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HYPERCONJUGATION: INTERMEDIATES AND TRANSITION STATES IN REPLACEMENT AND ELIMINATION

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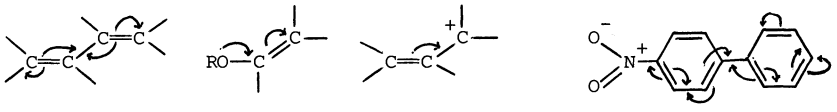
Abstract - A review is given of the development of experimental evidence for hyperconjugation in the form of electron-release to an unsaturated or electron-deficient centre from saturated H-C and C-C bonds. This type of electron-release can contribute regioselectively to the reactivity of organic molecules, and need not involve breakage of the H-C or C-C bond; under these circumstances, H-C and C-C bonds make similar contributions to the observed effects of alkyl and derived groups, the relative contributions varying with reaction and solvent. In the limit, however, this form of electron-release can result in breakage of the hyperconjugating bond, and in such circumstances (as in transition states leading to proton-loss or 1,2-elimination), H-C bonds become much more effective than C-C bonds because of the greater solvation of incipient protons than of incipient alkyl cations.

Evidence for the corresponding hyperconjugation by H-O bonds comes especially, but not exclusively, from the relative rates of electrophilic aromatic replacements affected by H-O and R-O groups. Recent experiments on the effects of these groups on nucleophilic replacements in aromatic side-chains show that the electron-releasing power of the H-O group is quite variable, and suggest that the impact of H-O hyperconjugation is more dependent on the reaction and the solvent than that of H-C hyperconjugation has been shown to be. Reaction pathways in the hydrolysis of $RO.C_6H_2Br_2.CHBr_2$ and $RO.C_6H_3Br.CHBr_2$, which can lead to products both of replacement and of elimination, are discussed, and isotope effects in H-C and H-O hyperconjugation are compared.

1. HYPERCONJUGATION FROM H-C AND C-C BONDS

The term conjugation, in its chemical sense, refers to a situation in which one unsaturated system has attached directly to it another unsaturated system or an atom carrying a pair of electrons or deficient in a pair of electrons. A consequence is that formally localized electrons become in part delocalised, as in the examples shown in Fig. 1.



1 2 3 4

Fig. 1. Electronic movements in structural situations involving conjugation.

Such conjugation is recognisable from the thermodynamic and kinetic behaviour of the molecules concerned. Thus butadiene (1) is more stable than would otherwise be expected by analogy with ethylene (Ref. 1); with some electrophiles it is less reactive than ethylene (Ref. 2). The vinyl ether (2), likewise stabilised thermodynamically by conjugation (Ref. 3), is much more reactive with electrophiles than ethylene is (Ref. 4); and electrophilic attack on both compounds is initiated at a terminus of the conjugated system. Similarly, the formation of the allylic carbocation (3) by heterolysis is more rapid than that of the propyl cation (Ref. 5).

When the two parts which form the conjugated system are the same, electronic movements resulting from conjugation can occur in both directions. When these two parts are different, the electronic movements are predominantly [as in (2)] or exclusively [as in (3)] in one direction. The effects on the chemistry of the system in general appear in most pronounced form at the termini of the system. Reagents in perturbing the conjugation may

evoke electronic movements in the direction opposite to that which is predominant in the ground state of the molecule, as when the *p*-nitrophenyl substituent is itself *o*,*p*-directing (structure 4) (Ref. 6).

The corresponding interaction between electrons of single bonds and an unsaturated system can be represented as in Fig. 2, where propene and the ethyl cation are chosen as examples.

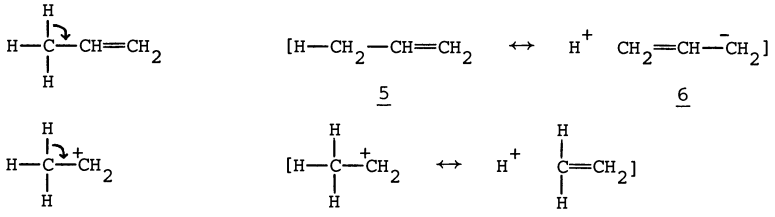
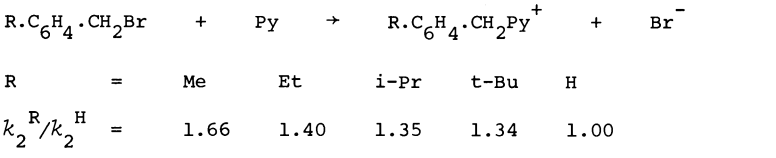


Fig. 2. Electronic movements involving saturated groups attached to an unsaturated system: "no-bond resonance" : "hyperconjugation".

The delocalisation of the electrons of the single bonds of the methyl group can be represented for propene in the formalism of valence-bond theory as in structure 6, and its extent would be measured by the weight of the contribution of structures of this kind to the resonance hybrid describing the molecule in question.

The term "no-bond resonance" was used by some to describe this type of electronic interaction; but its analogy with conjugation led Mulliken to propose the term "hyperconjugation" (Ref. 7) in 1939, and to argue that its contribution to chemical structure, though often small, must not be neglected (Ref. 8). The acceptance of his theories, and their overall importance to chemistry, was marked in 1966 by the award of a Nobel Prize.

Hyperconjugation is a very general phenomenon, occurring in a variety of situations. For a detailed subclassification, Mulliken's contribution to the 1959 Conference on Hyperconjugation should be consulted (Ref. 8). In the present paper, consideration is restricted to electron-releasing hyperconjugation from sp^3-hybridised bonds. Even in this limited context, the phenomenon is of general and widespread occurrence, since it is not limited to H-C bonds, but applies to R-X bonds generally. Often, therefore, it will appear as a differential change in stability or in reactivity, superposed upon other structural features influencing the property being measured. The first sets of results to be analysed in these terms were provided by Baker and Nathan in 1935 (Ref. 9) (Fig. 3).



R	=	Me	Et	i-Pr	t-Bu	H
k_2^R/k_2^H	=	1.66	1.40	1.35	1.34	1.00

Fig. 3. Relative rates (k_2^R/k_2^H) of reaction of substituted benzyl bromides with pyridine in acetone at 40°C.

The reaction is facilitated by electron-release; and in other circumstances, the t-Bu-group is more electron-releasing than the methyl group. The order of reactivity, Me > t-Bu > H, was interpreted, therefore, as indicating the existence of a superposed effect to which H-C bonds made a greater contribution than C-C bonds.

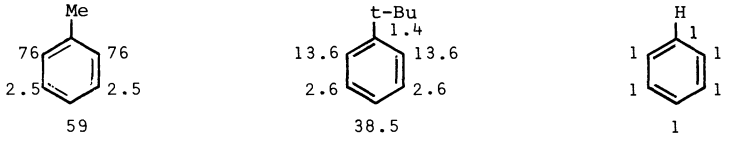
Baker and Nathan's rate differences were small. Their explanation attributed the electron-release to an effect of conjugative origin, and (predating as it did Mulliken's introduction of the term hyperconjugation) was so unconventional in the context of the theories current in 1935 that it was greatly criticised by some workers, though strongly supported by others. In the following years, however, a great many examples were adduced to support the contention that the Baker-Nathan order of apparent electron-release, Me > t-Bu > H, is often observed in comparisons of chemical reactivity. An early and important example was provided by the solvolyses of diphenylmethyl chlorides (Fig. 4) which occurs by the S_N1 mechanism and

R	Me	Et	i-Pr	t-Bu	H
$10^6 k_1/sec^{-1}$	83.5	62.6	47.0	35.9	2.82
E/kcal mol^{-1}	18.9	19.4	19.8	20.0	21.0

Fig. 4. Rates (k_1) and activation energies (E) for solvolyses of diphenylmethyl chlorides, *p*-R.C_6H_4.CH(Ph).Cl, in acetone containing 20% of water at 0°C. (Refs. 10, 11a).

involves a strongly electron-demanding transition state (Refs. 10, 11a).

Aromatic substitution also involves an electron-demanding transition state having much carbocationic character. Halogenation was claimed (Ref. 12) to provide examples of the Baker-Nathan order, and this claim has been sustained through many later examples (Fig. 5) (Ref. 13).

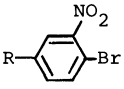


Reagent: $BrOH_2^+$ in 50% dioxan at 25°C.

Fig. 5. Partial rate factors in halogenation of alkyl benzenes (Ref. 13).

The Baker-Nathan order of effects of alkyl substituents can be seen also in reactions facilitated by electron-withdrawal. An example is the bimolecular nucleophilic aromatic replacement illustrated in Fig. 6 (Ref. 14).

R	=	Me	t-Bu	H
k_2^R/k_2^H	=	0.114	0.170	1.00

Fig. 6. Relative rates (k_2^R/k_2^H) of reaction of  with piperidine at 25°C.

Alternative explanations of the Baker-Nathan order devised to be applicable to situations of rate-facilitation were not easily used to interpret results of this kind (Refs. 14, 15).

It became clear, however, that the Baker-Nathan order was not always found, even for reactions in which it might be expected. An instructive example of the complexities encountered is that of the alkaline hydrolysis of ethyl p-alkylbenzoates, a reaction which in aqueous ethanol follows the hyperconjugation order, whereas in aqueous acetone it follows the inductive order (Fig. 7) (Ref. 16).

R in p-R.C_6H_4.CO_2Et	:	Me	t-Bu	H
k_2^R/k_2^H in 56% aqueous acetone	:	0.41	0.31	1.00
k_2^R/k_2^H in 85% aqueous ethanol	:	0.44	0.56	1.00

Fig. 7. Relative rates (k_2^R/k_2^H) of alkaline hydrolysis of substituted ethyl benzoates (Ref. 16).

Steric effects of various kinds, including steric effects on solvation, were considered as possible contributors to the complex small differences between the apparent electron-releasing effects of alkyl groups. Some of these minor structural influences may indeed play roles in interpretation of small irregularities in the sequences of effects of those groups; but concurrently with these suggestions, evidence of other kinds was accumulating to reinforce and extend the scope of the original hypothesis.

Hyperconjugation provides an explanation of the Baker-Nathan order provided it is assumed that H-C hyperconjugation is more important than C-C hyperconjugation (Fig. 8). It might

Fig. 8. Valence-bond representation of H-C and C-C hyperconjugation in the alkyl benzenes.

seem intuitively acceptable that hyperconjugation would be greater for hydrogen than for most other common substituents, because the valence-bond structures involved in H-C hyperconjugation show a proton bearing a positive charge, and protons are classically more stable entities than alkyl cations are. But this intuitive feeling is not reflected clearly in theory, and the next advance came in the recognition that the Baker-Nathan order reflects the differential effect of H-C versus alkyl-C hyperconjugation, and in the proposal (Ref. 17) that alkyl-C hyperconjugation played a major role in determining the total effect of the t-butyl group in a number of reactions, particularly but not exclusively those in which the Baker-Nathan order was evident (Fig. 9).

Compound	Benzene	Methylbenzene	t-Butylbenzene
Relative rate of molecular chlorination	0.29	100	32
Relative rate of molecular bromination	0.215	100	24.7

Fig. 9. Relative rates of molecular halogenation of benzene, methylbenzene, and t-butylbenzene in acetic acid at 25°C (Refs. 12, 17).

The argument really took the form of an expression of opinion, that it was not really plausible to ascribe the big rate-difference between benzene and t-butylbenzene to the inductive effect of the t-butyl group alone, especially when it was evident from the known orienting power of the substituent that the effect is highly regioselective, being manifest in much higher reactivity at the *para*- than at the *meta*- position.

Much effort was spent over the following decade in amplifying and extending the results available to illustrate the importance of hyperconjugation. M.M. Kreevoy and R.W. Taft Jr. (Refs. 18, 19), P.D. Bartlett (Ref. 20), and H.C. Brown (Ref. 21) were among the proponents of the use of linear free-energy relationships in the interpretation of the effects of alkyl groups on reactivity of adjacent unsaturated systems. These approaches led to an estimate that for alkyl groups attached to a benzene ring the averate ratio of hyperconjugative effects of H-C and Me-C bonds is about 1.3, but is subject to variations dependent on perturbing influences of which that of the solvent is important. Values extracted from tabulations (Ref. 22) of substituent constants for alkyl groups are shown in Fig. 10, together with those for the electron-withdrawing nitro-group and the electron-releasing methoxy-group.

R	NO_2	H	Me	Et	i-Pr	t-Bu	OMe
σ_m	0.71	0	-0.07	-0.07	-	-0.10	+0.12
σ^+_m	0.67	0	-0.07	-0.06	-0.06	-0.06	+0.05
σ_p	0.78	0	-0.17	-0.15	-0.15	-0.20	-0.27
σ^+_p	0.79	0	-0.31	-0.30	-0.28	-0.26	-0.78

Fig. 10. Some estimates of substituent constants measuring the electronic effects of alkyl and some other groups.

These parameters, which are proportional to free-energy differences and hence reflect changes in rate on a logarithmic scale, illustrate a progressive change in the relative importance of inductive and conjugative effects. The Baker-Nathan order of electron-release is clearly evident in the values at the bottom of the Table. Comparison of σ^+_m with σ^+_p illustrates that the influences attributed to conjugation (for the OMe group) and to hyperconjugation (for the alkyl groups) are strongly regioselective.

Evidence for hyperconjugation from studies of structural effects was extended by examination of isotope effects. E.S. Lewis (Refs. 23, 24) and V.J. Shiner (Ref. 25) were two of the earlier contributors here. It became clear that in situations dominated by inductive influences the C-C bond appeared to be slightly more electron-releasing than the H-C bond; whereas the reverse was true, and the effect was larger, in conjugative situations (Fig. 11, Ref. 24).

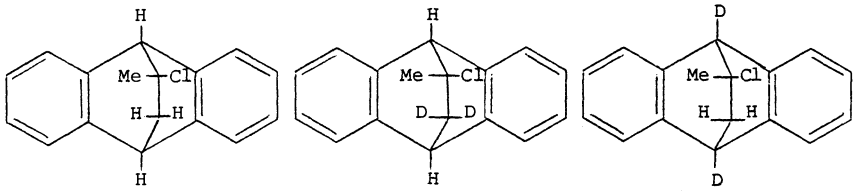
Similar small but significant differences were obtained for other solvolytic reactions by Shiner and Verbanic (Ref. 26) and for aromatic replacements by Swain, Knee, and Kresge (Ref. 27).

V.J. Shiner (Ref. 28) showed also by studies of secondary isotope effects that the electron-releasing effect of an H-C bond can be inhibited sterically by constraining it so that its

Parent compound	Comparison	$k_1(CH_3)/k_1(CD_3)$	Solvent
p-$CH_3.C_6H_4.CH(CH_3)Cl$	α-CH_3/α-CD_3	1.20	CH_3CO_2H
	p-CH_3/p-CD_3	1.08	CH_3CO_2H
	p-CH_3/p-CD_3	1.01	Me_2CO-H_2O
m-$CH_3.C_6H_4.CH(CH_3)Cl$	m-CH_3/m-CD_3	0.99	Me_2CO-H_2O

Fig. 11. Isotope-effects on the rates of solvolysis of $R.C_6H_4.CH(CH_3)Cl$ (Ref. 24).

sp^3 orbital cannot overlap with a developing carbocationic centre. Thus the stereoselective and hence the hyperconjugative nature of the electron-release was elegantly confirmed (Fig. 12).



Relative rate of solvolysis	9.01	7.84	9.20
k_H/k_D (per replaced hydrogen atom)	1.00	1.14	0.986

Fig. 12. Steric inhibition of the electron-releasing power of an H-C bond in solvolysis (Ref. 28).

Accumulation of evidence of these various kinds has led to a general incorporation of hyperconjugation into theoretical accounts of reactivity. Thus the well-known fact that tertiary carbocations, $H_3C.C^+(R_1)(R_2)$ are formed in solvolysis much more rapidly than are the corresponding secondary carbocations, $H.C^+(R_1)(R_2)$ is believed to be determined in considerable part by hyperconjugative stabilisation of the incipient carbocation by the methyl group. This view has been supported (Ref. 29) by the establishment of a linear free-energy correlation between the CH_3/H rate-ratio and the CH_3/CD_3 secondary β-deuterium isotope effect of the form shown in Fig. 13, and by detailed analysis of the expected contribution from hyperconjugation in a number of examples.

$$\log_{10}(k_{CH_3}/k_{CD_3}) = 0.02024 \log_{10}(k_{CH_3}/k_H)$$

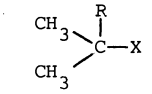
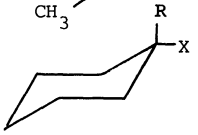
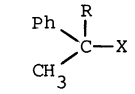
Selected examples: Compound	k_{CH_3}/k_H	k_{CH_3}/k_{CD_3}
	10^6	1.33
	$10^{4.36}$	1.21
	$10^{3.26}$	1.17

Fig. 13. Linear free-energy correlation between α-methyl substituent effects and methyl-d_3 isotope effects (Ref. 29) in solvolyses of secondary and tertiary esters.

Hyperconjugative electron-release has been discussed also in relation to experimental results from ion cyclotron resonance spectroscopy (Ref. 30).

2. HYPERCONJUGATION IN RELATION TO IONISATION OF C-H BONDS AND ELIMINATION REACTIONS

The valence-bond description of hyperconjugation uses contributions from non-bonded canonical structures (e.g. 6, Fig. 2), and hence it was natural that the possibility of complete loss of a proton by loosening of the H-C bond should be considered. This was proposed by R. Robinson (Ref. 12b) as a preferable interpretation of Baker and Nathan's order of reactivity. In the limit, then, reactions showing this order might turn out to be in part elimination-addition processes (Fig. 14).

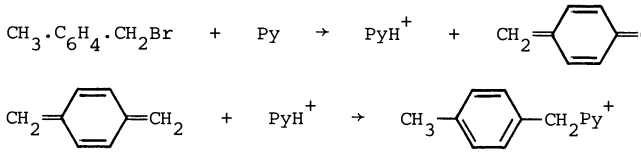


Fig. 14. Reaction of 4-methylbenzyl chloride with pyridine formulated as an elimination-addition sequence.

This type of interpretation did not receive general acceptance; it was disproved formally for the important example of the solvolyses of substituted diphenylmethyl chlorides (Refs. 10, 11a). It is apparent that the relatively small hydrogen/deuterium kinetic isotope effects observed under conventional hyperconjugating situations are consistent with a relatively small loosening of the H-C bond in the transition states for the reactions under study. The transition state for ionisation of "active hydrogen" from a carbon or other atom attached to an unsaturated system is, however, clearly stabilized by hyperconjugation (Fig. 15).

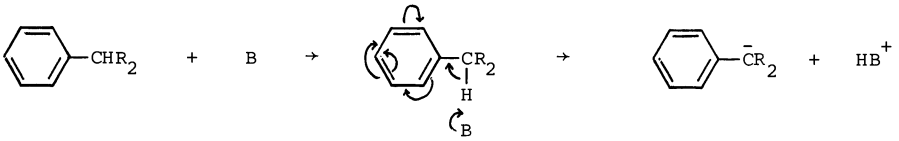


Fig. 15. Hyperconjugation in the stabilisation of transition states for ionisation of C-H bonds.

The kinetic acidities of hydrocarbons follow the sequence $CH_4 < PhCH_3 < Ph_2CH_2 < Ph_3CH$, changing with the availability and importance of this type of delocalisation (Ref. 31). The expected types of steric constraint reduce the effectiveness of this hyperconjugative electron release (Ref. 32).

Both uni- and bimolecular eliminations likewise involve transition states stabilised by hyperconjugation (Fig. 16).

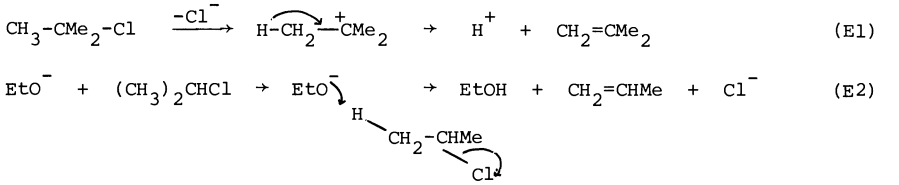


Fig. 16. Hyperconjugation in typical E1 and E2 eliminations.

In both cases the transition state for the reaction is stabilised by delocalisation: for the E1 case with the vacant orbital of the already formed carbocation, and for the E2 case with the π-orbitals of the forming double bond. Among the ways in which these reactions differ from those considered earlier, we can note that they can be, and usually are, associated with much larger hydrogen/deuterium kinetic isotope effects (Fig. 17), consistent with their formulation as processes in which the H-C bond is considerably broken in the transition state.

It is apparent also from our knowledge of general chemistry that, in this manifestation of hyperconjugation, electron-release from H-C bonds is customarily much easier than the corresponding release from C-C bonds. Rather special structural situations are needed for realisation of 1,2-eliminations in which a $\rangle C—C$ bond releases electrons to provide a carbocationic fragment (Fig. 18) (Refs. 35, 36).

Isotopic exchange of α-hydrogens in $CD_3.C_6H_5$ with lithium cyclohexylamide in cyclohexylamine	: k_H/k_D	= *ca.* 12 (Ref. 33)
Dehydrobromination of CD_3CH_2Br with EtO^- in EtOH at 25°C	: k_H/k_D	= 6.7 (Ref. 34)
Proton-loss from $CH_3CH_2.C(CD_3)_2^+$	: k_H/k_D	= 2.3 (Ref. 25)

Fig. 17. Kinetic isotope effects in typical ionisations of H-C bonds, and in 1,2-elimination reactions.

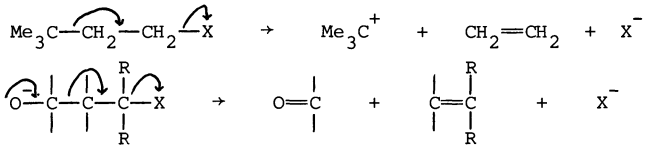


Fig. 18. Hyperconjugative electron-release from C-C bonds leading to fragmentation (Refs. 35, 36).

In general, therefore, H-C bonds are much more easily heterolysed than C-C bonds under hyperconjugative situations, and the most reasonable interpretation of this is that breaking H-C bonds are greatly stabilised by the solvation of the incipient proton, whereas breaking C-C bonds are not so readily stabilised.

3. HYPERCONJUGATION FROM H-O BONDS

Theory allows all sp^3-hybridised bonds to hyperconjugate with a suitably placed unsaturated centre, and hence predicts no qualitative difference between the effects of H-C, H-O and other H-X bonds. The first mention of H-O hyperconjugation of which I am aware was by Ingold (Ref. 12c) and the first application to a specific chemical situation was by Robertson, de la Mare, and Swedlund (Ref. 37). They attributed the fact that the phenol molecule is more reactive than its methyl ether (anisole) in molecular bromination to a contribution from H-O hyperconjugation. In 1959 an attempt was made (Ref. 38) to correct for the possibility that the reactivity of anisole is somewhat reduced by steric inhibition of resonance. It was concluded that at least about half of the extra reactivity of phenol at the *para*-position can be attributed to H-O hyperconjugation. The effect is a small one; the partial rate factor for bromination *para* to the MeO-group is about 10^{10}, and the additional reactivity attributed to differential hyperconjugation by the HO group as compared with the MeO-group involves a rate factor of about 20 (i.e. $10^{1.3}$). It makes, however, a significant contribution; by using these results and those for related electrophilic substitutions and other reactions, the value of σ^+ for the *p*-HO-group has been estimated (Ref. 39) to be -0.91 when that for the *p*-MeO-group is taken as -0.78.

The conformation suitable for overlap of the electrons of the H-O bond with the attached unsaturated system is not the most suitable for the associated conjugation of a single lone pair on oxygen. On the other hand, the nearly free rotation about the C-O bond, with a barrier (Ref. 40) of only about 13 J mol^{-1} (1100 cm^{-1}), will at ordinary temperatures allow significant contributions from conformations other than that which requires the HO bond to be in the plane of the benzene ring; and any polarization of the H-O bond in the sense $H^{\delta+}-O^{\delta-}$ must enhance the electron-releasing power of the lone-pair electrons on oxygen. It has been argued, therefore (Ref. 41), that the contribution of HO-hyperconjugation to the rate of electrophilic substitution in phenol is not precluded, although it may be reduced, by the stereoelectronic requirements of conjugation and hyperconjugation.

It has remained an open question whether the processes described by these rates involve a transition state in which the H-O bond becomes necessarily broken if the energy-maximum on the reaction coordinate is passed. Several possibilities (Refs. 41, 42) all of which could give the dienone as the major kinetically-controlled product, are shown in Fig. 19. In this figure, H-O hyperconjugation is represented (structure 7) as playing a part in the reaction: either with proton-loss from oxygen in the rate-determining stage, thus leading to 11 directly or *via* 10; or without proton-loss from oxygen in the rate-determining stage, thus giving the intermediate 8 and thence by one of three possible pathways to 11. All the stages other than those leading to the bromophenol 12 are probably reversible, and the protonated dienone 9 has been shown for suitably substituted cases to be an intermediate in one pathway for the conversion of bromodienones into bromophenols (Ref. 43).

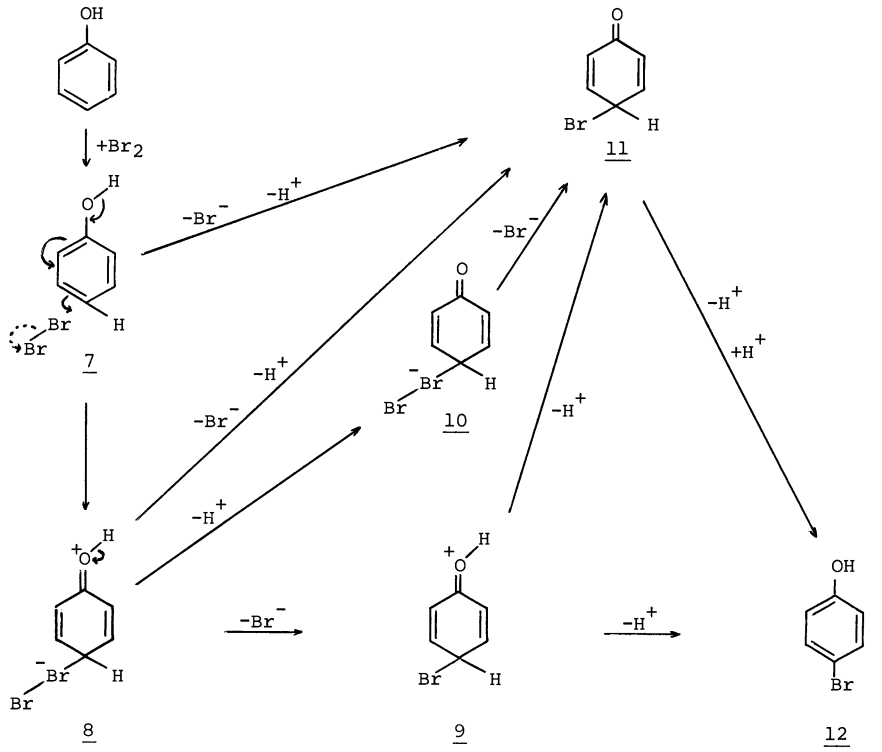
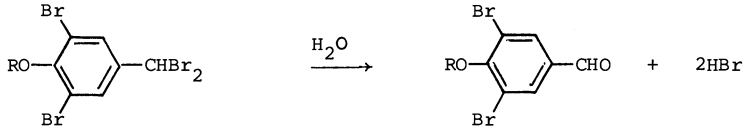


Fig. 19. Possible pathways in the bromination of phenol.

Direct proof distinguishing between these possibilities has not been provided; but I now think it likely that one of the more complicated pathways is probably adopted, with loss of the hydroxylic proton delayed beyond the rate-determining stage of the reaction. Solvolyses of halides by the S_N1 mechanism are, like aromatic substitutions, powerfully facilitated by conjugative electron-release; but until recently the influence of the HO-group on the rates of these reactions had not been established. The observation has now been made that the reaction shown in Fig. 20 is very much more rapid for R = OH than for R = OMe (Ref. 44).



(R = H, Me)

Fig. 20. Solvolysis of 2,6-dibromo-4-dibromomethylphenol and its methyl ether.

Three possible pathways were envisaged for the reaction of the phenol (Fig. 21). In the first, the proton comes off reversibly, and the O^- substituent then powerfully activates the nucleus for the first stage of an S_N1 displacement. The resulting quinone methide (structure 14) is then the result of a 1,6-dehydrobromination. In the second, the same product is the result of concerted 1,6-dehydrobromination. In the third, the hydroxy-group promotes an S_N1 heterolysis of bromide in the first stage of the reaction, which is followed by proton-loss to give the product of dehydrobromination, or by reaction with water to give the product of replacement. For our compounds this then reacts further to give a carbonyl compound (structure 17) because of the extreme lability of side-chain halogen in Ar.CR(Br)(OH) (structure 16, with R' = Br).

To make our compounds amenable to careful kinetic examination, we used as solvent 1,4-dioxane containing 5% of water. We showed kinetically that only starting material, quinone methide, and the aldehydic product were detectable in the reacting system by ultraviolet spectroscopy. The first pathway, involving reversible proton-loss in the first step, was available for 2,6-dibromo-4-dibromomethylphenol at sufficiently high pH, but was nearly cut out by acidities greater than about 10^{-3} *M*, when the reaction proceeded smoothly but with a very strong reversal by added or developing bromide ion. For 2-bromo-4-dibromomethylphenol, the first mechanism was not observed, and the third was predominant for acidities greater than about 10^{-4} *M*. Major participation of the concerted process was ruled out by the fact that

rate-reduction by developing or added bromide ion was very marked, but there was no corresponding rate-reduction by developing or added hydrogen ion.

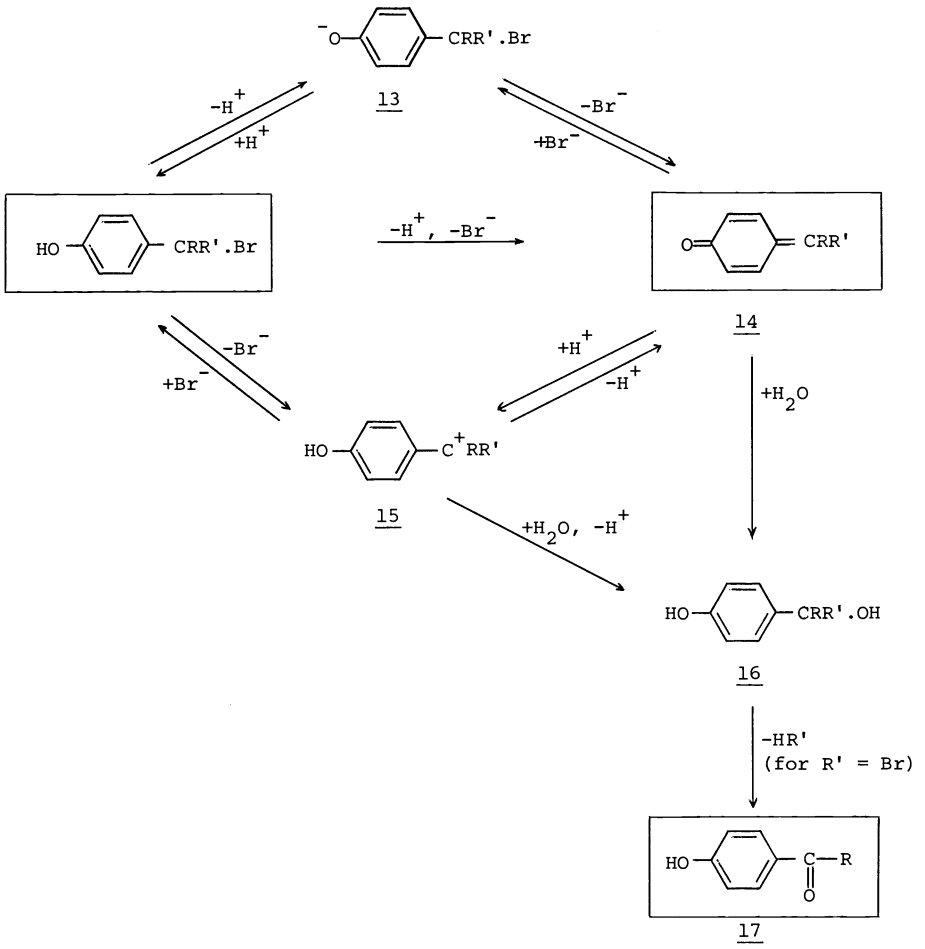


Fig. 21. Possible reaction pathways in the hydrolyses of *p*-hydroxybenzyl bromides.

From these kinetic observations it was concluded that the initially measured rates are those of S_N1 processes, and that the true activating power of an HO-group for an S_N1 solvolysis can thence be estimated. Direct comparison has been made with the reactivity of the corresponding methyl ether, which under these conditions undergoes solvolysis about 3200 times less rapidly. These nucleophilic displacements can be assumed to have a ρ^+-value of about -6.0 (Ref. 45). On this basis, the value of $\sigma^+_{p\text{-OH}}$ is -1.36 when measured by relative rates of this reaction, in contrast with the value of -0.92 from electrophilic displacements, on a scale in which $\sigma^+_{p\text{-OMe}}$ is accepted (Ref. 38) to have a uniform value of about -0.78. The value for the hydroxy-group is therefore highly reaction-dependent, as is consistent with activation by a process subject to hydrogen-bonding of a kind specific to the particular conditions of the reaction.

Isotope effects as determined both for nucleophilic and for electrophilic (Ref. 41) processes are consistent with this interpretation (Fig. 22). The observed isotope effects are larger than is found typically for reactions accelerated by H-C hyperconjugation when the H-C bond does not break, but are still small in comparison with what would be expected if the H-O bond were half-broken in the transition state.

It remains an open question whether or not C-O hyperconjugation makes an important contribution to the electron-donating power of the methoxy-group. It would be difficult to disentangle any such influence from the larger effects of the lone pairs of electrons; there are two such lone-pairs, so geometric constraints cannot reduce their combined conjugative power to zero. Extreme examples of transition states which must in part be stabilised by C-O hyperconjugation, analogous electronically to those concerned in some fragmentation reactions, are of course well known (Fig. 23).

Nucleophilic replacements in aqueous dioxan

$$\frac{k_1(HO.C_6H_2Br_2.CHBr_2 \text{ in dioxan}/H_2O)}{k_1(DO.C_6H_2Br_2.CHBr_2 \text{ in dioxan}/D_2O)} = 1.95$$

$$\frac{k_1(HO.C_6H_3Br.CHBr_2 \text{ in dioxan}/H_2O)}{k_1(DO.C_6H_3Br.CHBr_2 \text{ in dioxan}/D_2O)} = 1.71$$

$$\frac{k_1(MeO.C_6H_3Br.CHBr_2 \text{ in dioxan}/H_2O)}{k_1(MeO.C_6H_3Br.CHBr_2 \text{ in dioxan}/D_2O)} = 1.30$$

Electrophilic substitution by bromine in acetic acid

$$\frac{k_2(C_6H_5OH \text{ in HOAc})}{k_2(C_6H_5OD \text{ in DOAc})} = 1.8 - 1.9$$

Fig. 22. Isotope effects for some reactions of phenols (Refs. 41, 44).

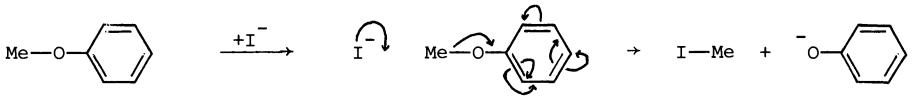


Fig. 23. C-O hyperconjugation in the transition state for demethylation.

By way of summary, I show in Fig. 24 some of the features in which H-O and H-C hyperconjugation resemble each other.

1. They are regioselective effects of electron-release, with prominent influence only at conjugated positions.
2. Their effects on reaction-rates can be recognised even when the H-O or H-C bond is retained subsequent to passage through the rate-limiting transition state.
3. Their prominence relative to other structural influences is reaction-dependent, and this dependence is probably solvent-dependent also.
4. They display a normal deuterium isotope effect ($k_H/k_D > 1$), which is small when the H-C or D-C bond is retained past the transition state.
5. Breakings of the H-O or H-C bond in or following passage through the first transition state can be observed in suitable cases, and involve hyperconjugative stabilisation of the relevant transition states.
6. The corresponding breakings of Me-O or Me-C bonds, though possible in special cases, are not normally competitive with the processes dependent on H-O and H-C hyperconjugation.

Fig. 24. Points of resemblance between effects of H-O and H-C hyperconjugation.

I believe that further instances of H-X-hyperconjugation will in due course be recognised as playing significant roles in determining chemical reactivity.

Be that as it may, I conclude by expressing my appreciation to all those who have helped me through the years, so much, and in so many different ways. They are too many to enumerate, but I do indeed acknowledge them and thank them most warmly. And I thank you all also for your attention.

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APPENDIX

(a) Relative magnitude of energy differences provided by C-C and H-C hyperconjugation

The view has been expressed (Ref. 48) that C-C hyperconjugation may intrinsically be able to stabilise transition states by electron-release more than the corresponding H-C hyperconjugation can. If this is so, then the frequent (though not universal) appearance of the Baker-Nathan order of electron release must be a manifestation of factors which often can increase the effectiveness of H-C at the expense of C-C hyperconjugation. It seems likely that these are factors depending on solvation of particular initial and transition states (Ref. 46).

(b) Isotope effects in the bromination of phenol

The bromination of phenol by molecular bromine has been shown (Ref. 47) to have the kinetic form $-d[Br_2]/dt = k_2[ArH][Br_2]$. The solvent isotope-effect for molecular brominations of mesitylene having this kinetic form have been examined by Keefer and Andrews (Ref. 48) under several conditions. Values of $k_2(HOAc)/k_2(DOAc)$ are reported as being 2.5, 1.4, and 1.3 under slightly different conditions. If the aberrant high value is neglected, and the others are accepted as giving the best available estimate of the solvent isotope effect on this mode of bromination, then the composite isotope effect for the bromination of phenol in acetic acid (1.8 - 1.9; Fig. 22) can be corrected to give the true structural isotope effect as 1.3 - 1.4, very like the corrected structural isotope effect for the reported solvolyses.

(c) The conformation of the phenolic hydroxy-group in solution

Although the phenol molecule is planar in the gas phase, the barrier preventing the H-O bond from rotating out of the plane of the ring is small (Ref. 40), and can be overcome by crystal forces, since in a number of quite simple phenols (Ref. 49) the phenolic hydrogen is considerably out of the plane of the benzene ring in the solid state. Phenols are known to form hydrogen bonds not only with themselves but also with hydroxylic and with donor solvents, and the writer believes that in dilute solution at ordinary temperatures, in the solvents considered in the present investigation, the contribution from conformations other than the planar form would be considerable. It is noteworthy, in view of the particularly large influence of the hydroxy-group on the rate of solvolysis of 2-bromo-4-dibromomethylphenol in aqueous dioxan, that dioxan reduces the rate of methylation of phenol through hydrogen-bonding (Ref. 50).

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