304. *The Kinetics and Mechanisms of Aromatic Halogen Substitution. Part VI.* Some Observations relating to Substitution* meta- *to principally* ortho–para-*Directing Substituents; and to Steric Inhibition of Tautomeric Electron Release from the Acetamido-group.*

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The rates of chlorination, by molecular chlorine in acetic acid, of 4-acetamidodiphenyl, 1 : 4-diacetamidobenzene, and 2 : 6-dimethylacetanilide are compared with the corresponding rates of chlorination of 2-methylacetanilide, 4-methylacetanilide, *N*-methylacetanilide, *m*-xylene, and benzene. The phenyl and the acetamido-group only slightly deactivate for *meta*-chlorination. The proportion of 6-chloro-derivative formed in the chlorination of 2-methylacetanilide has been determined by isotopic dilution as 20·0%; that of the 4-chloro-derivative in the chlorination of 2 : 6-dimethylacetanilide is 2·6%; and that of 3-chloro-derivative in the chlorination of 4-acetamidodiphenyl is 90%. These values, together with the rate-ratios, allow the effect of steric inhibition of tautomeric electron release from the acetamido-group in these compounds to be estimated.

INTEREST has recently been renewed[1, 2] in the relationships between the rates of substitution *para* and *meta* to substituents in the benzene ring. For powerfully *ortho–para*-directing substituents, relevant information is difficult to obtain directly, because the proportion of *meta*-substitution is too small, as, *e.g.*, in the nitration of anisole.[3]

One approach[4, 5] involves the study of compounds of the type *p*-R·C_6H_4X, where R is varied, and X is a group more powerfully *ortho–para*-directing than R. Reliable predictive use of the method requires the knowledge that the effects of substituents on the rates of displacements from the benzene nucleus are independent and additive in the free energies of activation for substitution in the various positions. This " additivity hypothesis " has been extensively tested and shown to be a good approximation by Bradfield, Brynmor Jones, and their co-workers[6] for the bromination of phenolic ethers. It seems also to hold reasonably well for the chlorination and bromination of anilides, examined by Orton, Bradfield, Brynmor Jones, and their co-workers,[7-10] provided that the potentially basic nature of anilides[8, 11, 12] is recognised, and, where necessary, allowed for.

Three qualifications relating to the applicability of the additivity hypothesis should be mentioned: (1) It is not to be regarded as numerically accurate for small differences, as Bradfield and Jones[6] observed in comparing the relative reactivities (0·6 : 1) of the compounds (I) and (II). (2) When two substituents are conjugated through the benzene ring (as, *e.g.*, in *p*-nitroacetanilide) their directive influence will be modified by this conjugation, and the additivity principle is likely to break down. As far as we are aware, no

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* Part V, de la Mare and Hassan, *J.*, 1957, 3004.

[1] Cf. Brown and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 6292; Brown and Smoot, *ibid.*, 1956, **78**, 6255.
[2] de la Mare, *J.*, 1954, 4450.
[3] Bunton, Minkoff, and Reed, *J.*, 1947, 1416.
[4] de la Mare and Vernon, *J.*, 1951, 1764.
[5] Cf. Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons, London, 1953.
[6] Bradfield and Jones, *Trans. Faraday Soc.*, 1941, **37**, 726.
[7] Orton and King, *J.*, 1911, **99**, 1369.
[8] Orton and Bradfield, *J.*, 1927, 986.
[9] Bradfield and Jones, *J.*, 1928, 3080.
[10] Jones, *J.*, 1934, 210.
[11] Dadswell and Kenner, *J.*, 1927, 1106.
[12] Robertson, de la Mare, and Johnston, *J.*, 1943, 276.

direct kinetic test of this qualification has yet been made, but its influence on product-composition has been discussed (cf. Dewar[13] and de la Mare[14]). (3) The effects of substituents will not be additive when the activation or deactivation of the aromatic nucleus by the substituent involves a tautomeric electron release which is altered by steric interaction with an adjacent substituent. We have now estimated the influence of steric inhibition, by *ortho*-methyl substituents, of tautomeric electron release from the acetamido-group. Further, the effects of a phenyl and of an acetamido-group *meta* to the position of electrophilic substitution have been compared with that of a *meta*-methyl substituent, by comparing the relative rates of chlorination by molecular chlorine in acetic acid of 4-acetamidodiphenyl and of 1 : 4-diacetamidobenzene with those of acetanilide and of 4-methylacetanilide.

EXPERIMENTAL

Acetic acid, m. p. 16·5—16·6°, was prepared by standard methods[7-10, 12] and was stable to chlorine. " AnalaR " benzene was dried (Na) and fractionated, the middle portion, b. p. 80°, being collected. Toluene, b. p. 110°, was purified similarly. The rates of chlorination of these compounds agree well with those recorded elsewhere,[15] the slight difference in temperature and solvent being borne in mind. The following compounds were commercial specimens, or were prepared from commercial specimens of the appropriate amine, distilled when necessary: acetanilide, m. p. 114°; 2-methylacetanilide, m. p. 112°; 4-methylacetanilide, m. p. 153°; 2 : 6-dimethylacetanilide, m. p. 177·5°; 4-acetamidodiphenyl, m. p. 172°; 6-chloro-2-methylacetanilide, m. p. 165°. 1 : 4-Diacetamidobenzene, prepared by Tröger and Westerkamp's method,[16] had m. p. 304°. 4-Chloro-2 : 6-dimethylacetanilide, m. p. 195°, was prepared from the corresponding amine[11] by acetylation with acetic anhydride. 4-Acetamido-3-chlorodiphenyl was prepared by chlorination of 4-acetamidodiphenyl in acetic acid;[17] yield, 62%, m. p. 147° after recrystallisation from aqueous ethanol. Chlorine solutions were prepared by passing dry chlorine into acetic acid. $^{36}Cl_2$ was generated from potassium permanganate and concentrated hydrochloric acid to which $H^{36}Cl$ had been added. The chlorine, after being washed free from hydrogen chloride, was dried (H_2SO_4) and dissolved in acetic acid. Methods of radioactive measurements have already been described.[18] Chlorine in solution was converted into lithium chloride for radioactive counting.

Rate Measurements.—These were carried out by standard methods in blackened bottles. Losses by evaporation were insignificant over the first three samples. The following is an example of a typical run, using 0·01582M-acetanilide and 0·0104M-chlorine: samples (2 ml.) were titrated against 0·00115N-sodium thiosulphate:

Time (min.)	0·0	0·60	1·25	1·78	2·43	3·40	4·49
Titre (ml.)	36·30	23·30	15·60	11·70	8·60	5·90	3·90
k_2 (l. mole^{-1} min.$^{-1}$)	—	54	55	56	57	55	56

The formula $k_2 = 2{\cdot}303\ \{\log_{10} b(a - x)/a(b - x)\}/t(a - b)$ was used to calculate second-order rate coefficients, where a and b are the molarities of aromatic compound and chlorine respectively, and x is the molarity of chlorine consumed at time t.

The rates of reaction of benzene and of toluene, being less rapid and more susceptible to error resulting from volatility, were determined in association with strict blank experiments;[15] the rate ratio, when comparison is made at the same concentration of aromatic compound, is 356, in reasonable accord with those (345, 344) recorded by other workers.[15a, b] Since the second-order rate coefficients are reduced, because the added aromatic compound reduced the ionising power of the solvent,[12] the recorded rate comparisons and partial rate factors have been corrected for this effect; the rate for toluene is included to allow direct comparison to be made with other experimentally available rate sequences.[15]

[13] Dewar, *J.*, 1949, 463.
[14] de la Mare, *J.*, 1949, 2871.
[15] (*a*) de la Mare and Robertson, *J.*, 1943, 279; (*b*) Brown and Stock, *J. Amer. Chem. Soc.*, 1957, **79**, 5175.
[16] Tröger and Westerkamp, *Arch. Pharm.*, 1909, **247**, 663.
[17] Scarborough and Waters, *J.*, 1926, 557.
[18] (*a*) de la Mare and Harvey, *J.*, 1956, 36, 131; (*b*) de la Mare and Hassan, *J.*, 1957, 3004.

The following is a summary of the observed rate-coefficients, all in acetic acid at 25°.

Compound	ArH (M)	Cl_2 (M)	NaOAc (M)	k_2 (l. mole^{-1} min.$^{-1}$)
Benzene	0·505	0·228	—	0·75 × 10^{-4}
	0·904	0·14	—	0·61 × 10^{-4}
Toluene	0·160	0·093	—	3·2 × 10^{-2}
	0·829	0·142	—	2·3 × 10^{-2}
Acetanilide	0·0158	0·0105	—	56
	0·0113	0·00452	—	56
4-Methylacetanilide	0·0169	0·00451	—	92
	0·0135	0·00450	—	92
2-Methylacetanilide	0·0221	0·00510	—	11·5
	0·0309	0·00956	—	11·7
4-Acetamidodiphenyl	0·0629	0·0393	—	15·2
	0·0553	0·0244	—	14·5
1 : 4-Diacetamidobenzene	0·0167	0·00806	—	13·7
	0·0114	0·00749	—	14·0
2 : 6-Dimethylacetanilide	0·0918	0·0697	0·0100	0·70
	0·0648	0·0688	—	0·71
	0·147	0·0827	—	0·73

Analysis of Products.—By isotopic dilution it has been shown that 2 : 6-dimethylacetanilide (0·0506M) and chlorine (0·04434M) in acetic acid give 2·6% of 4-chloro-2 : 6-dimethylacetanilide calculated on the consumption of chlorine. The main product is 3-chloro-2 : 6-dimethylacetanilide, which was isolated in a separate experiment, m. p. 146—147°, in over 80% yield.

Chlorination of 2-methylacetanilide (0·045M) with chlorine (0·0361M) in acetic acid similarly gives 20·0% of 6-chloro-2-methylacetanilide, and 4-acetamidodiphenyl (0·063M) with chlorine (0·051M) in acetic acid gives 90·0% of 4-acetamido-3-chlorodiphenyl.

DISCUSSION

Kinetics and Mechanism.—Reactions of chlorine with aromatic compounds have uniformly been found [6-10,15] to be of the kinetic form $-d[Cl_2]/dt = k_2[ArH][Cl_2]$, but this is slightly disturbed by the hydrogen chloride produced in the reaction, acting (*a*) as an electrolyte, accelerating the reaction by virtue of an increase in the ionising power of the medium; and (*b*), for basic substrates, as an acid, removing the reactant as the salt. The rate-coefficients used for comparison in this work have been determined, as far as possible, towards the early stages of reaction to minimise these disturbances, which indeed are quite small, as is shown, for example, by the rate of chlorination being only slightly influenced by the presence of a base, sodium acetate.

The effects of electrolytes on the rates of chlorination [15, 19] have been interpreted [15, 19, 20] as demonstrating that the reaction involves molecular chlorine as the electrophilic reagent, rather than chlorine acetate or " positive chlorine," and this conclusion is herein adopted, since the effects both of acids and of bases accord with those earlier established for other systems.

The rate coefficients now recorded for acetanilide and 2- and 4-methylacetanilide agree well with those recorded by Orton and Bradfield,[8] after allowance for the difference in solvent. The relative reactivity of acetanilide and *N*-methylacetanilide is derived from this work and that of Bradfield and Jones; [9] the value for the rate of chlorination of *m*-xylene is obtained by comparison with the data recorded by Robertson *et al.*[19]

Products of Reactions.—The products of monochlorination of acetanilide by chlorine in acetic acid were studied carefully by Orton and Bradfield.[8] There are formed 67·5% of 4- and 32·5% of 2-chloroacetanilide. The acetamido-group is so strongly *ortho–para*-directing that the position of substitution in 4-methylacetanilide must be *ortho* to the acetamido-group.

The only recorded product of monochlorination, in acetic acid, of 2-methylacetanilide is 4-chloro-2-methylacetanilide, isolated in 74% yield.[21] If the principle of additivity of

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[19] Robertson, Dixon, Goodwin, McDonald, and Scaife, *J.*, 1949, 294.

[20] Robertson, *J.*, 1954, 1267.

[21] Lellman and Klotz, *Annalen*, 1885, **231**, 317; Claus and Stapelberg, *ibid.*, 1893, **274**, 286.

substituent effects held, the 6-chloro-derivative would also be obtained, in about half the yield found in the 2-chlorination of acetanilide, and accordingly it would be predicted that 79·6% of 4- and 19·4% of 6-chloro-2-methylacetanilide would be produced in this reaction. The present results indicate that the proportion of the latter is 20·0%, in excellent agreement with the prediction.

The products of chlorination of 2 : 6-dimethylacetanilide do not seem to have been investigated in detail. Nitration gives the 3-nitro-derivative,[22] but this could be because the anilide is converted, under the conditions used for nitration, into the salt, and the two methyl groups would then automatically control the orientation. Bromination apparently gives 4-bromo-2 : 6-dimethylacetanilide, with some of the 3-isomer.[11] The main product of chlorination by molecular chlorine in acetic acid has been found [23] to be the 3-chloro-derivative, which can be isolated in excellent yield nearly pure. Isotopic dilution has now shown that 2·6% of the 4-chloro-isomer is formed in the reaction. Thus, for this reaction, the two methyl groups, rather than the acetamido-group, dominate the orientation.

Chlorination of *m*-xylene under the conditions of the kinetic measurements, gives 77% of the 4-chloro-derivative,[15b; cf. 24] a value in reasonable agreement with that (73%) calculated on the basis of additivity (cf. ref. 25).

Chlorination of *N*-methylacetanilide also has not been investigated in detail. For the purpose of the discussion, we adopt the view, least favourable though it is for the argument developed, that all the substitution in this compound is in the 4-position, since acetanilide gives 67% of 4-chlorination, and the extra *N*-methyl substituent is likely to impede 2-chlorination in the former compound.

The only recorded product of monochlorination of 4-acetamidodiphenyl is the 3-chloro-compound; [17] analysis by isotopic dilution has now shown that 90% of this material is produced in this reaction under conditions similar to those used for the kinetic measurements.

Partial Rate Factors for Chlorination.—The relative rates and product compositions discussed above allow the following tabulation of rates and partial rate-factors for chlorination in acetic acid at 25°.

R at position					10^{-5} × Partial rate factor at position					10^5 × Rel. rate (PhH = 1)
1	2	3	4	6	2	3	4	5	6	
NHAc	H	H	H	H	6·1	—	25·2	—	6·1	6·2
,,	H	H	Me	H	31	—	—	—	31	10·2
,,	H	H	Ph	H	4·5	—	—	—	4·5	1·65
,,	H	H	NHAc	H	2·3	2·3	—	2·3	2·3	1·5
,,	Me	H	H	H	—	—	6·2	—	1·56	1·29
,,	Me	H	H	Me	—	0·23	0·012	0·23	—	0·079
Me	H	Me	H	H	2·6	—	4·3	—	4·3	1·85
NMe·Ac	H	H	H	H	—	—	0·02	—	—	~0·0033

In the following discussion, we adopt the view that the principle of additivity of free energy changes as determined by substituents is a good first approximation, and that any large divergences from predictions based on this principle can be discussed in terms of the qualifications mentioned above.

Activation by the meta-*Methyl Substituent.*—Comparison of the rate of substitution *ortho* to the acetamido-group in 4-methylacetanilide (31 × 10^5) and acetanilide (6·1 × 10^5) shows that a methyl substituent increases the rate of substitution in the *meta*-position by a factor of about 5·1. This accords excellently with Brown and Stock's recent direct determination (5·0), the rate and proportion of *meta*-substitution in the chlorination of toluene being used.[15b]

Steric Inhibition of Tautomeric Electron-release.—On this basis, the partial rate-factors for 4- and 6-chlorination of 2-methylacetanilide should be 125 × 10^5 and 31 × 10^5

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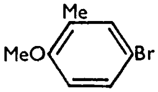
[22] Noelting, Braun, and Thesmar, *Ber.*, 1901, **34**, 2261.

[23] Beard and Hickinbottom, *Chem. and Ind.*, 1957, 1421.

[24] Kobe and Brennecke, *Ind. Eng. Chem.*, 1954, **46**, 728.

[25] Condon, *J. Amer. Chem. Soc.*, 1948, **70**, 1963.

respectively, whereas the observed figures are $6{\cdot}2 \times 10^5$ and $1{\cdot}6 \times 10^5$ respectively, *i.e.*, a diminution by a factor of 20. This is most reasonably interpreted as the result of steric inhibition of tautomeric electron-release from the acetamido-group, resulting from interference of the 2-methyl substituent with the hydrogen atom of the NH-group (III). Steric inhibition of tautomeric electron-release in *N*-methylacetanilide is likely to be, to a good approximation, of magnitude similar to that in 2-methylacetanilide, since in each case the extra impedance to the reaction results from interference between similarly placed methyl and hydrogen substituents (III and IV). On this account, therefore, *N*-methylacetanilide should have its reactivity reduced below that of acetanilide by a factor of about 20. In fact, it is less reactive than acetanilide by a factor of 1200; this further change, by a factor of about 60, is in the direction opposite to that expected on the basis of polar effects, but it accords with Robertson, de la Mare, and Swedlund's [26] suggestion that N–H hyperconjugation makes a significant contribution to the reactivity of acetanilide.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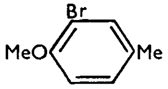
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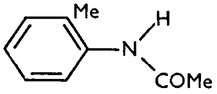
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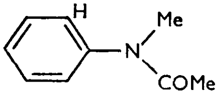
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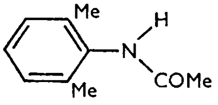
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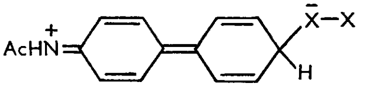
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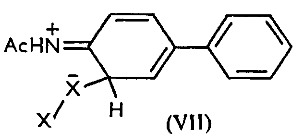
(VII)

The introduction of a second methyl substituent *ortho* to the acetamido-group increases still further the steric hindrance to the tautomeric electron-release from the latter group. Situations of this kind have been discussed by Wepster [27] with reference to other properties, including ultraviolet spectra and reactivities, of this and related compounds. Product-analysis by isotopic dilution shows that, for chlorination, only 2·6% of the product is the 4-chloro-derivative. After allowance for activation of this position by the methyl substituents, the reactivity *para* to the acetamido-group is reduced in this compound, as compared with 2-methylacetanilide, by a factor of $5 \times 6{\cdot}2 \times 10^5/0{\cdot}012 \times 10^5$, *i.e.*, *ca.* 2600. This figure is considerably larger than that (20) representing the effect of the first methyl group, because the interference of the *ortho*-methyl substituent with the COMe group is greater than that with hydrogen (V).

Polar Effect of the meta-*Acetamido-group.*—The present experiments enable two separate estimates to be made of the effect of the *meta*-acetamido-group. First, in 1 : 4-diacetamidobenzene the partial rate factor ($2{\cdot}3 \times 10^5$) compared with that in the *ortho*-position in acetanilide ($6{\cdot}1 \times 10^5$) shows that the substituent decreases the rate of substitution *meta* to it by a factor of 2·7. This is in the direction of overall electron-withdrawal, and shows that, in the *meta*-position, the inductive effect of this substituent is quantitatively more important than " second-order relay " of the tautomeric effect to the *meta*-position. The latter effect is not absent, however, as can be seen by the fact that the rate of substitution [15b] in the 4-position in *m*-xylene ($4{\cdot}3 \times 10^5$) is reduced in the corresponding position in 2 : 6-dimethylacetanilide to $0{\cdot}23 \times 10^5$, *i.e.*, by a factor of 19. This difference (roughly a factor of 7) is to be associated with the reduction, by the *ortho*-methyl substituents, of the tautomeric electron-release from the acetamido-group. This tautomeric electron-release is, however, not in this system reduced to zero; the reactivity

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[26] Robertson, de la Mare, and Swedlund, *J.*, 1953, 782.

[27] Wepster, in " Progress in Stereochemistry, II," ed. Klyne and de la Mare, Butterworths, 1958, in the press.

of the 4-position in 2 : 6-dimethylacetanilide is faster than that which would be expected *meta* to two methyl groups by a factor of about 0·012 × 10^5/5 × 5, *i.e.*, *ca.* 50; so even for the *meta*-position the acetamido-group in acetanilide must be contributing, by its tautomeric effect, an electron-release corresponding with a factor of considerably more than 7, a still larger electron-withdrawing effect being superimposed upon this.

Polar Effect of a meta-*Phenyl group*.—Comparison of the rate of *ortho*-chlorination in acetanilide (6·1 × 10^5) with the appropriate partial rate-factor for chlorination in 4-acetamidodiphenyl (4·5 × 10^5) enables us to deduce that the phenyl group is deactivating for this reaction by a factor of 1·3. This is considerably smaller than the corresponding factor for bromination by positive bromine.[18b] This result is consistent with the theory [2,18,28] that the inductive effects of substituents are more important in halogenations involving positively charged reagents, whereas the tautomeric effects are more important in those involving halogen molecules. Further discussion of the present results is postponed until the completion of a study, in progress, of orientation in the chlorination of diphenyl.

Orientation in Substitution in 4-Acetamidodiphenyl.—For chlorination and nitration, the 2- and 4-positions of acetanilide are activated to comparable extents, so that both 2- and 4-substituted derivatives are obtained from these reactions. Similar substitution in 4-acetamidodiphenyl requires discussion of the possibility that the activating power of the 4-substituent will be transmitted to the 4′-position of the unsubstituted ring through structures of the type shown in (VI). Since the alternative structure for 3-substitution avoids compression of the 2 : 2′-hydrogen atoms, and maintains the full aromatic resonance of the second ring, it is not surprising that reactions through transition states like (VII) are favoured—in the present experiments, in proportions which must be at least 4·5 : 1 when the statistical factor is included.

The present results confirm that there is a greater spread in reactivities for bromination in acetic acid than for chlorination; the overall rate-ratio, acetanilide : benzene, is 6·2 × 10^5 for the latter reaction, but is at least 10^8 for bromination.[12,15]

In Part V,[18b] we discussed the difference in $\frac{1}{2}o : p$-ratio between that for nitration of diphenyl in acetic anhydride at 0° (1·7; Dewar *et al.*[29]) and that for bromination by positive bromine in aqueous dioxan (0·68). The theoretical discussion was based in part on this comparison, and remains valid, except specifically in regard to the following proviso.

Professor F. Bell, of the Heriot-Watt College, Edinburgh, has pointed out to us that Jenkins, McCullough, and Booth [30] obtained, for nitration of diphenyl by a mixture of nitric and sulphuric acid at high temperatures, a $\frac{1}{2}o : p$-ratio in the neighbourhood of 0·5. We are indebted to Professor Bell for pointing out to us that we had misinterpreted their description. It seems that the nitration of diphenyl may be more dependent on the conditions of reaction than we had realised, but it seems also that it is not yet determined whether this dependence is a function of the reagent, temperature, or other variables.

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[28] de la Mare and Robertson, *J.*, 1948, 100.

[29] Dewar *et al.*, *J.*, 1956, 3572, 3576, 3581.

[30] Jenkins, McCullough, and Booth, *Ind. Eng. Chem.*, 1930, **22**, 31.