification would be to call it an inductomeric effect on conjugation, resulting from H-O no-bond resonance.

It is a consequence of this interpretation of electron release from the hydroxyl group that part of any total effect attributable to no-bond resonance from H-O or H-NR substituents is subject to the geometric restriction that affects conjugation, and part is not. The same principle could apply only to a second-order degree to this mode of electron-release by H-NR<sub>2</sub><sup>+</sup> substituents, as in the experiments discussed by Ridd and co-workers.<sup>23</sup>

H-O *Bond-breaking in the Rate-determining Step for the Bromination of Phenol*.—An early suggestion<sup>24</sup> that H-C hyperconjugation might as a consequence initiate hydrogen-exchange between the hyperconjugating bond and the solvent was negated, for the conditions under which hyperconjugation was then being invoked to interpret relative reactivities, by experiments which showed that no such exchange occurred.<sup>25</sup> The H-O bond, however, normally exchanges rapidly with hydrolytic solvents, so it might be expected that fission of the H-O bond might be concerned in the rate-determining step for the bromination of phenols if hyperconjugation or no-bond resonance were important in determining the rate of the reaction.

Three kinds of evidence can be adduced from the present study in support of this view. The first is a preliminary result (Table 2), that the bromination of phenol in deuterioacetic acid (*i.e.*, of PhOD in CH<sub>3</sub>•CO<sub>2</sub>D) is slower than that of phenol in acetic acid. It has been reported<sup>26</sup> that the third-order bromination of aromatic hydrocarbons is not subject to a solvent deuterium isotope effect of this kind. This result requires confirmation and extension to the second-order bromination before the results which we have obtained for phenol can be interpreted with certainty; it suggests, however, that there may be significant H-O bond stretching in the rate-determining step for the bromination of phenols.

The second is the fact that the third-order bromination of anisole (kinetic form,  $-d[\text{Br}_2]/dt = k[\text{ArH}][\text{Br}_2]^2$ ) is more easily accessible than the third-order bromination of phenol. This can be seen from the Figure. The graph of  $k_2$  against  $K/(K + \text{Br}^-)$  is more markedly curved for phenol than for anisole. It should be recalled that, whereas for anisole Robertson, de la Mare, and Johnston<sup>9</sup> noted a significant contribution from the

<sup>23</sup> Brickman, Johnson, and Ridd, *Proc. Chem. Soc.*, 1962, 228.

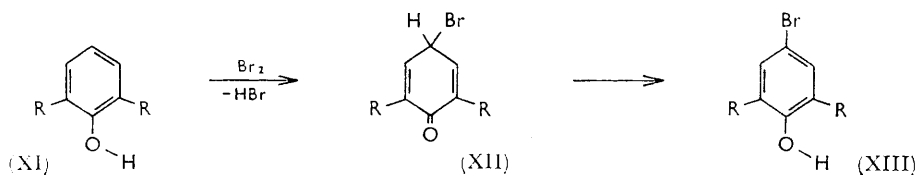
<sup>24</sup> Robinson, *Chem. and Ind.*, 1936, 55, 962.

<sup>25</sup> Hughes, Ingold, and Taher, *J.*, 1940, 949.

<sup>26</sup> Keefer and Andrews, *J. Amer. Chem. Soc.*, 1956, 78, 3637.

third-order mechanism in the bromination of anisole in the concentration region M/640, Yeddanapalli and Gnanapragasam<sup>27</sup> showed that the bromination of phenol was of the second order in this region. It is suggested, therefore, that there is a significant difference between the rate-determining transition states for the bromination of phenols on the one hand, and of anisoles and other similar compounds on the other. In both cases the kinetic form and the effects of added salts show that the transition state contains the whole aromatic molecule (including, for phenols, the HO proton) and the whole bromine molecule. In the first case, however, the transition state can be represented as in (VIII), and the proton is being removed in the transition state at the same time as bromide ion is being lost. The second type of compound involves, because of its structure, (IX), only loss of bromide ion in the transition state; and so its procedure forward towards the products of substitution is more susceptible to catalysis by bromine. Structure (X) is then a representation of the transition state for third order bromination. This formulation follows the pattern which we have adopted<sup>28</sup> for describing the paths of the second- and third-order reactions; it accords also with the views of others<sup>12,29,30</sup> concerning the reaction paths adopted in these processes. Despite the difference between the transition states for the three processes (VIII, IX, X), the effects of change in structure by the introduction of further groups seem to be similar, in that the additivity principle seems to apply in each case, and the effect of introducing methyl and t-butyl groups in the 2- and 4-positions is nearly the same for the three reactions provided that extra steric inhibition of resonance is not introduced.

**2,6-Di-t-butylphenol.**—The third source of support for the view that proton-loss from the hydroxyl group is important in the bromination of phenols comes from the fact that for suitably blocked phenols the reaction path can be established to be (XI)—(XIII).



For 2,6-di-t-butylphenol, the dienone intermediate (XII; R = t-Bu) can be isolated and characterised fully, though it slowly rearranges to the normal product of substitution. For 2,6-dimethylphenol, the build-up of the corresponding intermediate (XII; R = Me) can be established by spectroscopic measurements, but its decomposition to the normal product of substitution is rapid in acetic acid or in aqueous acetic acid. For the other phenols, any formation of such an intermediate is even more fleeting.

The first stage of the reaction (XI  $\longrightarrow$  XII) can thus be categorised formally as an electrophilic substitution with prototropic rearrangement; and the second (XII  $\longrightarrow$  XIII) as a prototropic rearrangement.

That such an intermediate as (XII) can be concerned in the electrophilic substitutions of phenols was apparently first suggested by Lapworth;<sup>31</sup> and there have of course been many reports of reaction sequences, involving phenols in which normal substitution is blocked,<sup>32-34</sup> where dienone intermediates have been shown to be concerned. The

<sup>27</sup> Yeddanapalli and Gnanapragasam, *J.*, 1956, 4934.

<sup>28</sup> de la Mare, in "Theoretical Organic Chemistry," Kekulé Symposium, Butterworths, London, 1958, p. 219 ff.

<sup>29</sup> Zimmerman and Berliner, *J. Amer. Chem. Soc.*, 1962, **84**, 3953.

<sup>30</sup> Keefer, Ottenberg, and Andrews, *J. Amer. Chem. Soc.*, 1956, **78**, 255.

<sup>31</sup> Lapworth, *J.*, 1901, **79**, 1265.

<sup>32</sup> Coppinger and Campbell, *J. Amer. Chem. Soc.*, 1953, **75**, 734.

<sup>33</sup> Grovenstein and Aprahamian, *J. Amer. Chem. Soc.*, 1962, **84**, 212.

<sup>34</sup> Elston, Peters, and Rowe, *J.*, 1948, 367.

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formation of this type of intermediate is important also in the chemistry of naphthols and related compounds;<sup>35,36</sup> Zollinger and his co-workers<sup>37</sup> have recently discussed in detail a closely analogous situation in the bromination of a naphtholsulphonic acid.

Reports of reactions of 2,6-di-*t*-butylphenols with electrophils indicate that these can generally be taken through to the normal product of substitution,<sup>38-40</sup> though it seems likely on general grounds that dienones may be isolable as intermediates in some of these cases also. Hart and Cassis<sup>38</sup> discussed the reactivity of 2,6-di-*t*-butylphenol in alkylation, and reported that the reaction was slower than with unhindered phenols; they appeared to consider that the reduction in reactivity derives from steric inhibition of resonance. Our results support the view that the reactivity of 2,6-di-*t*-butylphenol is less than would be expected on the additivity principle. The experimental value for the rate of formation of the dienone is 300 l. mole<sup>-1</sup> min.<sup>-1</sup>. Allowance being made for the environmental effects of added salts on the rate-coefficient (for the second-order reaction, from the data for 2,4-dimethylphenol, a factor of about 3; see Table 2), an experimental value of  $3 \times 300 = 900$  l. mole<sup>-1</sup> min.<sup>-1</sup>. needs therefore to be compared with a value calculated from the additivity principle of 45,000 l. mole<sup>-1</sup> min.<sup>-1</sup>. So the rate of attack of bromine on 2,6-di-*t*-butylphenol is less than would be expected by a factor of about 50.

It would be natural to follow Hart and Cassis<sup>38</sup> in attributing this rate reduction to steric inhibition of resonance, and to consider that the hydroxyl group is held out of the plane of the aromatic ring by the bulky adjacent *t*-butyl groups. The importance of steric inhibition of resonance in situations of this type is well authenticated for substituted anilides and anisoles,<sup>18,19,41</sup> and Lombroso<sup>42</sup> has interpreted the dipole moments of similarly substituted phenols in the same general way. There have, however, been various infrared studies which cast doubt on the validity of this approach. Comparison of the frequencies of the H-O stretching vibration in substituted phenols have been held by several independent groups of workers to show that the hydroxyl group in 2,6-di-*t*-butylphenol is coplanar with the aromatic ring; it is considered that the hydroxyl group is held in a pocket between the hydrogen atoms of one of the adjacent *t*-butyl groups.<sup>43-45</sup> A similar deduction has been made from the results of ultraviolet spectroscopy.<sup>46</sup> If this view is correct, then the relatively slow rate of bromination of this compound should be attributed not to steric inhibition of mesomerism, but instead to steric inhibition of proton-loss, the only other process likely to be hindered by the bulky adjacent *t*-butyl groups. This would fit in with our representation of the reaction-path, in which proton-loss from the hydroxyl group is concerned in the rate-determining transition state (cf. VIII).

On this view also, the smaller effect observed with 2,6-dimethylphenol might be attributed to steric inhibition of proton-loss, and there would then appear to be no need to assume that there is any steric inhibition of coplanarity in anisole itself. The whole, rather than only a part, of the rate-difference between anisole and phenol would then be discussed appropriately in terms of H-O no-bond resonance. In our opinion, however, some independent evidence for the planarity of 2,6-di-*t*-butylphenol is desirable.

*Solvent Effects on Reactivity.*—Both third- and second-order bromination of aromatic

<sup>35</sup> Fries and Schimmelschmidt, *Annalen*, 1930, **484**, 245; Fries and Oehmke, *ibid.*, 1928, **462**, 1.

<sup>36</sup> F. Bell, *J.*, 1961, 5293.

<sup>37</sup> Christen and Zollinger, *Helv. Chim. Acta*, 1962, **45**, 2057, 2066; Christen, Koch, Simon, and Zollinger, *ibid.*, p. 2077.

<sup>38</sup> Hart and Cassis, *J. Amer. Chem. Soc.*, 1951, **73**, 3179.

<sup>39</sup> Barnes and Hickinbottom, *J.*, 1961, 953.

<sup>40</sup> Kharasch and Joshi, *J. Org. Chem.*, 1962, **27**, 651.

<sup>41</sup> Wepster, in "Progress in Stereochemistry 2," ed. Klyne and de la Mare, Butterworths, London, 1958.

<sup>42</sup> Rumpf and Lombroso, *Bull. Soc. chim. France*, 1950, **17**, 283.

<sup>43</sup> Ingold, *Canad. J. Chem.*, 1960, **38**, 1092; 1962, **40**, 111.

<sup>44</sup> Bellamy and Williams, *Proc. Roy. Soc.*, 1960, *A*, **254**, 119; Bellamy, Eglinton, and Morman, *J.*, 1961, 4762.

<sup>45</sup> Wren and Lenthen, *J.*, 1961, 2557; Puttnam, *J.*, 1960, 486, 5100.

<sup>46</sup> Cohen and Jones, *J. Amer. Chem. Soc.*, 1963, **85**, 3402.

compounds proceed faster in aqueous acetic acid than in pure acetic acid. This is consistent with the theory<sup>47</sup> that reactions involving development of charge in the transition state are facilitated by increasing the ionising power of the solvent; the reactions at present under consideration (transition-state structures, cf. IX and X) involve initially neutral molecules and polarised transition states.

The same is true experimentally of the bromination of phenol, and the same theory applies (cf. structure VIII). If the solvent is changed from acetic acid to pure water, the corresponding change in rate is very large. Thus the second-order rate coefficient for the bromination of anisole in acetic acid containing a 2M-lithium perchlorate is  $k_2 = 34$  l. mole<sup>-1</sup> min.<sup>-1</sup>; that for bromination in water, according to Bell and Rawlinson,<sup>48</sup> is  $2.4 \times 10^6$  l. mole<sup>-1</sup> min.<sup>-1</sup>. It is interesting, however, that the second-order rate coefficient for the bromination of phenol ( $k_2 = 1.1 \times 10^7$  l. mole<sup>-1</sup> min.<sup>-1</sup>) in water is faster than that for anisole by a factor of only four.<sup>48</sup> This value is reported to be only approximate, since the reaction is so fast; but it is possible that the intrinsic reactivity of phenol is somewhat reduced in this solvent. It may be that the extra possibilities of hydrogen-bonding here help to stabilise the transition state; phenol forms a relatively stable hydrate, in which the hydroxyl groups are not coplanar with the ring,<sup>49</sup> and in this hydrate the infrared stretching vibration of the hydroxyl group is much modified.<sup>50</sup> Some further investigation is probably desirable, however, since *p*-bromophenol is much more reactive than *p*-bromoanisole ( $k_2 = 3.2 \times 10^3$  and 5 l. mole<sup>-1</sup> min.<sup>-1</sup>, respectively; the value given in the original paper for *p*-bromophenol is a misprint<sup>51</sup>).

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<sup>47</sup> Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 345.

<sup>48</sup> Bell and Rawlinson, *J.*, 1961, 63.

<sup>49</sup> Rhodes and Markley, *J. Phys. Chem.*, 1921, **25**, 527; Meuthen and Stackelberg, *Z. Elektrochem.*, 1960, **64**, 387.

<sup>50</sup> Badger and Greenough, *J. Phys. Chem.*, 1961, **65**, 2088.

<sup>51</sup> R. P. Bell, personal communication, 1963.

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