385. *The Influence of the Methoxyl Group in Aromatic Substitution.*

By P. B. D. de la Mare and C. A. Vernon.

The following compounds are compared in regard to their relative rates of bromination in acetic acid : anisole, methyl *p*-tolyl ether, the dimethoxybenzenes, *m*-xylene, *ψ*-cumene, and durene. It is deduced that a position *meta* to a methoxyl group is slightly activated, that the corresponding *o*- and *p*-positions are activated to an enormously greater extent, and that the *o* : *p* ratio for the bromination of anisole must be low. An attempt has been made to estimate the latter quantity experimentally. Some theoretical consequences of the facts and conclusions are discussed.

In modern electronic theories of aromatic substitution (cf. Ingold, *Chem. Reviews*, 1934, **15**, 225), activation of the *o*- and the *p*- as compared with the *m*-position by a group with a $+T$ effect is regarded as extremely selective. In other words, the extent of charge- or covalency-development in the transition state of the reaction, on which the rate is believed to depend, is very critically determined by the position in the benzene ring which is attacked by the electrophilic reagent. In anisole, the nuclear positions *o*- and *p*- to the methoxyl group are powerfully activated by the $+T$ effect. It is of interest to know whether the *m*-position is also activated, by " second-order relay " of this effect, or whether the electron-withdrawing inductive effect of the methoxyl group has dominant influence on the rate of substitution in this position. Direct determination of the rate of substitution in the *m*-position is, however, difficult, since the rates of substitution in the *p*- and the *o*-position are enormously greater. Bunton, Minkoff, and Reed, for example, were unable to detect the formation of any *m*-nitration product either from anisole or from phenol (*J.*, 1947, 1416).

Recently, in connection with studies of electrophilic halogenating agents (de la Mare, Hughes, and Vernon, *Research*, 1950, **3**, 192, 242), we have had occasion to examine the reactivities of anisole and the various dimethoxybenzenes. These experiments, which extend earlier measurements by Robertson and de la Mare (*J.*, 1943, 276, 279), enable us to throw further light on the effect of a methoxyl group in the *m*-position, in the following way.

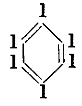
For third-order bromination in acetic acid at 25° ($-\mathrm{d}[Br_2]/\mathrm{d}t = k[A][Br_2]^2$), *p*-dimethoxybenzene reacts *ca.* 1·5 times as fast as methyl *p*-tolyl ether. In the latter compound, which is substituted almost entirely *o*- to the methoxyl group (cf. Stewart, *J.*, 1922, **121**, 2555), there are half as many reactive positions. It appears, therefore, that the methoxyl group activates the position *m*- to it rather less effectively than does the methyl group. The latter group is itself only weakly *m*-activating. The " partial-rate factor " for nitration of toluene in the *m*-position is about 3 (Ingold, Lapworth, Rothstein, and Ward, *J.*, 1931, 1959). Condon (*J. Amer. Chem. Soc.*, 1948, **70**, 1963) has estimated a similar figure of 5 for halogenation. It may reasonably be deduced, therefore, that the methoxyl group activates a position *m*- to it by a factor of between one and three.

The *o* : *p* ratio for the bromination of anisole does not seem to have been determined, though *p*-bromoanisole is known below to be the main product (cf. Slotta and Heller, *Ber.*, 1930, **63**, 3043 ; Wohl, *Ber.*, 1919, **52**, 51). Since phenol, on bromination in various solvents, gives about 90% of *p*-bromophenol (Holleman and Rinkes, *Rec. Trav. chim.*, 1911, **30**, 48), one might expect that bromination of anisole would also proceed with a low *o* : *p* ratio. In such a case it is well recognized that blockage of the *p*-position must reduce the rate of reaction, provided that the *p*-substituent does not activate strongly the position *o*- to the original activating group. Consistently, *p*-dimethoxybenzene and methyl *p*-tolyl ether are both brominated at a rate about one-tenth of that of anisole.

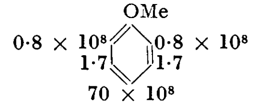
To correspond with the above interpretation, *o*-dimethoxybenzene should be brominated substantially in the two equivalent positions each *p*- to a methoxyl group, as is known to be the case (Moir and Purves, *Canad. J. Res.*, 1948, **26***B*, 694). Furthermore, the small additional activation by the second methoxyl substituent *m*- to the position of electrophilic attack, should, if the availability of two such positions is taken into account, result in a rate of bromination rather more than twice that of anisole. Baddeley and Smith (*Nature*, 1949, **164**, 1014) have recorded that *o*-dimethoxybenzene is brominated more rapidly than anisole, and we find that the rate ratio is 3·4 : 1.

There is considerable justification for believing that, provided that two substituents attached to the benzene ring are not effectively conjugated, their influence on the energy of activation of substitution is independent and additive. Thus Bradfield, Brynmor Jones, and their co-workers (cf. Bradfield, *Trans. Faraday Soc.*, 1941, **37**, 726; Brynmor Jones, *J.*, 1942, 418, 1676) have shown that the rates of chlorination of phenolic ethers such as p-RO·C$_6$H$_4$·X are affected independently by variation in R and by variation in X. Similarly, Condon (*loc. cit.*), assuming only similar additivity and a plausible *o* : *m* : *p* ratio for toluene, successfully correlated the relative rates of halogenation of the xylenes, mesitylene, and pentamethylbenzene, and predicted rates of bromination of *ψ*-cumene and of durene, which have now been measured. The agreement, within a factor or two for all these compounds, covering a very large range of reactivity, is remarkable.

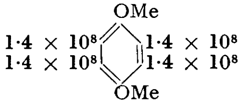
Methoxyl groups, being able only to donate, and not to withdraw, electrons by their tautomeric effect, might be expected, like methyl groups, to influence the rate of substitution additively. The rates of bromination of anisole and *o*- and *p*-dimethoxybenzene, together with the corresponding rate of bromination of benzene, which can be estimated by an indirect comparison, as in Robertson and de la Mare's work (*loc. cit.*), define, on this basis, the following partial-rate factors for the bromination of the various positions available for substitution in these compounds :



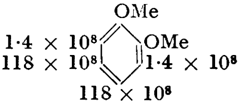
1



12·0 × 10⁸

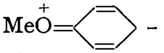


0·93 × 10⁸



40·0 × 10⁸

The main points, which we believe to be established, are illustrated by the above estimates, namely : (*a*) A position *m*- to a methoxyl group is slightly activated. (*b*) The corresponding *p*- and *o*-positions are, in comparison, activated to an enormously greater extent, *i.e.*, by a rate-factor of 10^8, for molecular halogenation. (*c*) The *o* : *p* ratio for the bromination of anisole must be low.

Dewar (*Discuss. Faraday Soc.*, 1947, **2**, 50) has calculated that *p*- and *o*-dimethoxybenzene should form " π " (*i.e.*, unsaturation) complexes, and should therefore react more readily than anisole with electrophilic reagents. Baddeley and Smith (*loc. cit.*) have pointed out that the experimental activation of substitution of *o*-dimethoxybenzene relative to anisole does not bear out this contention, seeing that the extent of the activation by the methoxyl group in this electrophilic substitution is no greater than that found in analogous nucleophilic processes. We support Baddeley's conclusion, in that we regard the " π " complex theory as paying too little account to the selectivity observed in orientation phenomena. It seems to us more helpful to consider these processes from the standpoint of the valence-bond description, in the following way. The contribution of structures such as  is increased by the approach of an electrophilic reagent,* with the result that substitution is almost completely localized at the *p*- and the *o*-carbon atoms. We can now reinforce this view by the observation that, although Dewar concludes from his calculations that *p*-dimethoxybenzene should be substituted more readily than anisole, the opposite is in fact the case.

Finally, since two of the positions available for substitution in *m*-dimethoxybenzene are activated each by one *p*- and one *o*-methoxyl group, the rate of bromination of this compound should be some 10^8 times faster than that of anisole. This rate is far too fast for quantitative confirmation, but we have observed that bromination of this compound, with reactants M/160 in acetic acid at 25°, proceeds to at least 99% reaction in 0·6 minute. A similarly rapid rate of bromination would be expected for the various tri- and tetra-methoxybenzenes.

Experimental.

Acetic acid was purified by the procedure of Orton and Bradfield (*J.*, 1927, 983) and had m. p. 16·4°. Bromine (AnalaR) was used without further purification. The substances examined had the following properties : Anisole, fractionated, b. p. 155°/760 mm.; *p*-dimethoxybenzene, recrystallised, m. p. 57—58°; *o*-dimethoxybenzene, fractionally frozen, then distilled *in vacuo*, m. p. 22·7°, n_D^{25} 1·5321; *m*-dimethoxybenzene, fractionated, b. p. 208—210°/758 mm., n_D^{25} 1·5221; methyl *p*-tolyl ether, fractionated, b. p. 174—175°/762 mm., n_D^{25} 1·5099; *m*-xylene, fractionated, b. p. 136—137°/752 mm.; durene, recrystallised, m. p. 80·5—81·5°; ψ-cumene, fractionated, b. p. 166°/760 mm., n_D^{25} 1·5015.

Rate-measurements were made essentially by the technique used by Robertson and de la Mare (*loc. cit.*). The following are details of two typical runs. *o*-Dimethoxybenzene, M/160, and bromine, M/160, in acetic acid at 25° : samples (4·00 ml.) were pipetted into potassium iodide solution containing excess of sodium thiosulphate, and back-titrated with 0·00500N-iodine :

Time (mins.)	0	2·08	3·92	8·43;	0	0·70	1·13	1·53	2·25
Titre (residual Br_2, expressed as ml. of 0·00500N-iodine) ...	10·09	7·08	6·05	4·65;	10·09	8·65	8·05	7·65	7·03

From the combined graph, x = 10% reaction, t = 0·43; x = 20%, t = 1·11.

The following results are all for bromination, with reactants in equal concentration, at 25° in acetic acid. For each compound, with constant bromine concentration, the rate was found to be proportional to the concentration of aromatic substance. The values for anisole and methyl *p*-tolyl ether are slightly greater than those recorded at 24° by Robertson and de la Mare (*loc. cit.*), and correction is made appropriately in the list of relative rates below.

o-Dimethoxybenzene, M/320, $x = 10, t = 1·52$; $x = 20, t = 3·68$; overall reaction order, n (M/160—M/320) = 2·8.

p-Dimethoxybenzene, M/80, $x = 10$, $t = 5·6$; $x = 20$, $t = 12·7$; M/160, $x = 10$, $t = 20·4$; $x = 20$, $t = 45·5$; n (M/80—M/160) = 2·9.

Anisole, M/160, $x = 10, t = 1·40$; $x = 20, t = 3·70$.

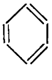
Methyl *p*-tolyl ether, M/160, $x = 10, t = 30$.

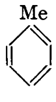
m-Xylene, M/10, $x = 10, t = 8·1$; $x = 20, t = 21·0$.

ψ-Cumene, M/10, $x = 10, t = 2·4$; $x = 20, t = 6·5$.

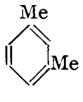
Durene, M/50, $x = 10, t = 80$; $x = 20, t = 195$; M/80, $x = 10, t = 202$; n (M/50—M/80) = 3·0.

The following relative rates can thence be deduced :

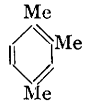

1



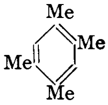
$3·5 \times 10^2$



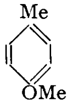
$4·4 \times 10^5$



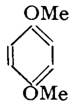
$1·4 \times 10^6$



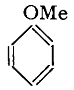
$2·6 \times 10^6$



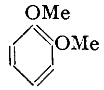
$5·6 \times 10^7$



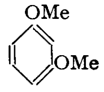
$9·0 \times 10^7$



$1·2 \times 10^9$

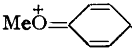


$4·0 \times 10^9$



$>10^{13}$

---

* If the electrophilic reagent is X^+, then there is reason to believe that complexes of the type  are intermediate in the reaction (cf. Melander, *Arkiv Kemi*, 1950, **2**, 213).

Attempted Determination of the o : p *Ratio for the Bromination of Anisole.*—Bromination of 0·1M-anisole with 0·05M-bromine in glacial acetic acid proceeded smoothly, but the reaction product on distillation left a residue of charred material, suggesting that a side reaction, perhaps demethylation, accompanied the monosubstitution. The slightly impure bromoanisole (14·7 g., 83%; f. p. 9·9°, b. p. 92—95°/15 mm.) was redistilled, and a middle fraction (12 g.; f. p. 10·7°, b. p. 217°/750 mm.) was collected. *p*-Bromoanisole, purified to constant f. p. 13·15° by fractional freezing, had f. p. 12·10° and 10·10° on admixture with 2·0 and 6·0% respectively of *o*-bromoanisole. A mixture, f. p. 9·8°, of *p*-bromoanisole (b. p. 216—218°/750 mm.) and *o*-bromoanisole (b. p. 217—219°/750 mm.) on similar distillation gave a middle fraction of almost unchanged f. p. (9·9°). It is believed, therefore, that the losses of bromoanisole, in the recovery by distillation of the reaction mixture, did not greatly affect the *o* : *p* ratio of the product, which contained, from its f. p., 95·3% of *p*-bromoanisole, in fair agreement with the value (97·3%) obtained from the kinetic data.

The authors are indebted to Professors E. D. Hughes, D.Sc., F.R.S., and C. K. Ingold, D.Sc., F.R.S., for discussion and criticism, and to Mr. E. Grayson for technical assistance.

William Ramsay and Ralph Forster Laboratories,
University College, Gower Street, London, W.C.1.

[*Received, February* 12*th*, 1951.]