Technical Papers

A New Steric Effect in Organic Chemistry[1]

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Current theories of organic chemistry, particularly those developed by the English school (*5*), have emphasized the polar factor of substituents to the almost complete neglect of their steric factor. That is to say, these theories have sought to explain the effect of a given substituent by considering only the effect of that substituent upon the charge distribution within the molecule, without also considering the role played by the steric requirements of the substituent in altering the properties of the molecule.

In part, this overemphasis of the polar factor is to be ascribed to the disrepute into which the classical concept of steric hindrance had fallen as a result of its indiscriminate use by early organic theorists. These theorists found in steric hindrance a convenient explanation of phenomena which they could not readily interpret in terms of existing theory. Since these phenomena were drawn largely from the complex, little understood field of reaction rates, it is not surprising that a number of the phenomena so explained have since found other interpretations. It is unfortunate, however, that such errors led to the wide-scale abandonment of the concept and to its consequent neglect in modern theory.

Several years ago the author and his students embarked upon a program of study of relatively simple equilibria, the dissociation of molecular addition compounds, in the hope that these studies would yield unambiguous evidence upon which the concepts of steric hindrance and steric strain[2] might be firmly founded. The results already obtained offer strong support for the idea that atoms or groups of atoms through their steric requirements can exert marked effects upon molecular properties.

For example, if only the polar factor of alkyl groups were considered, it would be predicted that the strength of aliphatic amines should increase regularly with the number of alkyl groups: $NH_3 < RNH_2 < R_2NH < R_3N$ (Curve A, Fig. 1). However, the order actually observed is $NH_3 < R_3N < RNH_2 < R_2NH$ (Curve B, Fig. 1). (This discrepancy is discussed below.) In the absence of pronounced steric effects, the relative stabilities of the addition compounds formed by these amines with any given trialkylboron should exhibit the same order. This is true because the relative "strength" of the base (1) and the relative "stability" of the addition compound (2) can both be correlated with the relative tendency of the nitrogen atom in the amines to share its free electron pair.

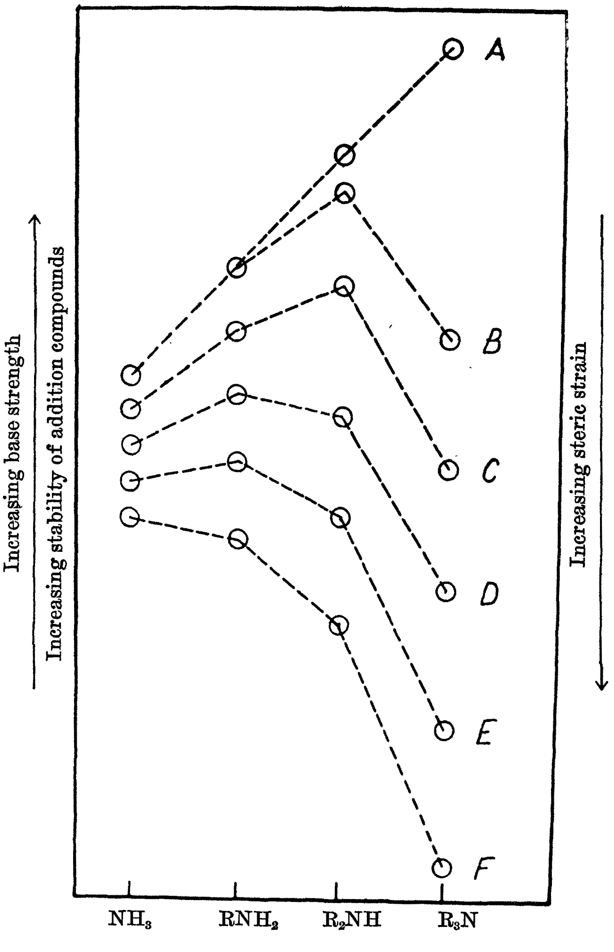

FIG. 1. Sequences shown by the aliphatic amines in comparisons of their base strengths and of the stabilities of their addition compounds with trialkylborons.

(1) $R_3N : H^+ \quad = \quad R_3N : \quad + \quad H^+$

(2) $R_3N : BR'_3 \quad = \quad R_3N : \quad + \quad BR'_3$

However, it has been possible to cause the observed order to vary from B to D, to E, and to F merely

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[2] The term "steric hindrance" is to be associated with a temporary condition in a reacting system; "steric strain," with an equilibrium condition in a relatively permanent system.

by increasing the size of the alkyl groups attached either to the nitrogen atom of the amine or to the boron atom of the other component of the addition compound (Fig. 1; Table 1) (*2*).

TABLE 1

SEQUENCES SHOWN BY AMINE SERIES WITH VARIOUS REFERENCE ACIDS

Amine series	Reference acid		
	H^+	$(CH_3)_3B$	$(t\text{-}C_4H_9)_3B$
Methyl	B	B	E
Ethyl	B	D	F
Isopropyl ...	B	E	
t-Butyl		F	

The relative tendency of these addition compounds to dissociate can be varied in a definite and predictable manner by varying the size and bulk of the alkyl substituents. It is therefore reasonable to conclude that the observed changes in the relative stabilities of these compounds must have a steric origin. More precisely, it is reasonable to attribute the increased dissociation to steric interference between the bulky alkyl groups attached to the nitrogen atom and those attached to the boron atom. Such interference would result in a strain at the "interface" between the two components, a strain which would tend to separate them. This "frontal" strain, in many respects similar to the classical concept of steric hindrance, has been termed F-strain to differentiate it from B-strain, which has no counterpart in classical theory (*3*).

B-strain was originally introduced to explain the anomalous weakness of tertiary amines (compare theoretical Curve A with observed Curve B, Fig. 1). It was suggested that, in such amines, the steric requirements of the three alkyl groups crowded about the small nitrogen atom are met by a spreading of the C-N-C bond angle from the 90° value predicted by quantum theory to a value somewhat greater than that of the tetrahedral angle. Such expansion of the bond angle is facilitated by the absence of a fourth group on the nitrogen atom. Addition of a proton (or other group) to the free electron pair tends to reduce the expanded angles to the tetrahedral value. This results in increased crowding of the three alkyl groups and the introduction of considerable strain into the molecule. This strain (called B-strain since it is localized at the "back" of the amine molecule) causes the amine to resist the addition of the proton (or other group) and leads to an apparent weakening of the strength of the base.

The hypothesis is strongly supported by observations on the behavior of phosphine and the methylphosphines. The greatly increased size of the central atom should result in the absence of B-strain. Experiment reveals that the base strength of these compounds increases regularly with the number of methyl groups, $PH_3 < CH_3PH_2 < (CH_3)_2PH < (CH_3)_3P$ (Curve A, Fig. 1) (*1*). The B-strain hypothesis offers a reasonable, simple explanation for this marked difference in the behavior of the phosphorus and nitrogen bases.

If three alkyl groups about a nitrogen atom bring about a condition of strain, it follows from the close similarity in the dimensions of the two atoms that three such groups about a carbon atom should also be a center of strain. This postulate offers a reasonable explanation of many hitherto unrelated peculiarities of branched-chain carbon compounds. A few of these may be briefly described.

(1) *Molecular rearrangements.* Alcohols with the structure R_2CHCH_2OH and R_3CCH_2OH exhibit a marked tendency to undergo rearrangement in reactions involving removal or replacement of the hydroxyl group (*6*). In such rearrangements either a hydrogen atom or an alkyl group attached to the tertiary or quaternary carbon atom migrates. The marked lability of such groups is easily explicable in terms of the strain postulated by the B-strain hypothesis at such carbon atoms.

(2) *Hydrolysis of alkyl halides.* Ingold, Hughes, and their co-workers have demonstrated conclusively that tertiary halides hydrolyze by a mechanism involving ionization of the halides as the rate-determining step (*4*). They have ascribed the greatly increased tendency of the tertiary halides to undergo such ionization to the cumulative inductive effect of the three alkyl groups attached to the carbon atom which holds the halogen. We wish to suggest that B-strain in the halide also facilitates the ionization, since such strain should be relieved by the expansion of the bond angles to 120° in the presumably planar carbonium ion.

$$R_3CCl \quad = \quad R_3C^+ \quad + \quad Cl^-$$

Indeed, a study of the effect of the size of the alkyl groups in such tertiary halides upon the rates of hydrolysis (recently completed at this university) has yielded results which would be exceedingly difficult to interpret without the aid of the B-strain concept.

(3) *Behavior of tertiary alcohols.* The unique properties of tertiary alcohols have never received an adequate explanation. According to the B-strain hypothesis, the strain resulting from the presence of the three alkyl groups furnishes a potent driving force to convert such alcohols to the relatively strain-free carbonium ions. Thus, reactions which involve carbonium-ion intermediates are greatly facilitated. Since the strain would also be relieved by the formation of the olefins, the marked tendency for such

compounds to undergo dehydration is also in accord with the hypothesis.

(4) *Selective dehydration of alcohols.* Dehydration of alcohols, such as $R_2CHCHOHCH_2R$, involving the possibility of loss of either an adjacent tertiary or an adjacent secondary hydrogen atom invariably proceeds by the first-mentioned path. Again, this is readily explicable in terms of the B-strain hypothesis.

Recent work has shown that the presence of two very bulky groups attached to a single atom may be the center of marked B-strain. The instability of such compounds as di-*t*-butylether and di-*t*-butylamine is ascribed to this cause. A quantitative estimate of the B-strain in such compounds has recently been made. Its magnitude, 5 to 7 kcal, is such as readily to account for the behavior of such substances.

It is believed that the B-strain hypothesis shows promise of being a fruitful unifying concept in organic chemistry. Experimental tests of the hypothesis are being prosecuted as vigorously as present conditions permit. It is hoped that these investigations will assist in drawing the attention of organic chemists to the desirability of including in their considerations both factors, polar and steric.

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The Detoxification by Acetylation of Soluble Antigens From *Shigella dysenteriae* (Shiga) and *E. typhosa*[1]

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The toxicity of available vaccines against typhoid and other gram-negative organisms has long been recognized as a serious defect, particularly under military conditions where the loss in personnel time due to vaccination reactions may be significant. Attempts to provide reasonable type-specific coverage against the more important dysentery organisms with polyvalent vaccines must also take into account the additive nature of the toxicities of the component organisms. The only solution at present is to reduce the amount of each component until the toxicity of the combination is within tolerable limits. Since the antigenic efficiency of a component is influenced by its concentration, it is obvious that additional injections must be made to reach a high level of protection, a procedure which apparently produces many administrative difficulties.

Numerous attempts have been made to detoxify either the whole organisms or selected antigenic fractions, but in spite of the application of a wide variety of reactions the loss in toxicity has almost invariably been accompanied by a corresponding decrease in antigenicity (*4, 6*). An exception may be noted for the action of ketene gas (*1*) on some gram-negative organisms, but this promising reaction does not seem to have been widely applied in practice.

In our studies on the development of a practical vaccine against *Shigella dysenteriae* (Shiga), we have favored the use of a soluble antigen—the somatic polysaccharide, or polysaccharide-protein complex (*6*). Although it was recognized that this might not be the only antigen responsible for protection, it was felt that elimination of less active components of the organisms might be advantageous, particularly if the material was to be incorporated into a polyvalent vaccine with the corresponding antigens of other members of the dysentery group. In searching for a method of detoxification we have noted the preparation by several workers of acetylated derivatives of bacterial polysaccharides (*3, 5*). Although quite complete chemical characterizations have been made, little or no data on the biological properties of the fractions are available, with the exception of the observation that acetylated antigens do not react well with antisera to the whole organisms.

We have therefore prepared a series of acetylated derivatives of the polysaccharide, or the polysaccharide-protein complex, of *Shigella dysenteriae* and of *E. typhosa* (Army strain 58) and have investigated their toxicity and antigenicity. The soluble toxic antigens were dissolved in a small amount of water, diluted with several volumes of pyridine, and allowed to react at room temperature with an excess of acetic anhydride. The general technique of Freeman (*3*) was followed, with the exception that samples were removed at shorter intervals, and the reactions stopped by pouring the aliquots into water. As acetylation proceeded, an increasing percentage of the antigens became insoluble in water.

In all cases even the water-soluble fraction isolated after the minimum time allowed for acetylation (1.5 hours) showed an appreciable decrease in toxicity over

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[1] Preliminary report. The work described in this paper was done with the assistance of Miss Claire B. Abrams and Mr. Ben A. Rubin, under a contract recommended by the Committee on Medical Research of the Office of Scientific Research and Development, and Yale University. The experiments were begun under a similar contract with Harvard University.