[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE, MASS.]

Effect of Structural Changes in Reactants on the Structure of Transition States[1,2]

BY C. GARDNER SWAIN AND EDWARD R. THORNTON

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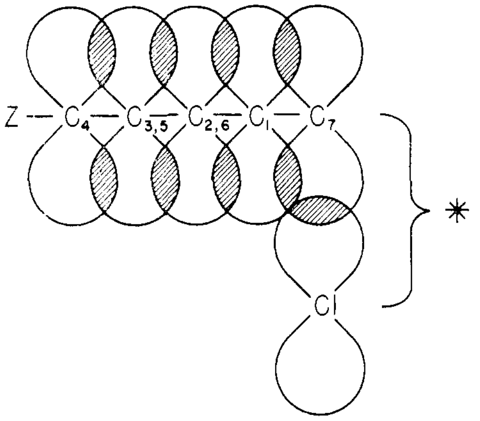
A generalization is suggested for the effect of structural changes in reactants on the structure of transition states: electron-supplying substituents lengthen the nearest bonds being made or broken at the transition state, but have an alternating effect on more remote such bonds. Reactions of alkyl halides and sulfonium salts, enolization and an oxidation with bromine illustrate this rule.

A rule, useful for deciding which bonds in a transition state will be lengthened and which will be shortened when a given change is made in the structure of a reactant, will be stated, illustrated by seven examples, and given some theoretical justification.

Statement of the Rule.—In a simple atomic orbital diagram of the transition state, locate all *reacting bonds*, bonds which are present in the transition state but entirely absent in either the reactants (for bonds being made) or the products (for bonds being broken). A *reacting orbital* defines an electron cloud, bounded by nuclei but containing no nuclei, which includes one reacting bond. Identify the reacting orbitals, each composed of the atomic orbital portions of a reacting bond plus all other atomic orbital portions which overlap with them at the transition state, each portion bounded by nuclei but with no interposed nuclei, *i.e.*, halves of a *p*- or *s*-orbital belong to different reacting orbitals. Starting at the point of structure change, star (*) the nearest reacting orbital(s) and *alternate* more remote reacting orbitals. Wavemark (∼) other reacting orbitals. The rule is that bonds utilizing starred orbitals are lengthened at the transition state by electron-supplying substituents and shortened by electron-attracting substituents; the opposite is true for bonds utilizing waved orbitals. A more electron-supplying substituent is one which is more basic toward a proton.[3]

Examples of Applications.—In the solvolysis of cumyl chlorides, the rule predicts that *p*- or *m*-methyl should increase the extent of CCl cleavage at the transition state, while *p*- or *m*-chloro should do the reverse. We should star the reacting orbital composed of the overlapping lobe of the chlorine atomic orbital and the lower lobes of the seven carbon 2p atomic orbitals. This is the only reacting orbital present.

Experimentally the sensitivity to solvent polarity (ratio of rates at 25°, methanol to ethanol or ethanol to 2-propanol) is larger for *m*-methyl and *p*-phenyl, but less for *p*- or *m*-chloro, *p*-carbomethoxy or *p*-trifluoromethyl.[4] This indicates that there is more complete ionization at the transition state when electron-supplying substituents are present.[5] Thus the rule fares better here than usual extensions of the Hammond postulate, which predict that the carbonium ion should be the best model for the transition state when least stabilized, but that if both carbonium ion and transition state are more stable the transition state should be reached sooner, before there is as much movement along the reaction coördinate.[6]



The reaction of sodium azide with substituted benzyldimethylsulfonium *p*-toluenesulfonates is near the other mechanistic extreme, since it involves a strong nucleophile but poor leaving group. Here NC bond formation should be more nearly complete with electron-attracting substituents. Here there are two reacting orbitals, one above the plane of the ring, one below. The substituent Z is symmetrically placed between these two reacting orbitals (whether it is *p*- or *m*-), so both must be starred. The ratio of second-order rate constants at 60° in 80% dioxane–20% water *vs.* 100% water decreases in the order *m*-chloro (240), unsubstituted (200), *p*-methyl (115), indicating that charge recombination is indeed more complete when electron-attracting substituents are present.[7] In the closely similar reaction with sodium hydroxide (instead of azide) in water at 60° the sulfur isotope effect (k^{32}/k^{34}) is larger for *p*-methyl (1.0096) than for unsubstituted (1.0093) or *m*-chloro (1.0082),[8] again as predicted.

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[1] Supported in part by the National Institutes of Health through Research Grant RG-3711 and by a postdoctoral fellowship to E. R. T. from the Division of General Medical Services, U. S. Public Health Service.

[2] *Cf.* following paper by C. G. Swain and E. R. Thornton, *J. Am. Chem. Soc.*, **84**, 822 (1962).

[3] For a reacting bond in which the substituent change changes one atom (*e.g.*, from CCl to CBr), the predicted change is for the *difference* between transition state and reactant or product lengths. Because it is more basic toward a proton, Cl is more electron supplying than Br. When there is more than one reacting orbital in an even-membered ring, the effect along the shortest path should prevail.

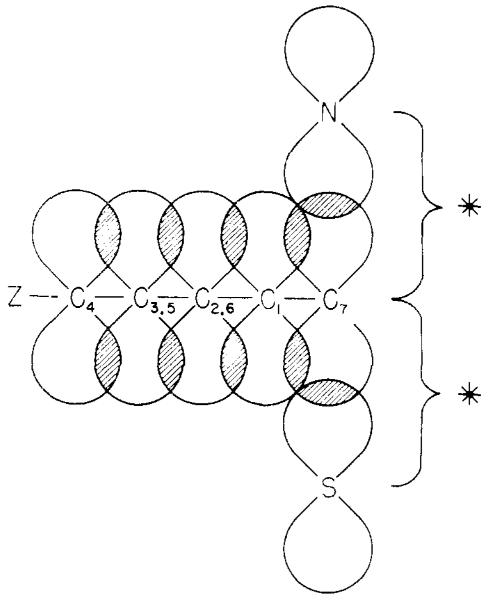
[4] Y. Okamoto, T. Inukai and H. C. Brown, *J. Am. Chem. Soc.*, **80**, 4975 (1958).

[5] E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 252 (1935).

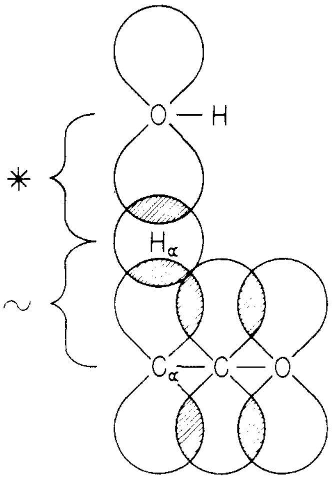
[6] G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955); K. B. Wiberg, *Chem. Revs.*, **55**, 733, 737 (1955).

[7] C. G. Swain, T. Rees and L. J. Taylor, paper to be published. The ratio $k/k°$ in water was 2.2 for *p*-methyl, 0.73 for *m*-chloro.

[8] C. G. Swain and E. R. Thornton, *J. Org Chem.*, **26**, 4808 (1961). The product alcohols were isolated in good yields. The ratio $k/k°$

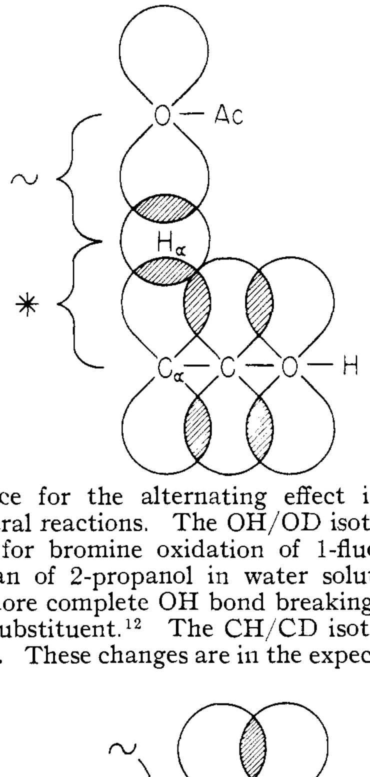


Enolizations of ketones catalyzed by acids or nucleophiles have transition states generally closer to products (enol or enolate ion and conjugate acid of the base) than to reactants as shown by the relatively large magnitudes of *solvent* (H_2O *vs.* D_2O) isotope effects when water or hydroxide ion is the nucleophile.[9] This is not an assumption, but a fact ascertained by the use of solvent isotope effects. Accordingly, the shortest bond to the α-hydrogen at the transition state is the one to the oxygen of the nucleophile, and the *α-hydrogen* isotope effect should be affected most by changes in the length of this OH bond. (Furthermore, the HC bond is further removed and so likely to be affected less by changes in the nucleophile.) Therefore, the stronger the base used, the larger should be the α-hydrogen isotope effect. Because hydroxide lacks the extra electron-attracting proton of water, it should give a longer starred bond and larger α-hydrogen isotope effect.

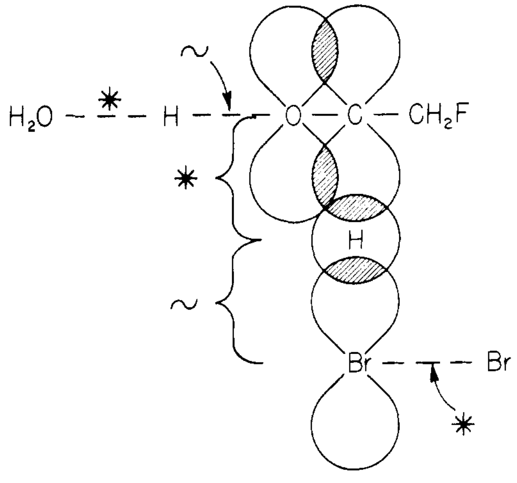


A symmetrical transition state gives maximum isotope effect because it has no vibration of the α-hydrogen to offset that in the reactant in either the asymmetric or symmetric stretch. There is in fact a progressive increase in this isotope effect from water to acetate ion to hydroxide ion for ionization of either nitromethane[10] or α-phenylisocaprophenone.[11] This is contrary to the Wiberg rule.[6]

Similarly the CH/CT isotope effect for enolization of α-phenylisocaprophenone is larger for acetic acid catalysis (11.4) than for acetate ion catalysis (10.2),[11] because the CH bond is shorter and the transition state more symmetrical with the electron-attracting proton on the carbonyl oxygen in place of no substituent.



Evidence for the alternating effect is derived from several reactions. The OH/OD isotope effect is larger for bromine oxidation of 1-fluoro-2-propanol than of 2-propanol in water solution, suggesting more complete OH bond breaking with the fluorine substituent.[12] The CH/CD isotope effect is smaller. These changes are in the expected directions.



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was 1.28 for *p*-methyl, 1.14 for *m*-chloro. The conclusion that a larger sulfur isotope effect means a longer CS bond in the transition state is based on the assumption that the secondary isotope effect due to the change in force constants of the two CS bonds *not* being broken in the transition state changes less with a change in substitution than the primary isotope effect. The effect of substituents on the secondary CS bonds must be *transmitted through* the primary (reacting) CS bond.

(9) C. G. Swain and E. R. Thornton, *J. Am. Chem. Soc.*, **83**, 3884, 3890 (1961); C. G. Swain and A. S. Rosenberg, *ibid.*, **83**, 2157 (1961).

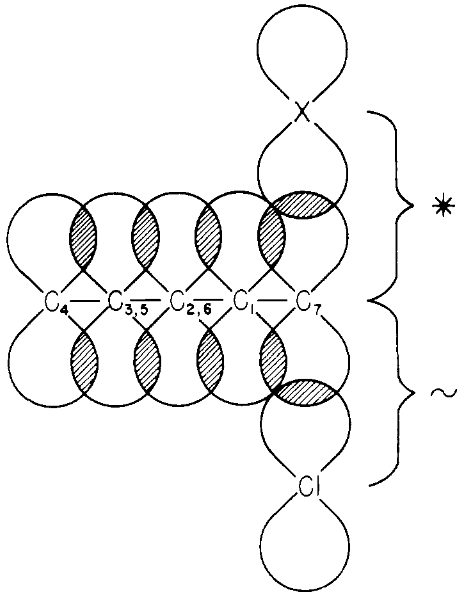
(10) O. Reitz, *Z. physik. Chem.*, **A176**, 363 (1936).

(11) C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *J. Am. Chem. Soc.*, **80**, 5885 (1958).

(12) C. G. Swain, R. A. Wiles and R. F. W. Bader, *ibid.*, **83**, 1945 (1961).

The OH bond would be conjugated and starred if the oxygen had no unshared pair, because the electrons would then have to come from the shared pair in the OH bond. However, *unshared pairs should be more nucleophilic than shared pairs.* Therefore we expect an unshared pair to be utilized instead, the HCO and COH planes to be nearly perpendicular at the transition state (90° dihedral angle for HC and OH), and the CO (π) and OH bonds to be orthogonal at the transition state and to belong to different reacting orbitals.

Likewise the Cl^{35}/Cl^{37} isotope effect for reaction of nucleophiles (X) with benzyl chloride at 30° in 80% dioxane–20% water by weight is larger with water (1.0074) than with the stronger bases cyanide ion (1.0068) or thiosulfate ion (1.0060).[13]



The transition state for

$$X + YX \rightleftarrows [X\text{---}Y\text{---}X]^* \longrightarrow XY + X$$

should be close to symmetrical, *i.e.*, the X—Y bond lengths should be nearly identical. The rule then predicts transition states resembling reactants more than products for the polar displacement

$$X + YZ \rightleftarrows [X{\sim}Y^*Z]^{\ddagger} \longrightarrow XY + Z$$

where Z is a weaker base than X (more electron attracting). A weaker base needs "less of a push" to reach the free energy maximum. For example, the reaction of hydroxide ion with a sulfonium ion should have a transition state close to reactants because the dialkyl sulfide Z is a weaker base than hydroxide ion X. The lyoxide isotope effect k_{DO^-}/k_{HO^-} with *p*-methylbenzyldimethylsulfonium *p*-toluenesulfonate in water at 60° is only 1.28,[14] less than the square root of 1.79 (the ratio of basicities of DO^- and HO^{-9}), indicating that hydroxide is indeed more loosely bonded at the transition state.

A stronger base acting as a nucleophile should also give a transition state closer to reactants. This should be true of chloride ion relative to bromide ion because chloride is more electron-donating than bromide. However, unlike basicity and leaving group reactivity, nucleophilicity (relative rate in a nucleophilic displacement) is not a good index of electron-donating ability. Nucleophilicity depends strongly on the ease of displacement of solvent molecules initially solvating ionic nucleophiles (*e.g.*, one or more of the four water molecules around chloride or bromide ion in water solution), which are more weakly held and more easily displaced in the case of bromide. This desolvation which occurs before the transition state in nucleophilic attack must, be the principle of microscopic reversibility, be a solvation occurring after the transition state in the reverse reaction when the group is a leaving group, and so it does not interfere with the correlation of leaving group reactivity with basicity.

Effects on rate or activation energy are harder to predict. They are generally resultants of opposing contributions, because starred and waved bonds are affected oppositely. Therefore it is preferable to apply the rule to individual bonds and to measure effects on the individual bonds by successive multiple isotopic substitution.

Models for Simple Bond Dissociations.—The rule is justified theoretically. Transition state bonds are generally electron deficient because they are longer than ordinary covalent bonds and this causes the electrons to concentrate more around the nuclei and less in the bond between. This is equivalent to the statement that there is less overlap of atomic orbitals in the transition state reacting bonds than in these bonds in either reactant (for bonds being broken) or product (for bonds being formed). This statement seems very reasonable, although it has not been proved.[15] If the conclusion that reacting bonds are electron deficient is accepted, the following arguments show how the effects predicted by the rule should arise.

Supplying electrons to an electron-deficient bond should tend to decrease internuclear repulsion and increase overlap possibility by increasing the effective size of one or the other of the atomic orbitals of that bond. Therefore the greater the electron density, the longer the bond should be when the free energy maximum for bond breaking is reached. In other words, more energy must be put into such a bond (but not necessarily into other bonds of the reactant) before its binding energy is overcome and the reaction starts downhill in energy. The effect of structural changes on bond lengths and force constants in the transition state can usually be shown to be much larger than comparable effects in the reactant by the smallness of measured infrared shifts in the reactant.

The rule has an easily demonstrated mechanical analogy as shown in Fig. 1. North poles of small alnico magnets repel at all distances r if only air is

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(13) J. W. Hill, "Chlorine Isotope Effects in the Reactions of Benzyl and Substituted Benzyl Chlorides with Various Nucleophiles," Ph.D. Thesis, Univ. of Arkansas, 1961, p. 101. We are indebted to Prof. Arthur Fry for a copy of this thesis.

(14) C. G. Swain and K. B. Jetter, unpublished work. A factor of 1/0.99 in a preliminary communication (C. G. Swain and E. R. Thornton, *Tetrahedron Letters*, **6**, 211 (1961)) is incorrect.

(15) Bimolecular nucleophilic transition states are electron rich *over-all*, but this does not mean that individual bonds are not electron deficient as indicated above. Positive values of the Hammett ρ-constant mean that certain *atoms* of the transition state are electron rich, but the reacting *bonds* are still electron deficient. The electrons are concentrated around the *nuclei* because the bonds are so long.

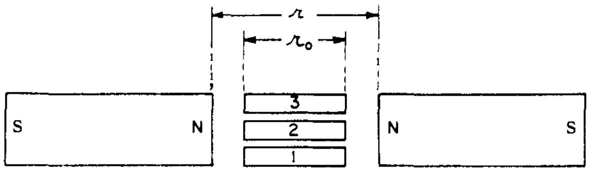

Fig. 1.—Magnetic analogy.

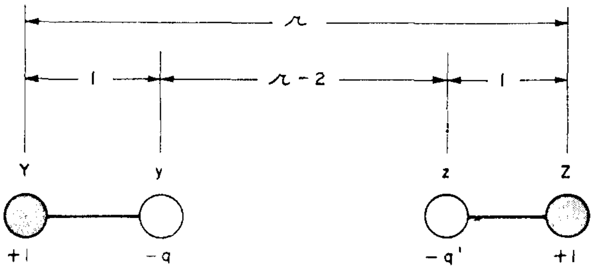

Fig. 2.—Electrostatic analogy.

present between them. Insertion of one to three pieces of soft iron (*e.g.*, square nuts) between them results in attraction at distances sufficiently close to the minimum distance r_0. Not only the force of attraction at r_0, but also the *transition state distance* r at the potential energy maximum (transition point from attraction to repulsion), *increases* with the mass of soft iron (number of nuts used). The north poles are analogous to positive nuclei and the polarizable soft iron to electron density.

An electrostatic analogy is shown in Fig. 2. Repulsion between positive nuclei Y and Z, and the Y-z and Z-y attractions between nuclei and centers of zones of high electron density with total charges of $-q$ and $-q'$ are calculated as for point charges. However, y-z interelectronic repulsion is neglected because the y and z zones are so very diffuse. Electronic repulsion is neglected also in first approximation molecular orbital treatments. The potential energy is then

$$E = -\frac{q + q'}{r - 1} + \frac{1}{r} \qquad (1)$$

Not only the energy necessary to separate the Yy and zZ systems to infinity from a fixed minimum r (*e.g.*, $r_0 = 2$), but also the *transition state distance* r at the potential energy maximum, *increases* with electron density $q + q'$ as shown in Fig. 3. Values of r for various equal values of q and q' at the transition state (arrow) are 2 for 1/8, 3 for 2/9, 4 for 9/32, 5 for 8/25, ∞ for 1/2. As electron density is increased, the bond must be stretched farther and farther before the attractive force drops to zero. Thus the bond becomes closer in energy and structure to no bond at the transition state. If the Y-y and Z-z distances are made variable and set equal to p instead of unity, the curves are qualitatively similar but the transition state distances are all multiplied by p. Thus increasing p has qualitatively the same effect as increasing q.

This calculation should apply equally to heterolysis in which both centers of electron density (y and z) remain $r - 1$ from Y because they move right simultaneously with Z. The higher energy rise shown in Fig. 3 for increased electron density might appear to be in conflict with the higher rate of hydrolysis of cumyl chlorides with electron-supplying substituents. However, Fig. 3 refers to only the CCl bond and its contribution to the net activation energy. Other bonds, *viz.*, the solvation hydrogen bonds between the partially negative chlorine and solvent molecules, will be shorter and will more than compensate this adverse influence on the rate. Our model may also be criticized because it assumes that Y and Z are equally "electronegative" (electron attracting), unlike C and Cl. This approximation thus omits a factor favoring heterolysis over homolysis, but this should not invalidate comparisons of two heterolyses with and without electron-supplying substituents.

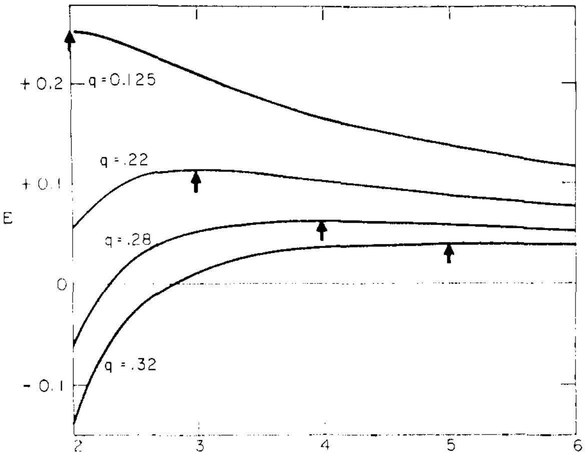

Fig. 3.—Plot of eq. 1 for $q = q'$.

The System X---Y---Z and the Alternating Effect.—Now consider the reaction

$$X + YZ \longrightarrow XY + Z$$

Supplying electrons at Z should lead to a longer YZ bond at the transition state. This is qualitatively predicted by using Fig. 3 as before to represent the dissociation of Y and Z. The effect on the XY bond should be smaller than the effect on the YZ bond since the XY bond is farther from Z, the point of structure change. For a change at X, the largest effect, on the XY bond, may be deduced similarly by using Fig. 3 to represent the potential energy change of the XY bond as X and Y approach one another from infinity in a bimolecular association reaction. Supplying electrons at X (increasing q) will tend to make X—Y a potentially stronger bond, but this will increase the distance r at which attraction begins, hence this bond will be longer at the transition state. Supplying electrons at Y should have the same effect on the YZ bond as supplying electrons at Z, and the same effect on the XY bond as supplying electrons at X. Therefore both will be lengthened at the transition state.

For more remote bonds, there are two opposing effects. For example, supplying electrons at X would (1) tend to increase over-all electron density in Y—Z as well as in X—Y, and thereby make Y—Z also longer, but (2) as a reult of making X—Y longer (more like the reactants) tend to cause Y—Z to be shorter (as in the reactants). This alternating effect (2) could also be considered to reflect 1,3-repulsions between X and Z, or the tendency of Y to maintain approximately constant total valence. The electrons of one reacting orbital are polarized, across the nucleus between, by the electrons of the other reacting orbital. Effect 2 should outweigh effect 1 for reacting orbitals X—Y—Z because these reacting orbitals are usually long and weak, and therefore especially polarizable. Thus the alternating effect should occur generally in systems of reacting orbitals. When the reacting orbital contains portions of *several* atomic orbitals, the predictions of increased bond length with electron-supplying substituents and the alternating effect will still apply because a single electron cloud not containing any nuclei will be polarized in the same way as the electron cloud associated with a single bond.

The use of "reacting orbitals" gives recognition to the efficient direct mechanism for transmitting electronic effects over long distances provided by continuous π-overlap. Within such conjugated systems it is not necessary to weaken one π-bond to strengthen another. Atomic *p*-orbitals easily overlap to form strong π-bonds with two or three neighbors at the same time as shown by the great stability of benzene and naphthalene. However, σ-bonds rarely exhibit this ability. Thus CH_5 and CH_6 are not very stable because the sp^3-orbitals on the carbon and the *s*-orbitals on the hydrogens of methane do not readily overlap with more than one other orbital. Hence there should be no alternation within a reacting orbital, but an alternation only for successive reacting orbitals.

The definition of electron-supplying substituents is obvious in systems where the *atom actually attacking (or leaving)* remains the same. For example, $HO^{\ominus}$ is more electron supplying than H_2O and p-$CH_3C_6H_4O^{\ominus}$ is more electron supplying than $C_6H_5O^{\ominus}$. Note that in all such cases more *electron-supplying* groups are stronger bases. The definition of electron-supplying groups is more complicated in cases where that atom changes. By analogy with the simple case, it seems reasonable operationally to define a group which is more basic toward a proton as being more electron supplying. Thus, $CN^{\ominus}$ is more electron supplying than H_2O, and $Cl^{\ominus}$ is more electron supplying than $Br^{\ominus}$. Although this latter definition may seem strange, since Cl is more electronegative than Br, it is a logical extension of the accepted ideas about atoms in the same *row* of the periodic table ($C^- > N > O > X$). Chloride is more electron donating than bromide in the sense that it forms a stronger bond to a proton, in analogy with the fact that electron-supplying substitutents in phenol increase the OH stretching frequency (and presumably the OH bond strength). The ionization potential of Br is less than that of Cl, but the electrons are *more densely distributed* in the 3p-orbital of Cl than in the 4p-orbital of Br.

The problem may be thought of in different terms: Why is $Cl^{\ominus}$ more basic than $Br^{\ominus}$ but m-$ClC_6H_4CO_2^{\ominus}$ less basic than m-$BrC_6H_4CO_2^{\ominus}$? The answer seems to be that the ClC (or ClH) bond has more electron density in the area between the nuclei than the BrC (or BrH) bond. Nevertheless this electron density is distributed so as to induce more of a positive charge on C (or H) when it is bonded to Cl than when it is bonded to Br. In valence-bond language, ionic structures contribute more in the case of ClC than in the case of BrC bonds, but the electron density is still greater between the nuclei for ClC.

If there are two or more potential barriers on the reaction path, the rule predicts the effect of substituents on each transition state in turn. In general, it is necessary only to write down the structure of the transition state under consideration, identify the reacting orbitals, then apply the rule. Since the effect of substituents on potential energy minima is small compared to the effect predicted by the rule for the highly polarizable transition states, it is not necessary to consider intermediates explicitly. The presence of two potential energy maxima of equal heights would make it difficult to interpret experimental results such as isotope effects in terms of transition state structure, but the application of the rule is still straightforward.

This rule is closely related to the Hammond and Wiberg rules[6] and various logical extensions of them by virtue of the fact that there is a close correlation between bond lengths, valence force constant for bond stretching, and bond strength.[16] It differs in the prediction on the effects of substituents in the central group in a displacement reaction, and in our extension of the above rules to include the alternating effect along a chain of reacting orbitals. While the Hammond and Wiberg rules are reasonable in most cases, they are thermodynamic relations based on relative rates or activation energies. We believe that this thermodynamic correlation is basically more difficult and likely to result in wrong predictions because thermodynamic quantities are resultants of many opposing contributions, such as specific solvation effects. Our rule is related to the properties of *individual bonds*. A satisfactory theoretical treatment of transition state effects requires consideration of detailed electron distribution and force constants.

Although the rule is stated in terms of bond lengths, it may be stated in more operational terms by noting that the lengthening of a bond at the transition state corresponds to the decrease of the stretching force constant in the transition state. This force constant can be experimentally determined in principle, at least for some transition states, by a normal-coördinate analysis followed by multiple isotopic substitution. If the transition state isotope effect of every atom were determined, the valence force constants in the transition state could presumably be determined.

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(16) For correlation of bond length with force constant, see R. M. Badger, *J. Chem. Phys.*, **2**, 128 (1934); **3**, 710 (1935). For correlation of force constant with bond strength, see the table of force constants in E. B. Wilson, Jr., J. C. Decius and P. C. Cross, "Molecular Vibrations," McGraw-Hill Book Co., Inc., New York, N. Y., 1955, p. 175 and the table of bond strengths in L. Pauling, "The Nature of the Chemical Bond," Ed. 3, Cornell University Press, Ithaca, N. Y., 1960, p. 85.