[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

Some Observations Concerning Steric Factors

BY MELVIN S. NEWMAN

In general it seems most fitting to discuss chemical reactivity in terms of polar and steric effects. At one time considerable attention was paid to steric factors but with the advent of modern electronic interpretations, there has been a tendency to discount steric and emphasize polar effects. More recently the realization of the importance of steric factors has stimulated renewed interest in this area.

In the most recent reviews[1,2,3] dealing with steric effects, the treatment of aliphatic series is quite unsatisfactory. Only in the case of the series, ethyl–propyl–isobutyl–neopentyl bromide, has the variation of rate been explained on almost purely steric grounds.[3] The recent publications of Brown and his co-workers[4] contribute greatly to our understanding of the effect of steric factors on the rates of reactions of aliphatic halides.

In the field of carbonyl addition reactions the general impression[1,2] is gained that branching of the chain on the carbon alpha to the carbonyl group is important. No great attention is paid to the difference between methyl and other alkyl groups. Furthermore, attention has not been drawn to those factors responsible for really great steric effects in contrast to those yielding only relatively small effects. In the discussion below an empirical rule will be made with the aid of which it should be possible to estimate fairly easily the degree of hindrance to be expected with doubly bonded functions.

As a basis for discussion of steric effects in reactions involving addition to the unsaturated function the acid-catalyzed esterification of carboxylic acids with methanol has been chosen because of the fairly large number of acids which have been carefully studied[5] (see Table I). Although there is little change in going from acetic to propionic acid there is a significant drop in the rate of esterification in going from propionic to butyric acid. Higher *n*-alkanoic acids esterify at the same rate as butyric. Since it appears unlikely that the structural changes involved can have any significant effect on the carboxyl group by altered inductive or hyperconjugative effects, a steric factor is probable. Smith[6] pointed out that in butyric acid a coiled structure, in which the hydrogens on the terminal methyl group come close to the oxygen of the carbonyl group, is possible and is probably responsible for the rate decrease. In this orientation approach of the alcohol molecule is sterically hindered in one direction. The fact that higher normal homologs esterify at the same rate as butyric acid is consistent with this explanation.[5b] It is also apparent that in going from propionic to butyric acid a significant change has been made.

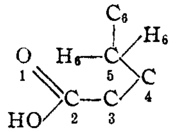

Fig. 1.—Coiled structure for acids, numbering shown.

If one numbers the atoms in an acid consecutively starting with the carbonyl oxygen as one, it is seen that the feature present in butyric acid and higher homologs that is absent in the lower members is the presence of atoms in the six position (see Fig. 1). It is then logical to propose the following empirical rule: *In reactions involving addition to an unsaturated function, the greater number of atoms in the six position the greater will be the steric effect.* For convenience this will be referred to as the *rule of six* and the number of atoms in the *six position* will be called the *six-number*. Of course, it must be kept in mind that branching on the alpha carbon is a contributory factor. However, really large steric effects are observed only in those acids containing nine or more atoms in the six position (see Table I).[7]

For example, the tri-α-substituted trimethylacetic acid (six-number, 0) esterifies at a rate approximately one-thirtieth that of acetic acid whereas the rate of the di-α-substituted diethylacetic acid (six-number, 6) is less than one-hundredth that of acetic. The rate for diisopropylacetic acid (six-number, 12) has not been measured but, from its reported resistance to esterification, must be extremely low.[8]

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[1] G. Vavon in V. Grignard "Trafte de Chimie Organique," Masson et Cie., Paris, France, 1936, Vol. II, part 2, p. 863 ff.

[2] A. E. Remick, "Electronic Interpretations of Ogranic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, Chap. IX.

[3] E. D. Hughes, "Quarterly Reviews," p. 107 (1948).

[4] H. C. Brown and N. R. Eldred, THIS JOURNAL, **71**, 445 (1949); H. C. Brown and R. S. Fletcher, *ibid.*, **71**, 1845 (1949); **72**, 1223 (1950).

[5] See page 877 and ff., ref. 1. In addition see (a) H. Smith and co-workers, THIS JOURNAL, **61**, 254 (1939); (b) **61**, 1176 (1939); (c) **62**, 1136 (1940); (d) **62**, 2733 (1940); (e) **63**, 605 (1941); (f) **66**, 1494 (1944).

[6] H. A. Smith and J. P. McReynolds, *ibid.*, **61**, 1963 (1939) give an excellent argument in favor of a coiled structure for effective steric hindrance. See also Dippy, *J. Chem. Soc.* 1222 (1938), for a similar but less convincing explanation with regard to the abnormally high dissociation constant of butyric acid.

[7] Smith and Burn, ref. 5f, proposed a system for estimating steric hindrance in aliphatic acids which involves the number of substituents in the α- and β-positions. This seems to be the first instance where the importance of substitution on the β-carbon is stressed.

[8] J. von Braun and F. Fischer, *Ber.*, **66**, 101 (1933).

TABLE I

SIX NUMBERS OF ACIDS IN RELATION TO RATES OF ACID-CATALYZED ESTERIFICATION

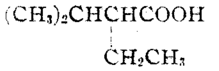
Acid	Atoms in 5 pos.			Atoms in 6 pos.			Ratio K_{CH_3COOH}/K_{RCOOH}	
	C	H	Total	C	H	Total	$MeOH_{25°}$ [a]	$EtOH_{25°}$ [b]
Acetic	0	0	0	0	0	0	1	1
Propionic	0	3	3	0	0	0	1.03	1.45
Butyric	1	2	3	0	3	3	2.04	2.95
Higher *n*-alkanoic	1	2	3	1	2	3	2.02 ± 0.04	2.92 ± 0.06
Isobutylacetic	1	2	3	2	1	3	2.00	3.22
Isobutyric	0	6	6	0	0	0	3.04	5.11
Methylethylacetic	1	5	6	0	3	3	10.8	21.0
Methylpropylacetic	1	5	6	1	2	3		20.3
Methylbutylacetic	1	5	6	1	2	3		23.3
Methylisobutylacetic	1	5	6	2	1	3		25.1
Isopropylacetic	2	1	3	0	6	6	9.11	15.4
s-Butylacetic	2	1	3	1	5	6	9.45	
Trimethylacetic	0	9	9	0	0	0	30.6	
Methylisopropylacetic	2	4	6	0	6	6		72.4
Diethylacetic	2	4	6	0	6	6	118	257
Dipropylacetic	2	4	6	2	4	6	139	279
Dibutylacetic	2	4	6	2	4	6	153	
Diisobutylacetic	2	4	6	4	2	6	295	
Diisopropylacetic	4	2	6	0	12	12	[c]	
Cycloheptanecarboxylic[d]								15.91
Cyclohexanecarboxylic[d]							5.02	9.83
Cyclopentanecarboxylic[d]								4.06
Cyclobutanecarboxylic[d]								1.46
Cyclopropanecarboxylic[d]								24.9

[a] Rates reported by H. A. Smith, ref. 5f. [b] Rates reported by J. J. Sudborough, ref. 9. [c] Difficulty of esterification reported by J. von Braun, ref. 8. [d] No attempt with 5 and 6 numbers because of rings.

There is some interest in speculating upon the steric effect of various types of branching on the rate. For example, triethylacetic acid (I), ethylisopropylacetic acid (II) and *t*-butylacetic acid (III) each represents an acid having a six-number of nine. The six-numbers being equal it is likely

$(CH_3CH_2)_3CCOOH$

I



$(CH_3)_2CH\underset{CH_2CH_3}{C}HCOOH$

II

$(CH_3)_3CCH_2COOH$

III

that the greater the branching at the α-carbon the lower the rate of reaction. That this will probably prove to be generally true is indicated by the fact that methylisopropylacetic acid (six-number, 6) esterifies more than three times as rapidly as diethylacetic acid (six-number, 6) with ethanol.[9] In this connection it will be especially interesting to compare the relative rates for trimethylacetic acid (a tri-α-substituted acid of six-number, zero) and *t*-butylacetic acid (a monosubstituted acetic acid of six-number, 9).

A number of other refinements to the rule of six will undoubtedly be desirable when suitable experiments have been carried out. For example, it is already obvious that ring formation involving two groups having atoms in the six position decreases the steric effect[5d] (note the rates for diethylacetic acid and cyclohexanecarboxylic acid). Furthermore, the size of the ring involved may also exert a small steric effect. For example, the relative rates of esterification of cycloalkanecarboxylic acids with ethanol (n = number of atoms in cycle) are as follows[9]: n = 7, 0.0499; n = 6, 0.0812; n = 5, 0.196; n = 4, 0.544; n = 3, 0.032. With the exception of cyclopropanecarboxylic acid, the rate is seen to fall with increasing size of ring, an effect which is undoubtedly steric. Inasmuch as the cyclopropyl ring has properties (*i. e.*, rearrangement reactions such as in the *i*-steroids, absorption spectral phenomena) approaching those of the vinyl group, it is of interest to point out that α,β-unsaturated acids esterify considerably more slowly than their saturated analogs.[9] An abnormally slow rate has also been observed in the reaction of methyl cyclopropyl ketone with perbenzoic acid as compared to other cycloalkyl methyl ketones.[10]

It should also be of interest to see what influence the kind of atom in the six position will have. Inspection of Table I reveals that a small decrease in rate may occur when a hydrogen in the six position is replaced by a carbon (*e. g.*, compare isopropylacetic with *s*-butylacetic, and dibutylacetic with diisobutylacetic). This change may cause an important increase in steric hindrance if multiplied. Information as to the effect of atoms other than carbon is lacking.

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(9) B. V. Bhide and J. J. Sudborough, *J. Ind. Inst. Sci.*, **8**, 89 (1925); *Chem. Zentr.*, **97**, I, 80 (1926).

(10) Communication from Dr. S. L. Friess, University of Rochester.

In considering steric factors in a reaction it is well to emphasize the point that the over-all effects are a result of all reagents and participants in the reaction. Specifically, when considering the effect of structure on the rate of esterification of an acid, as above, the function of alcohol was ignored. However, the structure of the alcohol undoubtedly plays a large, if less well understood, part. The rate constants of Table I involve methanol and ethanol and the steric hindrance factor becomes large when a six-number of nine or twelve is reached. However, with an alcohol of larger spatial requirements large steric effects might appear with less complicated acids. Note that the ratio of rates shown in Table I is greater in ethanol than in methanol.

Applications of the Rule of Six

The importance of variation of the alcoholic component of an ester on the rate of alkaline hydrolysis has not previously been stressed. It is possible that variations of this type may have larger effects on rates of reaction at the carbonyl than similar changes in the acid part. For instance the ratio of the rate of alkaline hydrolysis in 85% alcohol at 25° of ethyl acetate (six-number, 3) to ethyl trimethylacetate (six-number, 3) is about 260,[11] whereas the ratio of the rate of alkaline hydrolysis in 56 weight per cent. aqueous acetone at 25° of methyl benzoate (six-number, 0) to *t*-butyl benzoate (six-number, 9) is about 680.[12] The fact that *t*-amyl benzoate saponifies even more slowly (ratio 1840) indicates that the limit of steric hindrance may not have been reached. Similarly, the ratio of the rates for ethyl acetate and ethyl isobutyrate is 8.5[11] whereas the ratio of the rates for methyl benzoate and isopropyl benzoate is 20.[12] In each of the above pair of compounds it is to be noted that the replacement of a number of hydrogens in an ester by methyl groups causes a decrease in rate of saponification. However, changes in the alkyl component seem to be more effective than changes at the alpha position in the acid component. Of course, in the above examples, it is probable that steric factors are not alone responsible for the observed effects.

A realization of the large effects on rate of alkaline saponification that change in the alcoholic component of an ester can make may have important synthetic applications. For example, in the attempted condensation of Grignard reagents with the ketonic carbonyl of a ketoester, it should prove effective to use a rather large alkyl group in the ester. In recent studies[13] it has been shown that the yield of glycidic ester in the reaction of methyl isobutyl ketone with alkyl chloroacetates using sodium hydride increases from 50 to 59 to 64% in going from methyl to ethyl to isopropyl. In one experiment which we were unable to duplicate *t*-butyl chloroacetate gave a 68% yield after a very long induction period. We explain this trend by assuming that the side reaction which detracts from the yield involves condensation of the enolate of the alkyl chloroacetate with another molecule of chloroester. As the alkyl component of the ester increases in size the steric hindrance involved in this side reaction increases more rapidly than the steric hindrance involved in the condensation with ketone to form glycidic ester. A similar explanation may be given for the fact that di-*t*-butyl succinate is superior to methyl or ethyl succinates in the Stobbe condensation.[14]

In the aromatic series the rule of six is insufficient to explain the extreme unreactivity of di-orthosubstituted compounds, such as mesitoic acid (effective[15] six-number 6). It is true that in such an acid the coiled structure is always present because of the geometry of the molecule whereas in aliphatic acids, the chains are free to oscillate. The situation appears to have been adequately explained by Kadesch.[16] He pointed out that the inability of acetomesitylene to react with typical carbonyl reagents is explained if one assumes that *the attacking reagent must approach the carbonyl group from a direction perpendicular to the plane defined by the carbonyl group and the two contiguous atoms.* As long as this plane is essentially coplanar with the ring there is little steric hindrance since the reagent has an unhindered avenue of approach perpendicular to the plane of the benzene ring. However, if the ortho groups are of sufficient size to prevent free rotation about the bond connecting the function to the ring, then the plane containing this function must lie at an angle to the ring. In this orientation a perpendicular approach to this function is hindered by the ortho groups. It should be noted that one sufficiently large ortho group is able to prevent coplanarity of a function with the ring. However, reaction with such a monosubstituted derivative is still possible by a perpendicular approach from the side opposite to the ortho group. This accounts for the usually observed decrease in rate of reaction of mono-orthosubstituted aromatic compounds.

In considering the steric factors in diorthosubstituted carbonyl-containing compounds it seems important to point out the great increase in steric hindrance produced when the hydrogen atom attached to the carbonyl group in 2,4,6-

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(11) D. P. Evans, J. J. Gordon and H. B. Watson, *J. Chem. Soc.*, 1439 (1938). The rate constant at 25° for ethyl acetate was taken as 6.8×10^{-3} as calculated from Smith's data, THIS JOURNAL, **61**, 1172 (1939).

(12) E. Tommila, *Ann. Acad. Sci. Fennicae*, Ser. A, **59**, No. 3, 3–34 (1942); *C. A.*, **38**, 6171 (1944).

(13) Unpublished observations of Walter Bauer, Ohio State University.

(14) G. H. Daub and W. S. Johnson, THIS JOURNAL, **72**, 501 (1950).

(15) By "effective" is meant the number of atoms in the six position capable of yielding a coiled structure. The effectiveness of atoms in the six position in rings of various sizes was discussed earlier in this article (esterification of cycloalkane carboxylic acids).

(16) R. G. Kadesch, THIS JOURNAL, **66**, 1207 (1944); see also W. G. Brown and S. Fried, *ibid.*, **65**, 1841 (1943).

trimethylbenzaldehyde is replaced by a larger group or atom. This aldehyde, and others containing two ortho methyl groups, gives typical aldehyde reactions albeit at reduced rates,[17] whereas the corresponding ketones and acid derivatives are characteristically unreactive. Thus the aldehyde group must be just on the border line between groups capable of free rotation and those not. However, as soon as a larger group, such as methyl or chlorine, is substituted for the aldehydic hydrogen, the steric hindrance to free rotation is greatly increased so that a coplanar orientation, favorable for a perpendicular approach, is no longer possible under moderate reaction conditions. In this connection it is interesting to note that mesitoyl chloride, although extremely reactive to alcoholysis,[18] does not react with diazomethane.[19] The explanation is that the former reaction undoubtedly involves ionization to yield an oxocarbonium ion,[20] $(CH_3)_3C_6H_2C^+{=}O$ which would not be sterically hindered according to the above arguments, whereas the latter reaction involves addition to the carbonyl group.

The author has applied the rule of six as above outlined and modified to a number of experimental observations in the literature and found that many seemingly anomalous facts are readily explained thereby. The utility of this rule seems to be undeniable but it is beyond the scope of this article to point out further examples or to go into further detail at present.[21]

Finally, it should be pointed out that the application of the rule of six and of the concept of the perpendicular approach is not necessarily limited to carbonyl-containing functions but may be applied to all doubly-bonded functions. For example, the resistance of *asym*-dineopentylethylene (six-number 18) to oxidation[22] is undoubtedly due to steric hindrance. In the steroid field, the lesser reactivity of the double bond in between carbons 22 and 23 of stigmasterol as compared to the double bond between carbons 5 and 6 may be explained by the widely differing six-numbers.[23]

Summary

An empirical rule for the estimation of steric hindrance to addition reactions at a doubly-bonded aliphatic function is enunciated. If one numbers the atoms in branched compounds starting with the atom of the doubly-bonded function most distant from the chain then *the greater the number of atoms in the six position the greater the steric hindrance to addition*. Applications of this rule to many experimental facts are reviewed. Refinements of the rule are discussed.

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(17) L. I. Smith and J. Nichols, *J. Org. Chem.*, **6**, 489 (1941); Gattermann, *Ann.*, **347**, 374 (1906); however see G. Lock and E. Bayer, *Ber.*, **72**, 1064 (1939).

(18) J. F. Norris and H. H. Young, Jr., THIS JOURNAL, **57**, 1420 (1935).

(19) W. E. Bachmann and W. S. Struve in "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, Vol. I, ref. 18, p. 43.

(20) M. S. Newman and H. Gildenhorn, THIS JOURNAL, **70**, 317 (1948).

(21) It has been tacitly assumed, but not specifically stated, that all of the counted atoms involved in a chain are carbon or hydrogen. However, many other possibilities exist. In considering other atoms polar effects may overshadow steric effects.

(22) P. D. Bartlett, G. L. Fraser and R. B. Woodward, *ibid.*, **63**, 495 (1941).

(23) E. Fernholz, *Ann.*, **507**, 128 (1933).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Fluoranthene Derivatives. II. The Reaction of Acenaphthylene with Butadiene Derivatives[1]

BY MILTON C. KLOETZEL AND HOLLY E. MERTEL

Substitution reactions of fluoranthene (VI) result in formation of mixtures of 3- and 8-fluoranthyl derivatives, from which it is usually difficult to isolate either isomer in good yield.[2,3,4] In order to circumvent this difficulty, or to obtain fluoranthene derivatives containing substituents in positions other than 3 and 8, several methods have been developed for the synthesis of the fluoranthene nucleus with a group attached in the desired position.[5-11] For example, two highly-arylated fluoranthene derivatives were reported[11] from the reaction of acenaphthylene with complex cyclopentadienones at 250–300°.

We have now found that acenaphthylene reacts with simple butadiene derivatives, at 145–175°, to yield tetrahydrofluoranthenes (I–V) which can be dehydrogenated readily to the corresponding aromatic fluoranthene derivatives (VI–X).

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(1) Abstracted from the dissertation submitted by Holly E. Mertel to the Graduate School of the University of Southern California in partial fulfillment of the requirements for the degree of Doctor of Philosophy. For the previous paper in this series, see Kloetzel and Chubb, THIS JOURNAL, **72**, 150 (1950).

(2) von Braun and Manz, *Ann.*, **488**, 111 (1931).

(3) von Braun, Manz and Kratz, *ibid.*, **496**, 170 (1932).

(4) Campbell and Easton, *J. Chem. Soc.*, 340 (1949).

(5) Dilthey and Henkels, *J. prakt. Chem.*, **149**, 85 (1937).

(6) France, Tucker and Forrest, *J. Chem. Soc.*, 7 (1945).

(7) Forrest and Tucker, *ibid.*, 1137 (1948).

(8) Bergmann and Orchin, THIS JOURNAL, **71**, 1917 (1949).

(9) Campbell and Wang, *J. Chem. Soc.*, 1513 (1949).

(10) Campbell and Gow, *ibid.*, 1555 (1949).

(11) Dilthey, Henkels and Schaefer, *Ber.*, **71**, 974 (1938).