AN ASSESSMENT OF
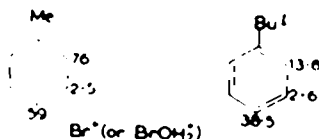# SOME EXPERIMENTAL APPROACHES TO NH AND OH
HYPERCONJUGATION

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IT is well known that the first experimental indications which were interpreted as showing that alkyl groups could release electrons conjugatively to attached unsaturated systems were those discussed by Baker and Nathan,[1] and depended on the observation that, whereas inductive electron release should be in the order Me $<$ Et $<$ Pr^i $<$ Bu^t, the order of electron release observed in suitable cases involved reversals towards the order Me $>$ Et $>$ Pr^i $>$ Bu^t. Many clear-cut examples are now established, and this aspect of the subject does not need further elaboration here.

Evidence for C-H *hyperconjugation in electrophilic aromatic substitution*

Aromatic substitutions are classically those reactions from which the theories of electronic displacements have been most extensively documented. Hyperconjugation would be expected to show up in such substitutions, since they are considerably facilitated by electron release, particularly of a conjugative character. Nitration seems to be an exception here; the inductive order has been observed for *para* substitution.[2] But since it was shown that in molecular bromination the methyl group is superior to the *tert*-butyl group in promoting reactivity,[3, 4, 5] a number of similar examples have been substantiated in full experimental detail. Some of these will be discussed below. A case in which we have been interested is the bromination, by positive brominating agents, of alkylbenzenes in aqueous dioxan. The following results were obtained:[6]

The results illustrate confirmation that the inductive effect dominates the reactivity sequence at the *meta* position, as has been illustrated by other workers also.[7]

[1] J. W. Baker and W. S. Nathan, *J. Chem. Soc.* 1844 (1935).
[2] H. Cohn, E. D. Hughes, M. H. Jones and M. Peeling, *Nature, Lond.* 169, 291 (1952).
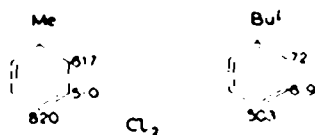[3] P. B. D. de la Mare and P. W. Robertson, *J. Chem. Soc.* 279 (1943).
[4] P. W. Robertson, P. B. D. de la Mare and B. E. Swedlund, *J. Chem. Soc.* 782 (1953).
[5] E. Berliner and F. J. Bondhus, *J. Amer. Chem. Soc.* 68, 2355 (1946); E. Berliner and F. Berliner, *Ibid.* 71, 1195 (1949).
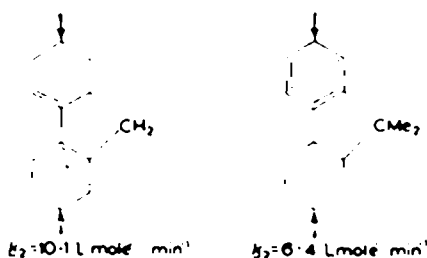[6] P. B. D. de la Mare and J. T. Harvey, *J. Chem. Soc.* 36 (1956); *Ibid.* 131 (1957).
[7] E. Berliner, F. Berliner and I. Nelidow, *J. Amer. Chem. Soc.* 76, 507 (1954); E. Berliner and F. Berliner, *Ibid.* 76, 6179 (1954).
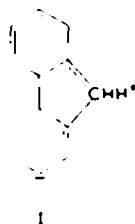
Two further examples are given; they involve chlorinations in acetic acid. The first was studied in part by us, but in full experimental detail by Brown and his co-workers.[8] For the partial rate factors given below we have used his isomeric proportions and our value[3] for the relative reactivities:

The second has been examined only in part; it is the comparison of the relative rates of chlorination in acetic acid of fluorene and 9:9-dimethylfluorene.[9]

Since fluorene is known to give almost exclusively the 2- and 2:7'-chloro derivatives,[10] the sequence is established for 2-substitution as being in the hyperconjugation order; in this example, hyperconjugation in its conventional description involves an extended conjugated system, of the type illustrated in formula (I).

I

C-C *hyperconjugation*

It has seemed reasonable intuitively that the C–H bond should be better capable of conjugative electron release than the C–C bond. There seems to be nothing, however, in the theories of hyperconjugation to indicate that C–C hyperconjugation could be completely neglected. Although C–C hyperconjugation has been considered theoretically by various workers, Berliner and Bondhus[11] were probably the first writers to apply to a specific chemical example the theory that the *tert.*-butyl group has an accelerating power determined considerably by C–C hyperconjugation. It

[8] H. C. Brown and L. M. Stock, *J. Amer. Chem. Soc* 79, 5175 (1957); and personal communication.
[9] P. B. D. de la Mare, D. M. Hall, M. M. Harris and M. Hassan, *Chem. & Ind.* 1086 (1958).
[10] J. Buffle, *Helv. Chim. Acta* 15, 1483 (1932).
[11] E. Berliner and F. J. Bondhus, *J. Amer. Chem. Soc.* 70, 854 (1948).

was held that the reactivity of *tert.*-butylbenzene in molecular bromination was too great, and too like that of toluene, for inductive effects to be the only factor determining reactivity *para* to the *tert.*-butyl group.

Although this view is still, in the writer's assessment, a matter of opinion, it is certainly not contradicted, and might perhaps be held to receive some support, from later experimental developments in this field. These illustrate the way in which alkyl groups promote *para* as compared with *meta* substitution, when reagents of different charge types are used. Partial rate factors for nitration[2] by NO_2^+, for bromination[4] by Br^+ and for chlorination[5] by Cl_2 are given in Table 1, and are plotted in Fig. 1 to show the relationship:

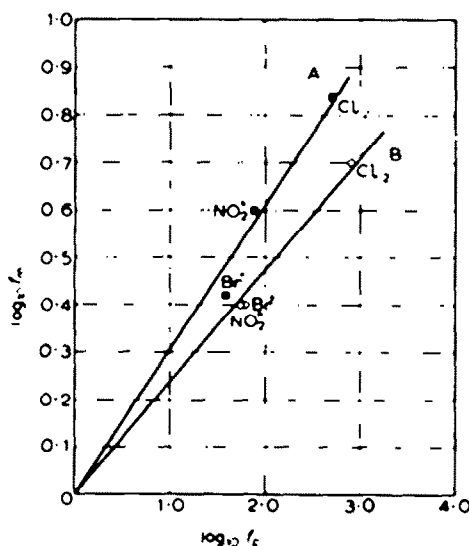$$\log_{10} f_m \cdot \text{const.} \log_{10} f_p \tag{1}$$

FIG. 1. Partial rate factors for substitution in: A, *tert.*-butylbenzene; B, toluene.

TABLE 1. PARTIAL RATE FACTORS FOR SUBSTITUTION IN ALKYLBENZENES

Compound	Reagent	f_m	$\log_{10} f_m$	f_p	$\log_{10} f_p$
Toluene	NO_2^+	2·5	0·40	58	1·76
	Br^+ (or $BrOH_2^+$)	2·5	0·40	59	1·77
	Cl_2	5·0	0·70	820	2·91
tert.-Butylbenzene	NO_2^+	4·0	0·60	75	1·88
	Br^+ (or $BrOH_2^+$)	2·6	0·42	38·5	1·59
	Cl_2	6·9	0·84	503	2·70

If the methyl group promoted reactivity considerably by a conjugative effect, but the *tert.*-butyl group only by an inductive effect, it might be expected, when reagents differing in charge type and electronic requirements were used (e.g., Cl_2, Br^+), that different

patterns would be obtained with the two substituents. In fact, both groups show in plots of equation (1) a reasonably good linear relationship.

A view essentially similar to that propounded by Berliner and Bondhus has recently been advocated by Brown and his co-workers[12] in regard to the relative rates of hydrolysis of the *para*-alkyl-substituted phenyldimethylcarbinyl chlorides. It is suggested that the inductive effect should be transmitted to the *para*-position no more strongly than to the nearer *meta* position, and hence that the considerable activation of the *para* position by the *tert.*-butyl group must be largely of a conjugative nature.

Structural effects on C–H hyperconjugation

In another paper presented at this Conference, J. W. Baker* deals in detail with the evidence that hyperconjugation from groups of the type CH_2R is affected by the nature of the group R. The direction of the change is that electron-withdrawing groups, which increase the acidity of the CH_2 hydrogen atoms, increase the hyperconjugative power of the group.[13] A qualitative indication of this can be seen, perhaps, in the fact that groups such as CH_2CO_2Et and CH_2Cl, are still mainly *o,p*-directing, though they decrease, or only slightly increase, the reactivity of the aromatic nucleus.[14]

O–H hyperconjugation

It has long been recognised that phenols are more reactive than their alkyl ethers in many electrophilic substitutions. But, since a number of these reactions (e.g., diazo coupling) which proceed in alkaline solution clearly involve the still much more reactive phenoxide ion, it has not so readily become recognised that the neutral phenol molecule, for example, is more reactive than anisole.

Such is, in fact, the case, however. The first kinetic investigation to establish this phenomenon was only of a preliminary nature,[4] but it established the key point, that phenol is brominated by molecular bromine in acetic acid about ninety times more rapidly than anisole, and that the rate of reaction is not depressed by the addition of sulphuric acid to the reaction medium.

Since that time, the kinetic form for the bromination of phenol has been examined by other workers in more detail;[15] within the limits imposed by the experimental technique, it resembles precisely that of anisole. The rate-comparison applies to the region of concentration in which the rate has the kinetic form: $-d[Br_2]/dt = k[ArH][Br_2]$. No indication is found of a fall-off in rate, specific to phenol, resulting from the HBr produced in the reaction. The rate-sequence, phenol > anisole, holds also for iodine-catalysed bromination in aprotic solvents.

Bromination is not the only electrophilic aromatic displacement for which the same rate-sequence has been established. Eaborn[16] has studied the proto–desilylation of a series of substituted phenyltrimethylsilanes, and has established that the reaction is promoted much more powerfully by the hydroxyl than by the methoxyl group, as is shown in the following values:

* Paper by J. W. Baker, page 135 of this volume.

[12] H. C. Brown, J. D. Brady, M. Grayson and W. H. Bonner, *J. Amer. Chem. Soc.* **79**, 1897 (1957).
[13] J. W. Baker, J. A. L. Brieux and D. G. Saunders, *J. Chem. Soc.* 404 (1956).
[14] C. K. Ingold and F. R. Shaw, *J. Chem. Soc.* 575 (1949).
[15] I. M. Yeddanapalli and N. S. Gnanapragasam *J. Chem. Soc.* 4934 (1956)
[16] C. Eaborn, *J. Chem. Soc.* 4858 (1956), C. Eaborn and D. F. Webster, *Ibid* 4449 (1957).

REACTION OF $p\text{-R} \cdot C_6H_4 \cdot SiMe_3$ WITH H^+

R	$p\text{-NMe}_2$	$p\text{-OH}$	$p\text{-OMe}$	$p\text{-Me}$	$p\text{-Bu}^t$	H	$p\text{-Cl}$
Relative rate	ca. $3 \cdot 10^7$	10,700	1510	21·1	15·6	1	0·13

The kinetic forms for proto-desilylation are such that the acid catalysis of the reaction is the same for both the hydroxyl and methoxyl substituents, a result which confirms that the reaction of the former compound involves the activation by the OH, rather than by the O^-, substituent.

A similar result has been established for deuterium exchange,[17] though here only *ortho* substitution has been investigated. Estimates of the relative electron-releasing power of hydroxyl and methoxyl groups have also been made by Deno and his co-workers[18] from data on equilibria of the type $Ar_3C \cdot OH + H^+ \rightleftharpoons Ar_3C^+ + H_2O$. These, expressed in terms of electrophilic substituent constants, σ^+, are: OH, 0·82; OMe, −0·64. The hydroxyl group is, by this criterion also, the more powerfully electron releasing.

Expected inductive effects

It is natural to enquire how the inductive effects of hydroxyl and methoxyl groups would be expected to affect the relative reactivities in the absence of conjugative factors. The most reliable estimates of the relative inductive effects of these groups seem to be those given in McDaniel and Brown's recent compilation.[19] They are derived from the thermodynamic dissociation constants of *meta*-substituted benzoic acids, and in terms of Hammett's σ values, σ_m, are: OH, $+0\cdot121$; OMe, $+0\cdot115$. The methoxyl group is slightly less electron withdrawing than the hydroxyl group, just as the CH_2Me group is slightly more electron releasing than the CH_3 group. Values for σ_p (OH, $-0\cdot37$; OMe, $-0\cdot27$) are, as would be expected from the foregoing discussion, in the opposite direction; these indicate once again the superior conjugative power of the OH group.

It is also necessary to enquire how substituents attached to the OPh group would normally influence the rate of substitution in the phenyl group. This matter has been extensively documented, for chlorination of ethers and anilides, by Bradfield, Jones and their co-workers.[20] The changes in reactivity normally follow the inductive effect of the substituent; inductively electron-releasing groups enhance reactivity, and inductively electron-withdrawing groups diminish it, as is shown by the following sequence:

RELATIVE RATES OF CHLORINATION OF AROMATIC ETHERS, ROAr, IN ACETIC ACID

R	Pr^i	Et	Me	$p\text{-MeC}_6H_4 \cdot CH_2$	$Ph \cdot CH_2$	$p\text{-Cl} \cdot C_6H_4 \cdot CH_2$	$p\text{-NO}_2 \cdot C_6H_4 \cdot CH_2$
Relative rate	440	199	100	95	68	41	14

[17] D. P. N. Satchell, *J. Chem. Soc.* 3911 (1956).
[18] N. C. Deno and W. L. Evans, *J. Amer. Chem. Soc.* 79, 5804 (1957); N. C. Deno and A. Schriesheim, *Ibid.* 77, 3051 (1955).
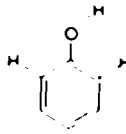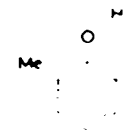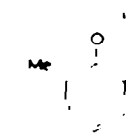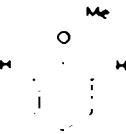[19] D. H. McDaniel and H. C. Brown, *J. Org. Chem.* 23, 420 (1958).
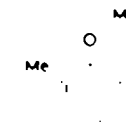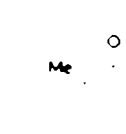[20] A. E. Bradfield and B. Jones, *Trans. Faraday Soc.* 37, 726 (1941).

Steric inhibition of resonance

Neither an unexpected inductive sequence, nor an unexpected effect of inductive substituents on electron release from OR groups, seems to provide an explanation of the superiority in this respect of hydroxyl over methoxyl.

We have therefore given consideration to the possibility that there is sufficient steric interaction between the OMe group and the hydrogen atoms *ortho* to it to reduce substantially the ease with which the activating group may indeed make a contribution to the observed rate difference. In Table 2 are given some new experimental data for the rates of bromination, in acetic acid at low concentrations, of methyl-substituted phenols; corresponding data are also given for substituted anisoles studied by Baddeley and his co-workers.[21]

TABLE 2. RELATIVE REACTIVITIES, WITH MOLECULAR BROMINE, OF PHENOL, ANISOLE AND THEIR *ortho*-METHYL DERIVATIVES

Compound	H—⟨O—H⟩—H	Me—⟨O—H⟩—H	Me—⟨O—H⟩—Me
Relative rate of bromination	90	450	550
Compound	H—⟨O—Me⟩—H	Me—⟨O—Me⟩—H	Me—⟨O—Me⟩—Me
Relative rate of bromination	1	6·3	0·39

All these compounds undergo bromination substantially in the 4-position,[22] so we can consider that the given relative rates refer to substitution *para* to the activating group. The introduction of a single *o*-methyl group does not prevent the approach towards coplanarity; so 2-methylanisole reacts with bromine about six times more rapidly than anisole; and *o*-cresol, about five times more rapidly than phenol. This factor of about five is very similar to that which represents the effect of a *meta*-methyl group in the bromination and chlorination of the methylbenzenes, and gives reasonable assurance that the principle that free energies of substitution are additive applies in the phenol series as in the anisole series.

A second methyl group, *ortho* to the activating group and *meta* to the position of substitution, should on this basis increase the reactivity by a further factor of five, to a relative rate (Ph · OH ≈ 90) of about 2300. In fact, the second methyl group only

[21] G. Baddeley, G. Holt, N. A. P. Smith and F. A. Whittaker, *Nature, Lond.* 168, 386 (1951); G. Baddeley, N. A. P. Smith and M. A. Vickars, *J. Chem. Soc.* 2455 (1956).
[22] T. Zincke and A. Hedenström, *Liebigs Ann.* 350, 274 (1906); A. F. Holleman and I. J. Rinkes, *Rec. Trav. Chim. Pays-Bas* 30, 48 (1916); P. B. D. de la Mare and C. A. Vernon, *J. Chem. Soc.* 1764 (1951); K. Auwers and T. Markovits, *Ber. Dtsch. Chem. Ges.* 41, 2336 (1908); A. N. Meldrum and M. S. Shah, *J. Chem. Soc.* 123, 1982 (1923).

slightly enhances the reactivity. So one can attribute to steric inhibition, by a H——Me repulsion, of electromeric electron release, a reduction in rate by a factor of about four.

In anisole, the steric hindrance, additional to that in phenol, to attainment of planarity results also from a single H——Me repulsion. It must, therefore, be energetically very similar in magnitude to that in 2:6-dimethylphenol. So a reduction in rate by a factor of about four might be assigned to this cause. In fact, the rate factor is about ninety. It seems very unlikely that the whole, or even a large part, of this difference arises because of deficiencies in our assumptions; and hence it is suggested that a large portion of this rate-factor of twenty-two is to be attributed to OH hyperconjugation.

It is clear, of course, that steric inhibition of conjugation plays a part in determining these rate sequences. This is further confirmed by the small reactivity of 2:6-dimethylanisoles; the latter compound is about ninety times less reactive than would have been expected allowing for activation by two methyl groups *meta* to the position of substitution. Here the rate-reduction results from one Me——Me repulsion, and it is to be noted that even this interaction only causes about as much rate reduction as results from the replacement of the phenolic hydrogen in phenol by a methyl group.

We have deduced that a rate-reduction of about four may be attributed, in anisole, to steric inhibition of mesomerism. It is interesting to examine whether in a suitable cyclic ether the rate can be enhanced by holding the alkoxyl group in its best position for conjugation. Baddeley and his co-workers[21] have provided evidence on this point by measuring the rate of reaction of coumaran. Relative reactivities of this and of analogous compounds[20,21] are shown in Table 3.

TABLE 3. RATE OF REACTION OF COUMARAN AND ANALOGOUS COMPOUNDS

Compound				
	CH$_2$ O CH$_2$	CH$_3$ O CH$_3$	CH$_3$ O CH$_2$ CH$_3$	CH$_3$ O CH$_2$ CH$_2$ Ph
Relative reactivity*	76	6·3	12·6*	7·5†

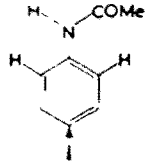* Baddeley *et al*[21]
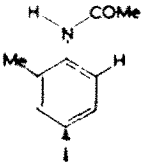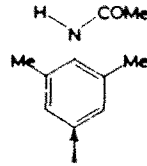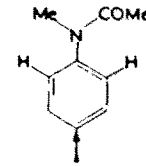† Estimated from data given by Bradfield *et al*.[20]

If we regard ethyl o-cresyl ether as the correct standard of comparison, the ring compound is more reactive by a factor of about six. If we regard 2-phenylethyl o-cresyl ether as a more satisfactory basis, the corresponding factor is about ten. Agreement with the small factor of four is sufficiently good to give us confidence that some reason other than steric inhibition of mesomerism must be sought for the great reactivity of phenol as compared with anisole.

The stereochemistry of the OH group in phenol needs to be considered in relation

to the possibility of OH hyperconjugation. It would seem to be generally considered that OH hyperconjugation requires that the hyperconjugating bond be out of the plane of the benzene ring. If OH hyperconjugation is important, therefore, the OH bond cannot be accurately in the plane of the ring in the transition state adopted for bromination of phenol; and a substantial contribution to the rate comes by way of activation from conformations in which the OH bond, and therefore also the axes of the lone pairs of electrons, are out of the plane of the ring. This does not seem in our view to be improbable; positions which allow the OH bond to hyperconjugate also allow the lone pairs of electrons to conjugate, though imperfectly; but the position which forces the OH bond out of hyperconjugation also can be regarded as holding one of the lone pairs of electrons in an unsuitable geometrical position. It is to be noted also that the total activation of the nucleus by the hydroxyl group is represented by a rate factor of about 10^{10};[12] the contribution attributed to the OH hyperconjugation, a factor of about twenty, is only a very small part of this.

Evidence relating to NH hyperconjugation is of a similar nature. Partial rate factors for the chlorination of acetanilide and 2-methylacetanilide are now available,[23] as shown, with that for N-methylacetanilide,[24] in Table 4.

TABLE 4. PARTIAL RATE FACTORS FOR CHLORINATION, *para* TO THE NRAc GROUP, OF ANILIDES IN ACETIC ACID AT 25°

Compound	H–N–COMe (H, H)	H–N–COMe (Me, H)	H–N–COMe (Me, Me)	Me–N–COMe (H, H)
Partial rate factor	24×10^6	$6{\cdot}2 \times 10^6$	$0{\cdot}012 \times 10^6$	ca. $0{\cdot}02 \times 10^6$

The bulky acetyl group ensures in this series that the introduction of a single methyl substituent in the *ortho* position has a secondary steric effect by introducing hindrance to adoption of a planar configuration. One such group reduces the reactivity by a factor of about twenty, when allowance is made for the expected activation of the position of substitution, *para* to the directing group and *meta* to the methyl group, by a factor of about five. In N-methylacetanilide, on the other hand, the steric impedance to coplanarity must be of magnitude similar to that in 2-methylacetanilide, but the reactivity is very considerably diminished; by a rate-factor of about 1000. So a diminution in rate by a factor of about forty has to be given some alternative explanation, and it is suggested that this is the result of NH hyperconjugation. It is suggested also that part of the reason why this factor seems to be rather larger than for phenol is because the adoption of a coplanar conformation is energetically more difficult in the anilide series, when such a conformation requires that the H and the COMe groups are coplanar; so there is relatively greater activation by the lone pair of electrons from such non-coplanar conformations, and hence a greater opportunity for NH hyperconjugation because the stereo-electronic requirements are more suitable.

[23] P. B. D. de la Mare and M. Hassan, *J. Chem. Soc.* 1519 (1958).
[24] A. E. Bradfield and B. Jones, *J. Chem. Soc.* 3073 (1928).

The evidence relating to electron release from amino and methylamino groups seems to be less decisive. The Hammett σ_p values[19] fall at least partly in the inductive order (NH_2, $-0\cdot66$; NHMe, $-0\cdot84$; NMe_2, $\cdot0\cdot83$). It is of interest ,however, that Berliner and Monack[25] have found, for the reaction of 4-substituted-2-nitrobromo-benzenes with piperidine, a notable reversal of the inductive order of electron release for the extremes of these groups.

To summarise, therefore, the following conclusions are drawn:

(a) There is good experimental evidence, both from measurements of equilibria and from reactivities, that the hydroxyl group releases electrons to a position conjugated with it more effectively than does the methoxyl group.

(b) There are indications that the corresponding phenomenon also occurs with the related nitrogen substituents.

(c) Although part of this difference is attributable to steric inhibition of resonance, estimates of the quantitative magnitude of the latter contribution suggest that some other fact also contributes strongly to the difference.

(d) It is not unreasonable to identify this factor with OH or NH hyperconjugation.

[25] E. Berliner and L. C. Monack, *J. Amer. Chem. Soc.* **74**, 1574 (1952).