Chemical Effects of Steric Strains.

A CENTENARY LECTURE DELIVERED AT BURLINGTON HOUSE ON JUNE 2ND, 1955.

By HERBERT C. BROWN.

STERIC effects as a factor in chemical behaviour appear to have originated with Kehrmann's observations on the chemical inertness of quinones containing *ortho*-substituents.[1a] Investigation of similar phenomena in the esterification of hindered aromatic acids was later pursued with considerable success by Victor Meyer and numerous contemporary workers.[1b,c]

With the years, evidence accumulated that steric effects were of widespread importance in chemical behaviour. Thus Conant and his co-workers noted that the tendency of the dialkyltetraphenylethanes (I) and the dialkyldixanthyls (II) to dissociate into free radicals increased with the increasing bulk of the alkyl groups ($Me < Et < Pr^i < Bu^t$).[2a,b] Likewise the discovery of diphenyl isomerism opened up an entire area of chemistry resulting from steric forces.[2c,d] Certain peculiarities in *ortho*-substitution led Holleman to suggest that steric effects were an important factor in aromatic substitution,[2e] and Le Fèvre later utilized this explanation to account for the observed directive effects in the nitration and sulphonation of *p*-cymene (III):[2f]

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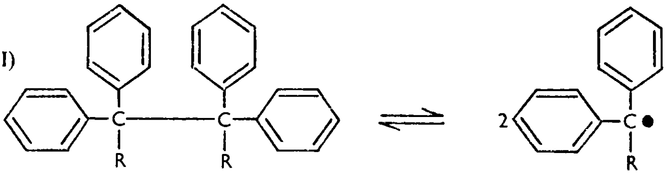

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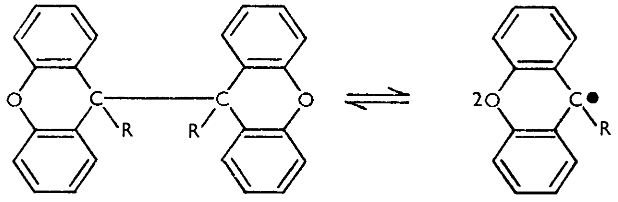

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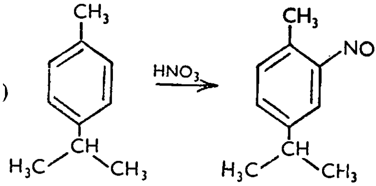

Moreover, Polanyi utilized the concept to account for the decreasing rates of the reactions of iodide ion with methyl, ethyl, and *iso*propyl chloride.[2g,h]

The immense success achieved by the electronic theory in the 1930's led to the attempt to account for all chemical behaviour in terms of electronic effects. For example, Wheland suggested that the increased dissociation of the dialkyltetraphenylethanes (I) and the dialkyldixanthyls (II) with increasing bulk of the alkyl groups might be due to the increased possibility for resonance in which the alkyl groups participate.[3a] Likewise it was suggested that the directive effects in *p*-cymene were due, not to the relative steric requirements of the methyl and

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[1] (*a*) Kehrmann, *J. prakt. Chem.*, 1889, **40**, 257; (*b*) Meyer, *Ber.*, 1894, **27**, 510; (*c*) Cohen, "Organic Chemistry," Edward Arnold and Co., London, 1928, 5th edn., Vol. I, Chapt. 5.

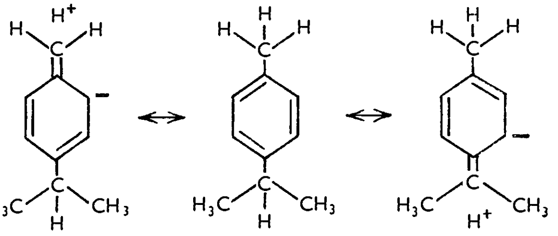
[2] (*a*) Conant and Bigelow, *J. Amer. Chem. Soc.*, 1928, **50**, 2041; (*b*) Conant, Small, and Sloan, *ibid.*, 1926, **48**, 1743; (*c*) Turner and Le Fèvre, *Chem. and Ind.*, 1926, **45**, 831; (*d*) Adams and Yuan, *Chem. Rev.*, 1933, **12**, 261; (*e*) Holleman, *ibid.*, 1924, **1**, 187; (*f*) Le Fèvre, *J.*, 1933, 977, 980; 1934, 1501; (*g*) Meer and Polanyi, *Z. phys. Chem.*, 1932, **19**, *B*, 164; (*h*) Evans, *Trans. Faraday Soc.*, 1946, **42**, 719.

[3] (*a*) Wheland, *J. Chem. Phys.*, 1934, **2**, 474; (*b*) Baker and Nathan, *J.*, 1935, 1844; (*c*) Ingold, *Chem. Rev.*, 1934, **15**, 225; (*d*) Hinshelwood, Laidler, and Timm, *J.*, 1938, 848.

*iso*propyl groups, but instead to their relative ability to participate in hyperconjugation (IV).[3b] Similarly, the decreased reactivity toward bimolecular displacement reactions in the series, MeX, EtX, Pr^iX, and Bu^tX, was attributed to the polar effect of the alkyl substituents.[3c,d]

As a result of these developments there had arisen by 1940 a widespread scepticism as to the importance of steric effects in chemical behaviour. The excellent book published in 1940 by Professor Hammett played a major rôle in the development of physical organic chemistry in the United States. Yet steric effects are conspicuously absent from its discussions.[4a] Similarly, in the book by Professor Remick, published in 1944, there appears no discussion of the rôle of steric effects in organic theory.[4b] Perhaps the prevalent view is best expressed in the words of a textbook published at this time : "Steric hindrance . . . has become the last refuge of the puzzled organic chemist."[4c] It was in this atmosphere that our programme for investigating the rôle of steric effects in chemical behaviour was undertaken.

(IV)



(3 forms) (1 form)

It was apparent that if steric effects were again to receive serious consideration as a major factor in chemical behaviour there would be required a technique of study which could provide quantitative data on the magnitudes of the steric effects in the systems under investigation. The dissociation of molecular addition compounds offered promise of providing such a tool and their study was therefore undertaken.

The original studies utilized essentially qualitative competition experiments.[5] Their success encouraged the development of quantitative methods of determining thermodynamic data for the dissociation of addition compounds. The main reliance has been on the measurement of the dissociation constants for the gaseous systems over a range of temperatures.[6] More recently calorimetric procedures have been utilized for addition compounds which cannot be handled as gases.[7] The results of these studies are summarized in Tables 1 and 2.

Space will not permit a review of the various studies which were made in an effort to test the postulate that steric effects were a major factor in chemical behaviour. We shall be content therefore to outline two studies which will serve to illustrate the utility of the approach based on molecular addition compounds.

The heat of dissociation of ammonia–trimethylboron is 13·75 kcal./mole. This rises to 17·64 for methylamine- and to 18·0 for ethylamine–trimethylboron. These increases are readily attributed to the inductive effects of the methyl and the ethyl groups. The heat of dissociation of trimethylamine–trimethylboron is 17·62, not significantly different from that of the methylamine derivative. However, triethylamine–trimethylboron is a highly unstable substance with a heat of dissociation in the neighbourhood of 10 kcal./mole. How can we account for the observation that one ethyl group has about the same effect as one methyl group, that three methyl groups are not significantly different than one methyl group, but that three ethyl groups bring about an enormous decrease in the stability of the addition compound ?

A possible explanation is that the steric requirements of three ethyl groups are far larger than those of three methyl groups and therefore result in much larger steric strains in the addition compound. Indeed, an examination of the molecular models suggests that it is possible

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[4] (*a*) Hammett, " Physical Organic Chemistry," McGraw-Hill Book Co., New York, N.Y., 1940; (*b*) Remick, " Electronic Interpretation of Organic Chemistry," John Wiley and Sons, Inc., New York, N.Y., 1944; (*c*) Ray, " Organic Chemistry," J. B. Lippincott Co., New York, N.Y., 1941, p. 522.

[5] Qualitative studies of steric strains : Brown, Schlesinger, and Cardon, *J. Amer. Chem. Soc.*, 1942, **64**, 325; Brown, *ibid.*, 1945, **67**, 374, 378, 503, 1452; Brown and Pearsall, *ibid.*, p. 1765; Brown and Johannesen, *ibid.*, 1950, **72**, 2934; Brown and Sujishi, *ibid.*, 1948, **70**, 2793.

[6] Gaseous dissociation techniques : (*a*) Brown, Taylor, and Gerstein, *ibid.*, 1944, **66**, 431; (*b*) Brown and Gerstein, *ibid.*, 1950, **72**, 2923.

[7] Calorimetric techniques : (*a*) Brown and Horowitz, *ibid.*, 1955, **77**, 1730; (*b*) Brown and Gintis, *ibid.*, in the press.

TABLE 1. *Thermodynamic data for the dissociation of molecular addition compounds in the gaseous phase.*

Compound	K_{100}	ΔF°_{100}	ΔH	ΔS
Ammonia–trimethylboron [8a]	4·6	−1134	13·75	39·9
Methylamine–trimethylboron [8a]	0·0350	2472	17·64	40·6
Dimethylamine–trimethylboron [8a]	0·0214	2885	19·26	43·6
Trimethylamine–trimethylboron [8a]	0·472	557	17·62	45·7
Ethylamine–trimethylboron [8b]	0·705	1965	18·00	43·0
Diethylamine–trimethylboron [8b]	1·22	− 147	16·31	44·1
Triethylamine–trimethylboron [8b]	Unstable	—	~10	—
Methylamine–trimethylboron [8a]	0·0350	2472	17·64	40·6
Ethylamine–trimethylboron [8b]	0·0705	1965	18·00	43·0
n-Propylamine–trimethylboron [8c]	0·0598	2088	18·14	43·0
n-Butylamine–trimethylboron [8c]	0·0470	2266	18·41	43·2
n-Pentylamine–trimethylboron [8c]	0·0415	2359	18·71	43·9
n-Hexylamine–trimethylboron [8c]	0·0390	2404	18·53	43·2
Methylamine–trimethylboron [8a]	0·0350	2472	17·64	40·6
Ethylamine–trimethylboron [8b]	0·0705	1965	18·00	43·0
*iso*Propylamine–trimethylboron [8d]	0·368	740	17·42	44·7
sec.-Butylamine–trimethylboron [8d]	0·373	732	17·26	44·3
tert.-Butylamine–trimethylboron [8d]	9·46	−1665	12·99	39·3
Triethylamine–trimethylboron [8b]	Unstable	—	~10	—
Quinuclidine–trimethylboron [8e]	0·0196	2916	19·94	45·6
Pyridine–trimethylboron [8f]	0·301	890	17·00	43·2
2-Picoline–trimethylboron [8f]	Unstable	—	~10	—
3-Picoline–trimethylboron [8f]	0·138	1468	17·81	43·9
4-Picoline–trimethylboron [8f]	0·105	1671	(19·40)	(47·5)
Dimethylamine–trimethylboron [8a]	0·0214	2885	19·26	43·6
Ethyleneimine–trimethylboron [8g]	0·0284	2640	17·59	40·1
Trimethyleneimine–trimethylboron [8g]	0·000332	5960	22·48	44·3
Pyrrolidine–trimethylboron [8g]	0·00350	4190	20·43	43·5
Piperidine–trimethylboron [8g]	0·0210	2864	19·65	45·0
Methylphosphine–trimethylboron [8h]	Too highly dissociated to be measured			
Dimethylphosphine–trimethylboron [8h]	9·8	−1690	11·41	35·1
Trimethylphosphine–trimethylboron [8h]	0·128	1525	16·47	40·0
Methylphosphine–boron trifluoride [8i]	Too highly dissociated to be measured			
Dimethylphosphine–boron trifluoride [8i]	10·5	−1740	14·7	44·1
Trimethylphosphine–boron trifluoride [8i]	0·0669	1986	18·9	45·3

TABLE 2. *Calorimetric heats of reaction of pyridine bases with reference acids.*

		Heats of reaction, $-\Delta H$ (kcal./mole) [a]			
Compound	pK_a [12d]	$CH_3{\cdot}SO_3H$ [12e]	$\frac{1}{2}(BH_3)_2$ [12i]	BF_3 [12f]	BMe_3 [12h]
Pyridine	5·17	17·1	17·9	25·0	15·3
2-Picoline	5·97	18·3	17·2	23·3	9·95
2-Ethylpyridine	5·97	18·2	16·9	22·7	9·0
2-*iso*Propylpyridine	5·83	18·1	16·7	21·7	7·7
2-*tert.*-Butylpyridine	5·76	18·0	12·1	14·8	<0
3-Picoline	5·68	17·8	18·2	25·3	15·6
3-Ethylpyridine	5·70	18·1	—	25·2	—
3-*iso*Propylpyridine	5·72	18·0	—	25·3	—
3-*tert.*-Butylpyridine	5·82	18·2	—	25·6	—
4-Picoline	6·02	18·4	18·5	25·5	15·9
4-Ethylpyridine	6·02	18·3	—	25·3	—
4-*iso*Propylpyridine	6·02	18·4	—	25·4	—
4-*tert.*-Butylpyridine	5·99	18·3	—	25·3	—
2 : 6-Lutidine	6·75	19·5	16·3	17·5	<0

[a] At 25° in nitrobenzene solution : Base (soln.) + Acid (soln.) = Product (soln.).

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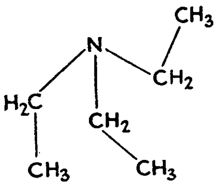
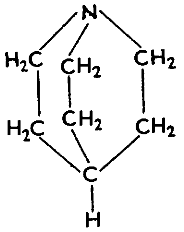
[8] Dissociation data for gaseous addition compounds : (*a*) Brown, Bartholomay, jun., and Taylor, *J. Amer. Chem. Soc.*, 1944, **66**, 435; (*b*) Brown and Taylor, *ibid.*, 1947, **69**, 1332; (*c*) Brown, Taylor, and Sujishi, *ibid.*, 1951, **73**, 2464; (*d*) Brown and Barbaras, *ibid.*, 1953, **75**, 6; (*e*) Brown and Sujishi, *ibid.*, 1948, **70**, 2878; (*f*) Brown and Barbaras, *ibid.*, 1947, **69**, 1137; (*g*) Brown and Gerstein, *ibid.*, 1950, **72**, 2926; (*h*) Sujishi, Thesis, Purdue, 1949; (*i*) Fletcher, Thesis, Purdue, 1952.

to rotate only two of the three ethyl groups out of the path of the trimethylboron molecule—the third must project in such a way as to interfere with the adding molecule (V).



(V)

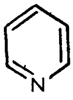
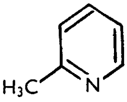
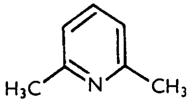


(VI)

To test this explanation quinuclidine (VI) was synthesised and tested. In this molecule the third ethyl group of triethylamine has been rotated to the back of the amine and effectively held there as part of the cage structure. Quinuclidine forms an exceedingly stable addition compound with trimethylboron. The heat of dissociation, 20·0 kcal./mole, is the highest observed for any tertiary amine (Table 1). It does not appear possible to account for the enormous difference between quinuclidine and triethylamine in terms of polar effects, whereas the steric interpretation provides a simple, reasonable explanation for the observed phenomena.

As a second illustration of this approach, consider the interaction of the pyridine bases with various reference acids. The introduction of a methyl group in the 3-position of pyridine results in an increase of the pK_a value from 5·17 for pyridine to 5·68 for 3-picoline. This increase is attributed to the inductive effect of the methyl group. 3-Picoline likewise exhibits a consistent increase over pyridine in its heat of reaction with methanesuphonic acid, diborane, boron trifluoride, and trimethylboron, all in nitrobenzene solution (Table 2).

The effects of the methyl group in the 2-position do not exhibit the same consistency. The pK_a value and the heats of reaction with methanesulphonic acid show a regular increment with one and then two methyl groups in the series, pyridine, 2-picoline, 2 : 6-lutidine, suggesting that we are observing the polar effects of the methyl groups uncomplicated by their steric requirements. However, with borine, boron trifluoride, and trimethylboron, the heats of reaction exhibit a decrease rather than the expected increase. Moreover, the discrepancy increases quite sharply with the increasing steric requirements of the reference acid.

			
pK_a	5·17	5·97	6·75
$-\Delta H$, Me·SO$_3$H	17·1	18·3	19·5
$-\Delta H$, $\frac{1}{2}$(BH$_3$)$_2$	17·9	17·2	16·3
$-\Delta H$, BF$_3$	25·0	23·3	17·5
$-\Delta H$, BMe$_3$	15·3	9·95	<0

The phenomenon is represented graphically in Fig. 1. It does not appear possible to account for these results in terms of any polar effects of the different reference acids. However, a simple explanation is afforded in terms of the steric requirements of the acids. In the case of the proton in water (pK_a) and methanesulphonic acid, the steric requirements are so small that a regular increase in base strength results from the presence of one and two methyl groups in the pyridine base. Borine is sufficiently large to cause steric interaction with the methyl groups in the 2-position. The resulting strains cause a small decrease in the heat of reaction of diborane with 2-picoline and a larger decrease in the case of 2 : 6-lutidine. With the increasing steric requirements of boron trifluoride and trimethylboron, the strains become much larger, and the observed heats of reaction drop sharply below those to be expected. Finally, trimethylboron fails to add to 2 : 6-lutidine in spite of the fact that it is a stronger base than pyridine itself.

It was of interest to synthesize a number of pyridine bases with bulky alkyl substituents in the 2- and the 6-position in order to ascertain whether steric strain involving addition of a proton could be realised. The final member of this group, 2 : 6-di-*tert*.-butylpyridine, possesses highly interesting and unusual properties. It reacts with hydrogen chloride, but not with boron trifluoride, thus providing a simple method of distinguishing between protonic and Lewis acids. The base fails to react with methyl iodide. On the other hand, in contrast to less sterically hindered pyridine bases, it reacts readily with sulphur trioxide (at $-10°$ in liquid sulphur dioxide) to form a nuclear-substituted sulphonic acid, presumably the 4-derivative. Apparently, with addition to the nitrogen atom effectively blocked by the two *tert.*-butyl groups, the electrophilic reagent readily attacks the heterocyclic nucleus.[9a]

The pK_a values of 2 : 6-di*iso*propyl- and 2-*tert.*-butyl-6-*iso*propyl-pyridine are perfectly regular and agree with values calculated from those of the simpler derivatives. However, 2 : 6-di-*tert.*-butylpyridine is 1·4 pK_a units weaker than the calculated value (Fig. 2). This result suggests that the steric requirements of the lone pair on the nitrogen atom must be less than those of the proton with the bonding electron pair.

FIG. 1. *Relative strengths of pyridine, 2-picoline, and 2 : 6-lutidine as a function of the steric requirements of the reference acid.*

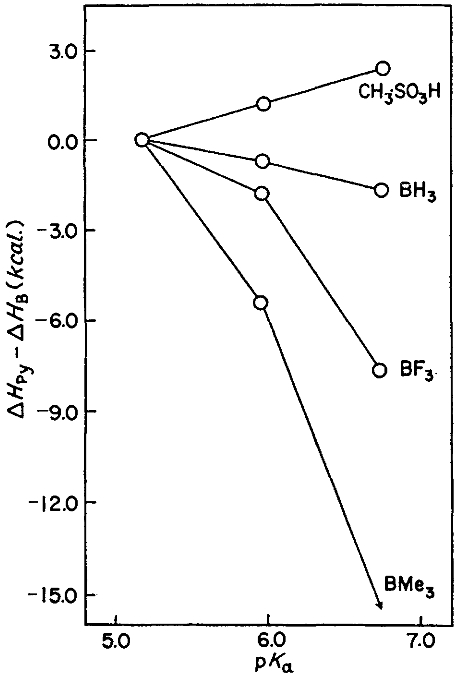
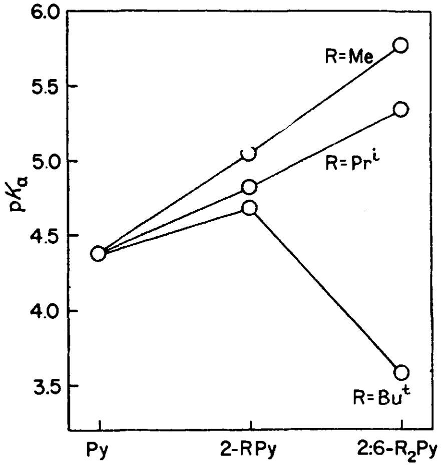


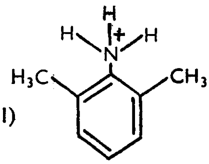
FIG. 2. *Effect of alkyl groups in the 2 : 6-positions on the strength of pyridine bases (in 50% ethanol).*

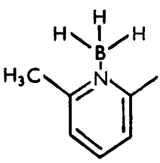


Methyl groups in the *meta-* or *para*-position of aniline bases increase the base strength. This change is, of course, consistent with the postulated inductive effect of alkyl groups. In the *ortho*-position, however, such groups considerably decrease the base strength.[9c] Moreover, *tert.*-butyl groups, as in *o*-*tert.*-butyl- and 2 : 6-di-*tert.*-butyl-aniline, bring about a much sharper decrease in the strength of the substituted bases.[9d]

The geometrical requirements of 2 : 6-dimethylanilinium ion (VII) must be very similar to those of 2 : 6-lutidine–borine (VIII), a molecule in which strains of 2·8 kcal./mole are indicated

(VII)





(VIII)

(Table 2). Consequently, it appears reasonable to attribute the unexpected weakness of *o*-toluidine and 2 : 6-xylidine to the increase in the steric requirements of the $-NH_2$ group in its

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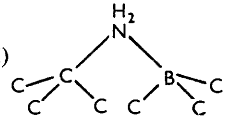
[9] Steric requirements of the proton : (*a*) Brown and Kanner, *J. Amer. Chem. Soc.*, 1953, **75**, 3865; (*b*) Brown and Cahn, *ibid.*, 1950, **72**, 2939; (*c*) Thomson, *J.*, 1946, 1113; (*d*) L. P. Wepster (Delft Univ.) unpublished data.

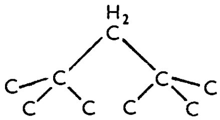
conversion into the $-NH_3^+$ group. Strains resulting from the conflicting steric requirements of the $-NH_3^+$ group and the methyl groups in the *ortho*-positions would enhance the tendency for the loss of a proton from the anilinium ion. The $\geqslant\overset{+}{N}-H$ group in the pyridinium ion and the $-NH_3^+$ in the anilinium ion are doubtless strongly associated with a sheath of solvating water molecules. To what extent it is necessary to consider this sheath of water molecules in estimating the steric requirements of the protonated groups is not yet clear.

It was suggested above that the strains in 2 : 6-dimethylanilinium ion (VII) are probably similar to those in 2 : 6-lutidine–borine (VIII). Unfortunately, it does not appear possible at present to test this point in these cases. In other examples it has been found possible to demonstrate the existence of similar strains in molecules of related structures.[10]

For example, *n*-butylamine and *tert.*-butylamine are primary amines of quite similar strengths. Consequently, it would be predicted that their addition compounds with trimethylboron should exhibit similar stabilities. In actual fact *tert.*-butylamine–trimethylboron, with a heat of dissociation of 13·0, is far less stable than *n*-butylamine–trimethylboron, with a heat of dissociation of 18·4 kcal./mole.[10b] The discrepancy of 5·4 kcal. is attributed to steric strain arising from the crowding of the two bulky groups attached to the common nitrogen atom (IX).

(IX)



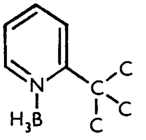


(X)

The structure of di-*tert.*-butylmethane (X) is quite similar to that of the addition compound. The covalent radius of nitrogen is slightly smaller than that of carbon, while that of boron is slightly larger. With the boron-to-nitrogen distance almost identical with the carbon-to-carbon distance, it is of interest to compare the strain in the hydrocarbon with that in the addition compound.

As a result of the very precise work carried out at the National Bureau of Standards in Washington on the combustion of hydrocarbons it is now possible to calculate the heat of combustion of any simple hydrocarbon with considerable precision. The heat of combustion thus calculated for di-*tert.*-butylmethane turns out to be 5·2 kcal./mole smaller than the experimental value.[10a] It appears, therefore, that the strain present in the hydrocarbon is essentially identical with that present in the addition compound.

Recently we have determined the heat of reaction of diborane with pyridine and the *tert.*-butylpyridines, and of trimethylboron and the methylpyridines. The results show that 2-*tert.*-butylpyridine–borine (XI) is less stable than the other isomers by 6·3 ± 0·2 kcal./mole, while 2-picoline–trimethylboron (XII) is less stable than the other isomers by 5·9 ± 0·2 kcal./mole. The heats of combustion of the isomeric *tert.*-butyltoluenes have recently been measured by Mr. Prosen and his associates at the Bureau of Standards. They find the *ortho*-isomer (XIII) to be less stable than the *meta*- and the *para*-derivative by 5·6 ± 0·8 kcal./mole. Thus, within the experimental error of the measurements, these three related systems possess identical strains of approximately 5·9 ± 0·2 kcal./mole.



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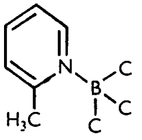

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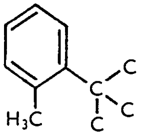

(XIII)

It is therefore reasonable to assume that molecules which are closely related structurally in this way will possess very similar steric strains. The term " homomorph " has been proposed for molecules which have similar molecular dimensions.

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[10] Strained homomorphs : (*a*) Brown, Barbaras, Berneis, Bonner, Johannesen, Grayson, and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 1; (*b*) Brown and Barbaras, *ibid.*, p. 6; (*c*) Brown and Berneis, *ibid.*, p. 10; (*d*) Brown and Bonner, *ibid.*, p. 14; (*e*) Brown and Johannesen, *ibid.*, p. 16; (*f*) Brown and Grayson, *ibid.*, p. 20; (*g*) Brown and Nelson, *ibid.*, p. 24.

Typical homomorphic systems are shown in Figs. 3, 4, 5. It has proved possible to examine typical structures in each system and to follow the effects of the strain upon the chemical behaviour of the molecule. Unfortunately, space will not permit a review of these results.[10]

It was previously pointed out that the preferred substitution in the position *ortho* to methyl in *p*-cymene was attributed by Le Fèvre to the operation of steric effects.[2f] However, this phenomenon has been attributed alternatively to electronic factors (IV).[3b] In an attempt to resolve this difference in interpretation we examined the isomer distribution in the nitration of toluene, and ethyl-, *iso*propyl-, and *tert.*-butyl-benzene. The experimental results are summarized in Table 3.

FIG. 3. *Homomorphs of di-*tert.*-butylmethane.*

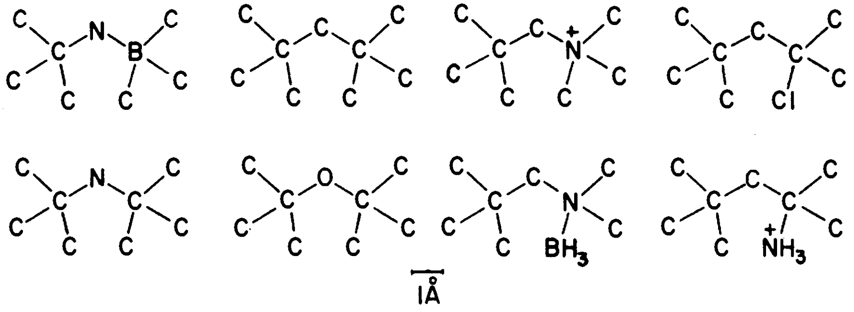
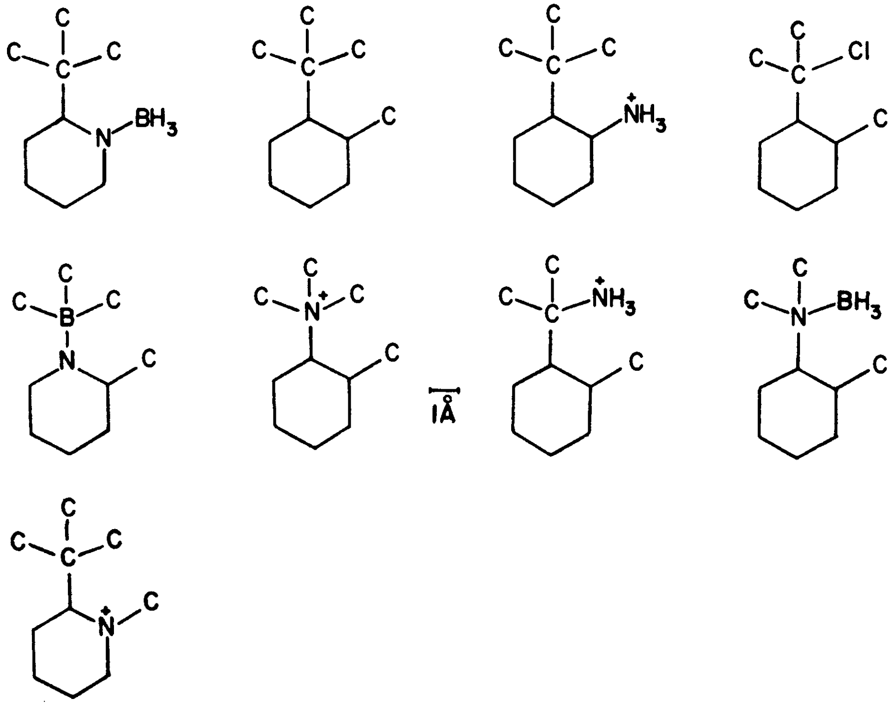


FIG. 4. *Homomorphs of* o-tert.*-butyltoluene.*



The *meta*-position is relatively insensitive to both resonance interactions and steric factors. Consequently, it offers a satisfactory position of reference. From the observation that the *para*/*meta* ratio is sensibly constant in the series of four compounds, we may conclude that there are no *major* differences in the hyperconjugative contributions of the four alkyl groups.

FIG. 5. *Homomorphs of* 2-tert.-*butyl*-1 : 3-*dimethylbenzene.*

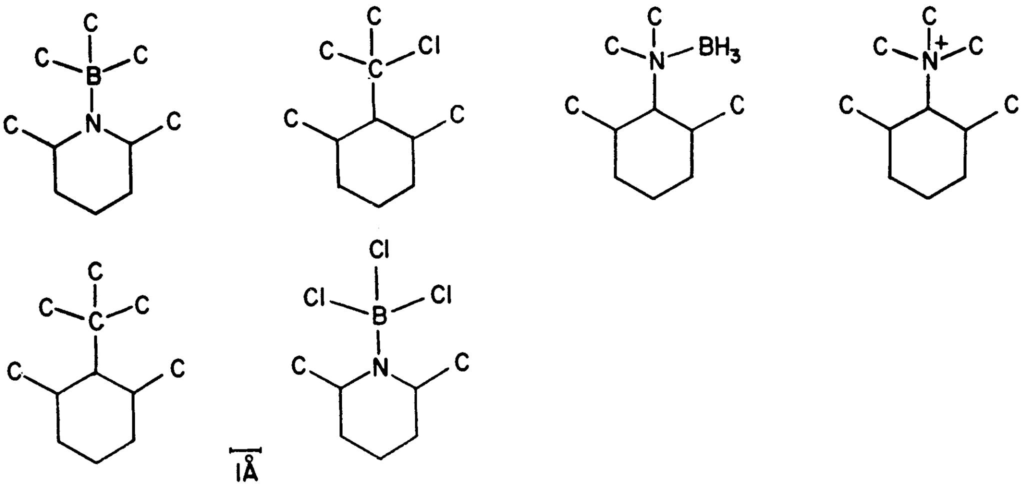


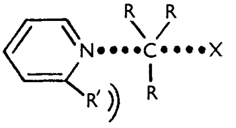
TABLE 3. *Isomer distribution in the nitration of the monoalkylbenzenes.*

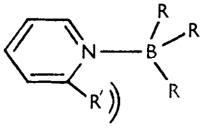
	Isomer distribution			Isomer ratio	
Monoalkylbenzene	*o*-	*m*-	*p*-	*o*-/*m*-	*p*-/*m*-
Toluene [11c]	58·45	4·4	37·15	13·3	8·5
Ethylbenzene [11b]	45·0	6·5	48·5	6·9	7·5
*iso*Propylbenzene [11b]	30·0	7·7	62·3	3·9	8·1
tert.-Butylbenzene [11a, d]	15·8	11·5	72·7	1·37	6·3

The sharp decrease in the *ortho*/*meta* ratios cannot then be the result of differences in the hyperconjugative contributions of the alkyl groups. The decrease is therefore more plausibly ascribed to the increasing steric requirements of these groups. The results therefore provide clear evidence of the importance of the steric factor in influencing substitution in the *ortho*-position.

The transition state for a typical displacement reaction (XIV) resembles rather closely molecular addition compounds of related structures (XV) :

(XIV)





(XV)

On this basis it appears resonable to expect that structural changes which result in an increase of strain in the addition compounds will also result in increased strain in the transition state. To test this idea we undertook a study of the reaction of a series of pyridine bases [12b] with methyl, ethyl, and *iso*propyl iodide.[12c]

As expected, the reaction rate decreases sharply from methyl to ethyl to *iso*propyl iodide with the activation energies showing corresponding increases. Introduction of an alkyl group into the 3- or 4-position results in a small increase in rate, with no significant difference for a methyl, ethyl, *iso*propyl, or *tert.*-butyl substituent. In the 2-position these substituents bring about decreases in rate and increases in activation energy which become more and more pronounced with the increasing steric requirements of the alkyl group.

[11] Steric effects in aromatic substitution : (*a*) Nelson and Brown, *J. Amer. Chem. Soc.*, 1951, **73**, 5605; (*b*) Brown and Bonner, *ibid.*, 1954, **76**, 605; (*c*) Jones and Russell, *J.*, 1947, 921; (*d*) Cohn, Hughes, Jones, and Peeling, *Nature*, 1952, **169**, 291.

[12] Steric effects in displacement reactions : (*a*) Brown and Eldred, *J. Amer. Chem. Soc.*, 1949, **71**, 445; (*b*) Brown and Murphey, *ibid.*, 1951, **73**, 3308; (*c*) Brown and Cahn, *ibid.*, 1955, **77**, 1715; (*d*) Brown and Mihm, *ibid.*, p. 1723; (*e*) Brown and Holmes, *ibid.*, p. 1727; (*f*) Brown and Horowitz, *ibid.*, pp. 1730, 1733; (*g*) Brown, Gintis, and Podall, *ibid.*, in the press; (*h*) Brown and Gintis, *ibid.*, in the press; (*i*) Brown and Domash, *ibid.*, in the press; (*j*) Brown *et al.*, *ibid.*, in the press; (*k*) Bartlett and Rosen, *ibid.*, 1942, **64**, 543; (*l*) Vernon, *J.*, 1954, 4462; (*m*) Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173.

The steric requirements of the base being constant, the rate of reaction decreases and the energy of activation increases with the increasing steric requirements of the alkyl halide (Fig. 6). Similarly, constancy of the steric requirements of the alkyl halide results in a rate which decreases and an energy of activation which increases with the increasing steric requirements of the pyridine base (Fig. 7). Simultaneous increases in the steric requirements of both the alkyl halide and the pyridine base cause cumulative changes in the reaction rates and activation energies. The experimental results are summarized in Table 4.

Fig. 6. *Effect of steric strain* (S) *on activation energies in the picoline series.*

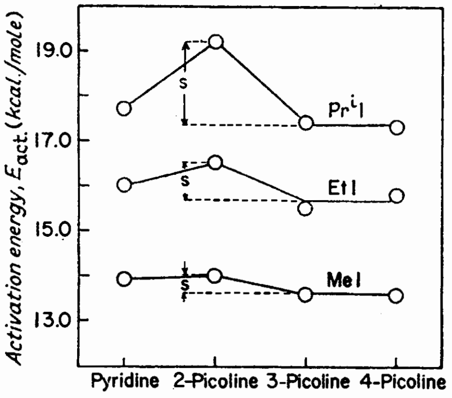


Fig. 7. *Effect of increasing steric strain on activation energies in reactions of 2-alkylpyridines.*

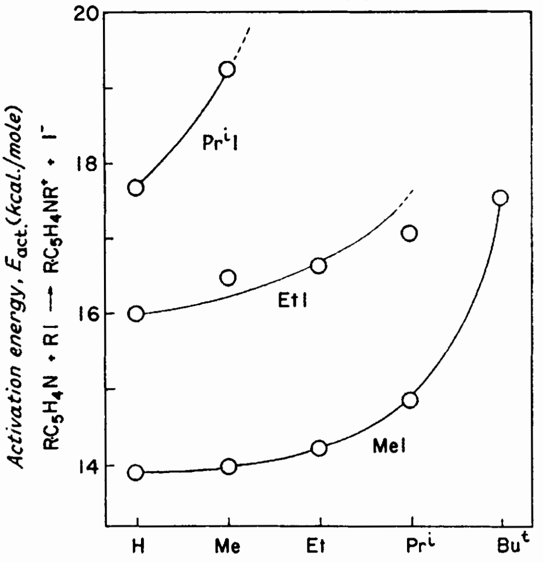


Table 4. *Rate data for the reaction of pyridine bases with alkyl halides in nitrobenzene solution.*

R in pyridine base $R{\cdot}C_5H_4N$	Methyl iodide			Ethyl iodide			*iso*Propyl iodide		
	$10^6k_2^{25}$	E_{act}	log A	$10^6k_2^{25}$	E_{act}	log A	$10^6k_2^{25}$	E_{act}	log A
H	343	13·9	6·72	18·3	16·0	6·98	0·941	17·7	6·93
2-Me	162	14·0	6·46	4·27	16·5	6·70	0·0509	19·2	6·80
2-Et	76·4	14·2	6·31	1·95	16·6	6·49	—	—	—
2-Pr^i	24·5	14·8	6·27	0·555	17·1	6·26	—	—	—
2-Bu^t	0·080	17·5	5·75	—	—	—	—	—	—
3-Me	712	13·6	6·82	40·0	15·5	6·98	1·73	17·4	7·01
3-Et	761	—	—	41·0	—	—	1·81	—	—
3-Pr^i	810	—	—	40·4	—	—	1·68	—	—
3-Bu^t	950	—	—	43·3	—	—	1·56	—	—
4-Me	760	13·6	6·86	41·9	15·8	7·12	1·99	17·3	6·98
4-Et	777	—	—	42·1	—	—	2·01	—	—
4-Pr^i	767	—	—	42·2	—	—	1·98	—	—
4-Bu^t	757	13·7	6·91	41·9	—	—	2·00	—	—

Bimolecular displacement reactions normally show a regular decrease in rate in the order :

$$CH_3X > CH_3{\cdot}CH_2X > (CH_3)_2CHX > (CH_3)_3CX$$

It was originally suggested by Polanyi that this decrease was the result of steric forces.[2g] The results of the study just reviewed appear to be in complete accord with this view. However, adherents of the electronic theory have maintained that the decrease was due to the inductive effect of the alkyl substituents, which by increasing the electron density at the central carbon atom would render the approach of an electronegative reagent increasingly difficult.[3c]

This viewpoint has been used to account for the large increase in activation energy observed in the reactions of triethylamine with methyl and *iso*propyl iodide [$E(Pr^iI) - E(MeI) =$ 6·3 kcal./mole] compared with the smaller increment observed in the corresponding reactions of pyridine (3·8 kcal./mole). According to the proposed interpretation, the central nitrogen atom of the strong base, triethylamine, would be strongly electronegative and would be greatly affected by the increasing negative (or decreasing positive) charge on the central carbon atom of the *iso*propyl group. On the other hand, the nitrogen atom in the weaker base, pyridine, would be less electronegative and would therefore be much less affected by changes in the polar nature of the central atom of the alkyl group.[3d]

The steric interpretation accounts for the phenomena equally well. According to this interpretation, a large increase in activation energy should accompany the reaction of a base with large steric requirements, such as triethylamine, with an alkyl halide with large steric requirements, such as *iso*propyl iodide. A much smaller increase in activation energy should be observed in the corresponding reactions of a base with small steric requirements, such as pyridine.

Quinuclidine offered a critical test of these alternative interpretations. It is a strong base, similar to triethylamine, but with relatively small steric requirements, resembling those of pyridine. On the basis of the polar interpretation, there would be expected a large increase in the activation energy in going from methyl to *iso*propyl iodide. However, the steric theory would predict that its behaviour should more closely resemble that of pyridine with a relatively small increment in the activation energy. The observed increment is small [$E(Pr^iI) - E(MeI) =$ 4·1 kcal./mole], strongly supporting the proposed steric interpretation for the phenomena.

A useful procedure for separating polar and steric effects is to separate the group from the reaction centre by means of an unsaturated system (aryl, vinyl, or ethynyl).[12k] The introduction of methyl groups in the γ-position of allyl chloride should not alter the steric factor while relaying the polar effect of the methyl groups to the reaction centre. Yet the exchange reaction with chloride ion in acetone shows an *increase* in rate accompanying the presence of the methyl groups.[12l] In the α-position the methyl groups sharply decrease the rate of the exchange reaction.[12l]

$CH_2{:}CH{\cdot}CH_2Cl$	1·00
$CH_3{\cdot}CH{:}CH{\cdot}CH_2Cl$	2·52
$(CH_3)_2C{:}CH{\cdot}CH_2Cl$	21·3
$CH_2{:}CH{\cdot}C(CH_3)_2Cl$	0·043

These results argue against the polar interpretation for the decrease in reactivity in the methyl—*tert.*-butyl halide series.

It has now been suggested that approximately half of the decrease with increased branching of the alkyl group is due to steric forces with the remainder due to the operation of polar forces.[12m] It would take us too far afield to consider the argument here. However, it is the Lecturer's view that there do not appear to be any experimental results at present available which require for their explanation a significant contribution from the polar factor in order to account for the observed decrease in reactivity in the alkyl halides under consideration.

It was suggested that steric hindrance effects in displacement reactions are primarily the result of steric strains in the activated complex and should be related to steric strains in molecular addition compounds of similar steric requirements. To test this proposal we have compared the strains in molecular addition compounds with strains present in the activated complexes.

In Fig. 8 there is plotted the heat of reaction of trimethylboron with various pyridine bases against their pK_a values. It will be observed that a reasonably good linear relation is indicated by pyridine and the 3- and 4-alkylpyridines, but that the 2-alkylpyridines deviate greatly. Moreover, the deviations from the line increase regularly from 2-methyl to 2-ethyl to 2-*iso*propyl, with a further sharp increase to 2-*tert.*-butyl. In other words the deviation can be correlated with the steric requirements of the 2-substituent.

With smaller steric requirements of the reference acid (boron trifluoride in Fig. 9 and borine in Fig. 10) the deviations decrease and the points for the 2-alkyl derivatives move toward the line. Finally, with methanesulphonic acid there is realized a complete linear relation for all of the alkylpyridines (Fig. 11).

Figs. 12—15 show similar plots of the heats of reaction of these reference acids with the bases *versus* the activation energies for their reaction with methyl iodide. Again large deviations are observed for trimethylboron, smaller ones for boron trifluoride, while borine yields a linear relation. On the other hand, methanesulphonic acid no longer yields a linear relation, with the 2-alkylpyridines tending to fall on the opposite side of a possible line.

In other words, where the steric requirements of the two reactions being compared are

Fig. 8.

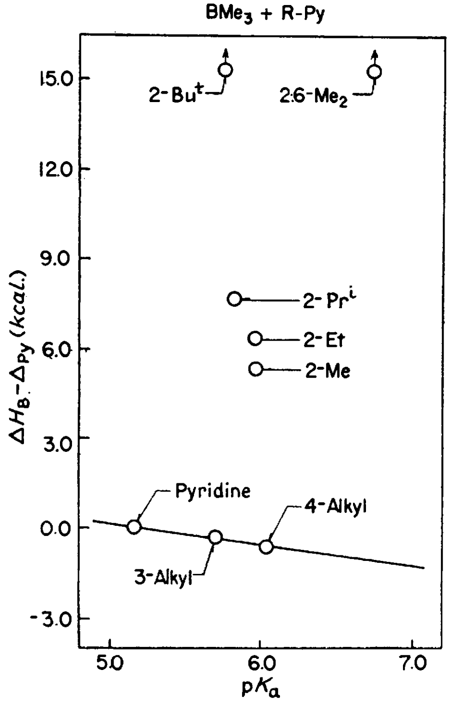


Fig. 9.

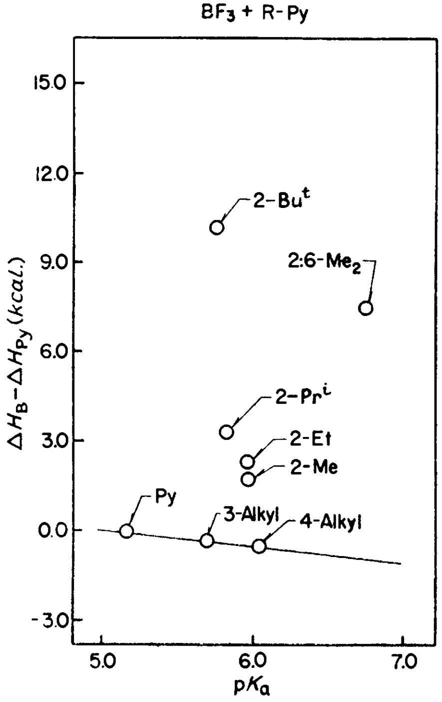


Fig. 10.

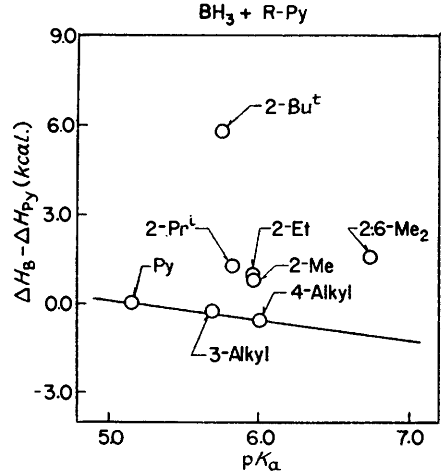
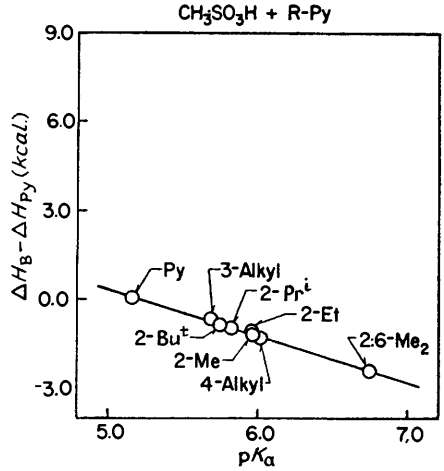


Fig. 11.



Figs. 8—11. *Relations between the strengths of alkylpyridine bases and their heats of reaction with (Fig. 8) trimethylboron, (Fig. 9) boron trifluoride, (Fig. 10) borine, and (Fig. 11) methanesulphonic acid.*

FIG. 12.

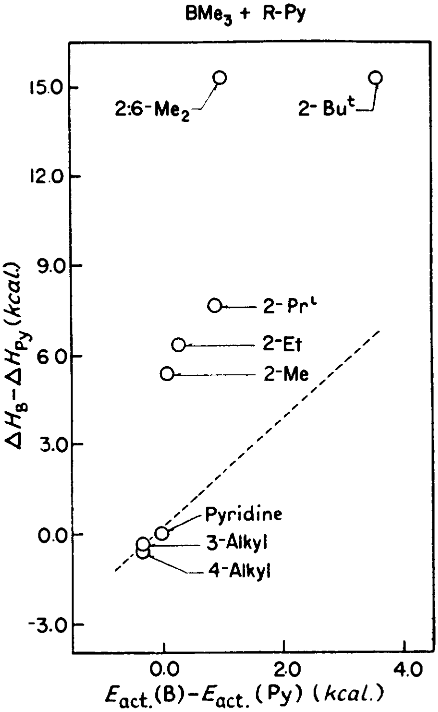


FIG. 13.

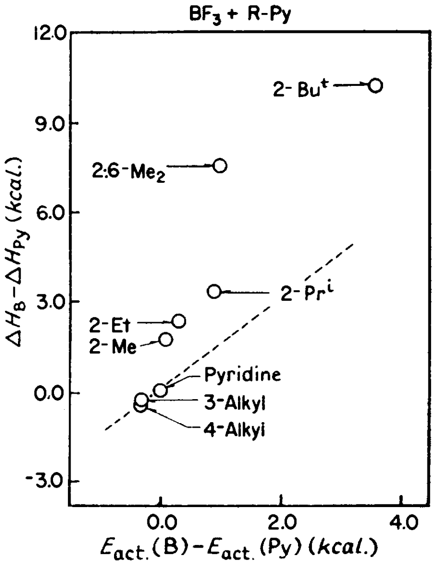


FIG. 14.

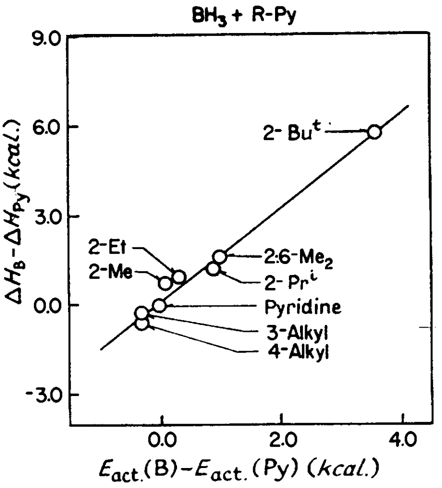
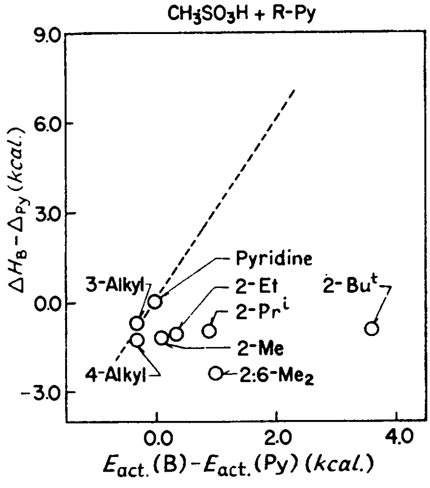


FIG. 15.



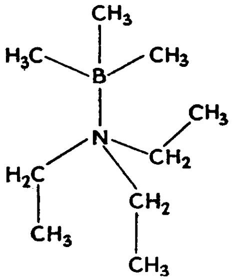
FIGS. 12—15. *Relations between the energies of activation for the reaction of methyl iodide with alkylpyridines and the heats of reaction of these bases with (Fig. 12) trimethylboron, (Fig. 13) boron trifluoride, (Fig. 14) borine, and (Fig. 15) methanesulphonic acid.*

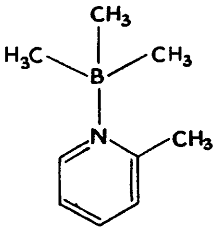
different, the 2-alkylpyridines fail to fit a linear relation. Where the steric requirements of the two reactions are similar (ΔH, Me·SO$_3$H *v.* pK_a; ΔH, $\frac{1}{2}$(BH$_3$)$_2$ *v.* ΔE_{act} MeI), satisfactory linear relations are obtained.

This realization of a linear relation between the strain energies in the activated complexes and the strain energies of related molecular addition compounds is encouraging. It suggests that the study of selected molecular addition compounds (XV) may provide considerable information as to the precise nature of the related transition states (XIV). It further supports the conclusion that steric effects constitute an important factor in controlling the rates of displacement reactions.

Up to this point the discussion has concerned itself with the steric effects arising directly from the conflicting steric requirements of the two atoms or groups of atoms involved in the reaction. Thus the instabilities of triethylamine–trimethylboron (XVI) and of 2-picoline–trimethylboron (XVII) obviously arise from the large strains accompanying the compression of the amine and trimethylboron molecules.

(XVI)





(XVII)

Strains of this type have been termed F-strain since it is due primarily to steric interactions at the " front " of the amine molecule. Such strain is directly related to the type of steric effect envisaged by Kehrmann and Meyer in their pioneer studies. It has been necessary to postulate a new type of strain in order to account for the complete behaviour of the aliphatic amines.[13a]

The $+I$ inductive effect of alkyl groups should result in an increase in the strength of aliphatic amines, $NH_3 < R{\cdot}NH_2 < R_2NH < R_3N$. On the other hand, the steric requirements of the aliphatic groups should tend to reduce the apparent strengths of the amines. In cases where the steric effect outweighs the polar effect, the opposite order should be observed.

By varying the steric requirements of the reference acid, it should be possible to vary the relative importance of the steric and the polar factor within wide limits. An increase in the bulk of the alkyl groups should have the same effect. Consequently, by decreasing the steric strain systematically through an alteration in these two variables, it should be possible to realize a systematic variation in the sequence from 1 to 7 :

1, $R_3N < R_2NH < R{\cdot}NH_2 < NH_3$.
2, $R_3N < R_2NH < NH_3 < R{\cdot}NH_2$.
3, $R_3N < NH_3 < R_2NH < R{\cdot}NH_2$.
4, $NH_3 < R_3N < R_2NH < R{\cdot}NH_2$.
5, $NH_3 < R_3N < R{\cdot}NH_2 < R_2NH$.
6, $NH_3 < R{\cdot}NH_2 < R_3N < R_2NH$.
7, $NH_3 < R{\cdot}NH_2 < R_2NH < R_3N$.

As was pointed out above, 1 and 7 represent the two possible extremes : dominant control by the polar effect of the alkyl substituents (sequence 7) and dominant control by the steric effect of the substituents (sequence 1).

We therefore varied the steric factor in the amines systematically by varying the steric requirements of the alkyl groups ($Bu^t > Pr^i > Et > Me$) and by varying the steric requirements of the reference acid ($Bu^t{}_3B > Pr^i{}_3B > Et_3B > Me_3B > BF_3 > H^+$). The observed results are summarized in Table 5.

It is apparent that decreases in the steric factor bring about systematic changes in the observed sequences from 1 to 2, to 3, etc., as predicted. However, a reduction of the steric factor to the minimum realizable, both by reducing the steric requirements of the alkyl groups

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[13] B-Strain : (*a*) Brown, Bartholomay, jun., and Taylor, *J. Amer. Chem. Soc.*, 1944, **66**, 435; (*b*) Spitzer and Pitzer, *ibid.*, 1948, **70**, 1261; (*c*) Lawton, Thesis, Purdue, 1952; (*d*) Sujishi, Thesis, Purdue, 1949; (*e*) Fletcher, Thesis, Purdue, 1952.

in the amine to methyl and by reducing the steric requirements of the reference acid to the proton, fails to achieve the theoretical limiting sequence for the complete absence of the steric factor. Instead the sequences appears to be approaching 5 as a limit. As was pointed out earlier, the steric requirements of the proton are exceedingly small. No steric effect towards the proton is exhibited by 2 : 6-lutidine in spite of large steric requirements which prevent it from combining with trimethylboron. Consequently, we appear to be forced to the conclusion that even with reference acids of essentially negligible steric requirements the limiting sequence contains a contribution from the steric factor.

TABLE 5. *Observed sequences for alkylamines.*[13c]

	Reference acids					
Amines	$\text{Bu}^t{}_3\text{B}$	$\text{Pr}^i{}_3\text{B}$	Et_3B	Me_3B	BF_3	H^+
Bu^t [a]	1	1	1	1	1 or 2	—
Pr^i [b]	1	1 or 2	1 or 2	2	2	5
Et	1 or 2	2	2	3	3	5
Me	2	2 or 3	3	5	5	5

[a] Complete order deduced from behaviour of ammonia and mono-*tert.*-butylamine.
[b] Complete order deduced from behaviour of ammonia and mono- and di-*iso*propylamine.

It is proposed that in the reaction of tertiary amines with a reference acid Z

$$\underset{\text{(strained)}}{\text{R}_3\text{N} + \text{Z}} \rightleftharpoons \underset{\text{(more strained)}}{\text{R}_3\text{N:Z}}$$

there is an increase in steric strain which is independent of the steric requirements of the reference acid Z. This strain has been termed B-strain since it arises primarily at the "back" of the amine molecule.

Calculations have been reported which suggest that such strains are too small to account for the observed effects.[13b] We have also attempted to calculate B-strain by utilizing spectroscopic data and the Urey–Bradley force field. Values ranging from 1·5 to 10 kcal./mole were obtained.[13e] We also carried out a calculation of the energy required to distort a molecule such as NA_3 (considered to be homomorphic with NMe_3) utilizing the potential function for argon. We again obtained an answer which points to the presence of considerable strain.[13e] Although these theoretical approaches support the presence of B-strain in trimethylamine and related molecules, the approximations which must be utilized are such as to give one much more confidence in the experimental approach to such problems.

If the strain in trimethylamine is the result of the crowding of the three methyl groups around the small nitrogen atom, the effect should be greatly reduced or absent in the corresponding phosphorus derivatives with their much larger central atom. Indeed, the methylphosphines yield the sequence corresponding to 7, $\text{PH}_3 < \text{MePH}_2 < \text{Me}_2\text{PH} < \text{Me}_3\text{P}$, with H^+,[13d] with BMe_3,[13d] and with BF_3 [13e] as reference acids.

We now have observations on (1) ionization in aqueous solution, (2) dissociation of addition compounds of boron trifluoride, (3) dissociation of addition compounds of trimethylboron, (4) volatility of 'onium salts, (5) vapour pressures in systems with acetic and trifluoroacetic acids, and (6) dissociation of compounds with *n*-dodecanesulphonic acid.[13d] In all cases, the results indicate order 5 with the amines and order 7 with the phosphines.

If three alkyl groups attached to nitrogen constitute a centre of strain, it follows from the similarity in atomic dimension that three alkyl groups attached to carbon should also constitute a centre of strain. Such strain should manifest itself in an increased reactivity of molecules in reactions where the transition state affords a decrease in strain.

Classically, steric effects have been considered synonymous with steric hindrance. The proposal that steric effects may serve to assist a reaction represents a sharp departure from tradition.[14a]

The validity of the proposal was examined in the solvolysis of the tertiary alkyl chlorides.

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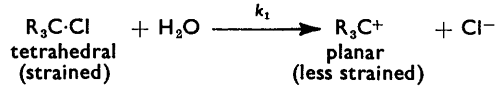
[14] Steric assistance in unimolecular reactions : (*a*) Brown, *Science*, 1946, **103**, 385; (*b*) Brown and Fletcher, *J. Amer. Chem. Soc.*, 1949, **71**, 1845; (*c*) *idem*, *ibid.*, 1950, **72**, 1223; (*d*) Brown and Stern, *ibid.*, p. 5068; (*e*) Brown and Fletcher, *ibid.*, 1951, **73**, 1317; (*f*) Brown and Kornblum, *ibid.*, 1954, **76**, 4510; (*g*) Burawoy and Spinner, *J.*, 1954, 3752; (*h*) Bartlett and Swain, *J. Amer. Chem. Soc.*, 1955, **77**, 2801; (*i*) F. Brown, Davies, Dostrovsky, Evans, and Hughes, *Nature*, 1951, **167**, 987; (*j*) Hughes, Ingold, and Shiner, jun., *J.*, 1953, 3827; (*k*) Winstein and Trifan, *J. Amer. Chem. Soc.*, 1949, **71**, 2953; 1952, **74**, 1147, 1154; (*l*) Bartlett, *J. Chem. Educ.*, 1953, **30**, 22.

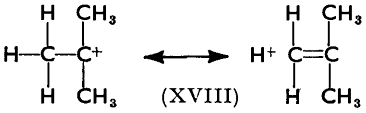
It was considered that strain present in the initial tetrahedral molecule should be greatly reduced in the formation of the transition state leading to the planar carbonium ion :



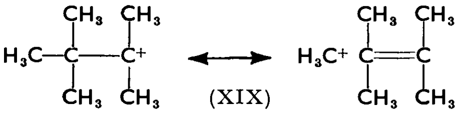
$$\underset{\substack{\text{tetrahedral}\\ \text{(strained)}}}{R_3C{\cdot}Cl} + H_2O \xrightarrow{k_1} \underset{\substack{\text{planar}\\ \text{(less strained)}}}{R_3C^+} + Cl^-$$

If steric assistance were indeed a factor in this reaction, the introduction of one or more bulky R groups into the tertiary halide should be accompanied by an enhanced rate of solvolysis. The replacement of one of the methyl groups in *tert.*-butyl chloride by a *tert.*-butyl group causes an increase in the first-order rate constant (80% ethanol) from 0·033 hr.$^{-1}$ to 0·040. A *tert.*-pentyl (1 : 1-dimethylpropyl) group causes the rate to rise further to 0·188 hr.$^{-1}$. These increases are in the direction predicted by the theory.[14b] However, it is necessary to enquire whether they might arise from other causes.

A dominant factor in the rapid solvolysis of *tert.*-butyl chloride must be the stabilization of the carbonium ion through hyperconjugation (XVIII). The replacement of the methyl group by the *tert.*-butyl (as in XIX) or the *tert.*-pentyl group would be expected to result in a decrease in the hyperconjugative stabilization and, consequently, a decrease in the observed rate of solvolysis.

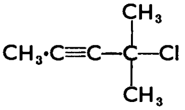


(XVIII)

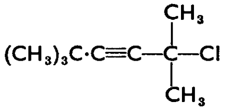


(XIX)

For the two compounds (XX, XXI), the steric factor at the reaction centre has been maintained essentially constant, so the solvolysis rates should reflect the respective electrical contributions of the methyl and *tert.*-butyl groups. In these compounds the *tert.*-butyl derivative exhibits much the slower rate of solvolysis (80% acetone).[14g]

(XX) 

$k_1 = 5{\cdot}13 \times 10^{-4}$ sec.$^{-1}$

 (XXI)

$k_1 = 2{\cdot}80 \times 10^{-4}$ sec.$^{-1}$

Consideration of other contributing factors, such as the ease of solvation of the incipient carbonium ion and the ease of electrophilic attack of the solvent on the halogen likewise leads to the prediction that the bulky *tert.*-butyl and *tert.*-pentyl substituents should decrease the solvolysis rate. The observed increases may therefore be considered to support the postulated rôle of steric strain in assisting the ionization.

Similarily the replacement of one of the methyl groups in *tert.*-butyl chloride by a *neo*pentyl group, giving a homomorph of di-*tert.*-butylmethane, results in a 21-fold increase in the reaction rate. Two *neo*pentyl groups raise the rate to 580 times that of *tert.*-butyl chloride.[10c]

Even larger effects have been realized by Bartlett and Swain [14h] and by F. Brown *et al.* [14i] in the solvolysis of *tert.*-alkyl derivatives containing a number of bulky substituents.

Bridging by neighbouring carbon has been utilized to account for the enhanced solvolysis rates exhibited by certain bicyclic systems.[14k] The possibility that similar phenomena may be responsible for the enhanced rates of ionization in the highly branched tertiary halides has been considered.[14l] However, all attempts to establish the importance of such bridging in compounds of the type under consideration here have yielded negative results.[14f] As a result there does not appear to be any need to bring in this additional factor in accounting for the enhanced ionization rates of highly branched tertiary derivatives.

The carbonium ion, once formed, can react by three different paths. It can react with the solvent to regenerate the original tetrahedral system (k_S), it can lose a proton, forming an olefin (k_E), or it can undergo rearrangement to form a new carbonium ion. It is reasonable that a carbonium ion containing bulky substituents should react somewhat more slowly with the solvent. Consequently such an ion should exhibit an enhanced tendency to undergo elimination and rearrangement. Typical data are summarized in Table 6.[14c]

TABLE 6. *Elimination in the solvolysis of tertiary chlorides at 25° in 80% ethanol.*

Carbonium ion	Me_3C^+	$Bu^tMe_2C^+$	Et_3C^+	$Bu^tEt_2C^+$	$Me{\cdot}CH_2{\cdot}Me_2C^+$	$Bu^t{\cdot}CH_2{\cdot}Me_2C^+$
Yield (%) of olefin...	16	61	40	90	34	65

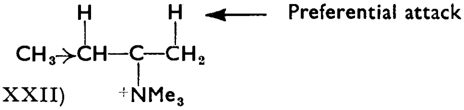
Alternative interpretations of these results have been presented.[14j] However, a considerable body of additional results now supports the original conclusions. Consequently, there appears to be no need to revise the interpretation as presented above.

It is observed that *tert.*-butyldiethylcarbinol (3-ethyl-2 : 2-dimethylpentan-3-ol) rearranges on reaction with hydrogen chloride at 0°,[14b] whereas the closely related compound *tert.*-butylethylmethylcarbinol (2 : 2 : 3-trimethylpentan-3-ol) reacts without rearrangement.[14f] It was pointed out that the *tert.*-butyldiethylcarbonium ion will have both faces of the ion blocked by the two ethyl groups so that the rate of substitution will be reduced, whereas the *tert.*-butylethylmethylcarbonium ion is relatively unhindered and a much faster rate of substitution appears likely for it. The rearrangement observed in the reaction of *tert.*-butyldiethylcarbinol is therefore attributed to the relatively low rate of substitution, providing a better opportunity for the ion to undergo structural change.

The concept of steric assistance provides a simple, unifying explanation for the effect of structure upon the ionization, elimination, and rearrangement reactions of highly branched carbonium ions.

The effect of structure upon the rate, yield, and directive effects of olefin formation in the elimination reaction had previously been given careful consideration by Hughes and Ingold and their co-workers.[15k] They concluded that hyperconjugative and polar factors were of importance and attributed all of the observed phenomena to the operation of these factors.

For example, in all unimolecular eliminations and in bimolecular eliminations of alkyl halides the major product is the most alkylated of the possible olefins (Saytzeff rule). This was attributed to hyperconjugative stabilization of the incipient double bond in the transition state by the alkyl groups. On the other hand, bimolecular elimination of 'onium salts yields preferentially the least alkylated olefin (Hofmann rule). It was suggested that under the influence of the positive charge in the 'onium group there is a flow of electrons from the β-carbon atoms. This is resisted by the inductive effects of alkyl groups, resulting in preferential attack by the base at the least heavily alkylated β-carbon atom (XXII).



$$CH_3{\rightarrow}\overset{H}{C}H{-}\underset{^+NMe_3}{C}{-}\overset{H}{C}H_2 \longleftarrow \text{Preferential attack}$$

(XXII)

On the other hand, Schramm has suggested that it is the steric requirements and not the charge of the 'onium group which is responsible for the observed direction of elimination.[15l]

Our studies of the solvolysis of *tert.*-alkyl chlorides had led us to the conclusion that steric effects were a factor in the yield of olefin in these unimolecular reactions. It appeared desirable to examine both unimolecular and bimolecular eliminations in order to test the importance of the steric factor in these reactions.

The solvolysis of a series of closely related tertiary bromides, $R{\cdot}CH_2{\cdot}CMe_2Br$, revealed that the yield and the nature of the product varied in a regular manner with the increasing steric requirements of the group R (Table 7). Moreover, in the last member of the series, R = Bu^t, the product consisted of 82% of the 1-olefin, a clear case of elimination in accordance with the Hofmann rule.[15a, b]

TABLE 7. *Experimental data on the yield and composition of olefins formed in solvolysis.*

			Composition (%)		
Compound *	R	Yield (%)	1-	*trans*-2	*cis*-2
Me_2EtCBr [a]	Me	27 [15b]	20	80	
Me_2Pr^nCBr [a]	Et	32·5 [15b]	29	71	
Me_2Bu^iCBr [a]	Pr^i	46 [15b]	41	59	
$Bu^t{\cdot}CH_2{\cdot}CMe_2Br$ [a]	Bu^t	57 [15b]	82	18	
$MePr^nCHBs$ [b]	Et	31·5 [15c]	15·7	48·8	35·5
$MeBu^iCHBs$ [b]	Pr^i	46·5 [15c]	19·7	53·0	27·3
$Bu^t{\cdot}CH_2{\cdot}CHMeBs$ [b]	Bu^t	68 [15c]	24·3	74·8	0·9

* Bs = p-$Br{\cdot}C_6H_4{\cdot}SO_2{\cdot}O$. [a] 85% $Bu^nO{\cdot}CH_2{\cdot}CH_2{\cdot}OH$ at 25°. [b] Anhyd. AcOH at 70°.

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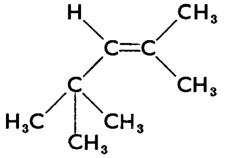
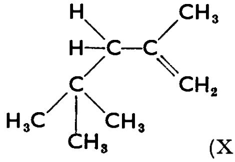
[15] Steric effects in elimination reactions: (*a*) Brown and Moritani, *J. Amer. Chem. Soc.*, 1955, **77**, 3607; (*b*) Brown and Nakagawa, *ibid.*, p. 3610; (*c*) *idem*, *ibid.*, p. 3614; (*d*) Brown and Okamoto, *ibid.*, p. 3619; (*e*) Brown and Moritani, *ibid.*, p. 3623; (*f*) Brown, Moritani, and Nakagawa, *ibid.*, in the press; (*g*) Brown, Moritani, and Okamoto, *ibid.*, in the press; (*h*) Brown and Nakagawa, *ibid.*, in the press; (*i*) Brown and Wheeler, *ibid.*, in the press; (*j*) Brown and Moritani, *ibid.*, in the press; (*k*) Dhar, Hughes, Ingold, Mandour, and Maw, *J.*, 1948, 2093; (*l*) Schramm, *Science*, 1950, **112**, 367.

It was suggested that in the simpler members of this series the predominant formation of the 2-olefin is due to its greater stabilization by hyperconjugation, as proposed by Hughes and Ingold. However, the 2-olefin contains the alkyl group R in a position *cis* to one of the methyl groups. As the steric requirements of R increase, the steric interactions between R and the methyl group likewise increase. With R = *tert.*-butyl (XXIII), the strains become sufficiently large to overcome the effect of hyperconjugative stabilization and the 1-olefin becomes the preferred product (XXIV).

This conclusion is confirmed by the results obtained in the solvolysis of the corresponding secondary derivative, $(CH_3)_3C{\cdot}CH_2{\cdot}CH(Bs){\cdot}CH_3$ (Bs = *p*-bromophenylsulphonyloxy). Here the solvolysis product is predominantly the *trans*-2-olefin. The molecule retains the electronic stabilization of the 2-olefin while avoiding the large strains of the *cis-tert.*-butyl–methyl relation in 2 : 4 : 4-trimethylpent-2-ene (XXIII). The experimental results are summarized in Table 7.



(XXIII)



(XXIV)

In treating the series of tertiary bromides $R{\cdot}CH_2{\cdot}CMe_2Br$ with potassium ethoxide (*E*2) we also observed a regular increase in the yield of 1-olefin in the product with the increasing steric requirements of R. By increasing the steric requirements of the alkoxide base (EtOK < Bu^{t}OK < $EtMe_2C{\cdot}OK$ < $Et_3C{\cdot}OK$)[15g] or the pyridine base (pyridine < 2-picoline < 2 : 6-lutidine)[15h] there was again observed with each of the alkyl halides a regular increase in the amount of the 1-olefin formed in the reaction.

Indeed, in the case of simple alkyl halides, such as *tert.*-pentyl, it proved possible to shift the elimination from typically Saytzeff to typically Hofmann type merely by varying the steric requirements of the base.

Finally, it was demonstrated that the yield of 1-olefin increases regularly with the increasing steric requirements of the leaving group.[15i, j]

The experimental results are summarized in Table 8.

TABLE 8. *Percentage of* 1-*olefin formed in the bimolecular elimination reactions of various* 2-*substituted derivatives* RX.[15]

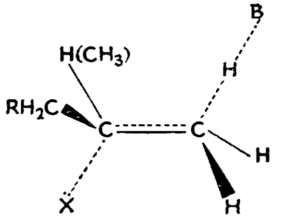
R	X [a]	Pyridine	2-Picoline	2 : 6-Lutidine	EtO^-	Bu^{t}O$^-$	$EtMe_2C{\cdot}O$	$Et_3C{\cdot}O^-$
MeEtCH	Br	—	—	—	19 [15k]	53	—	—
	OTs	—	—	—	—	62	—	—
	SMe_2^+	—	—	—	70 [15k]	—	—	—
MePr^{n}CH ...	Br	—	—	—	31	66	—	—
	I	—	—	—	30	—	—	—
	OTs	—	—	—	47	73	—	—
	SMe_2^+	—	—	—	87	—	—	—
	SO_2Me	—	—	—	89	—	—	—
	NMe_3^+	—	—	—	98	—	—	—
Me$_2$Pr^{i}CH ...	Br	10	18	37·5	21	73	81	92
	OTs	43	—	—	—	—	—	—
Me_2EtC	Cl	—	—	—	—	72	—	—
	Br	25	30	44·5	30	72·5	77·5	88·5
	OTs	37	—	—	—	—	—	—
	SMe_2^+	—	—	—	86 [15k]	—	—	—
	NMe_3^+	—	—	92·5	93	—	—	—
Me$_2$Pr^{n}C	Br	32	39	48	50	—	—	—
Me$_2$Bu^{i}C	Br	44	52	58	54	—	—	—
Bu$^t{\cdot}CH_2{\cdot}CMe_2$	Cl	—	—	—	86	—	—	—
	Br	70	74	82	86	98	—	97
	OTs	75	—	—	—	—	—	—
	NMe_3^+	88	95	99	100	—	—	—

[a] In order of increasing steric requirements : Br < OTs < SMe_2^+ < SO_2Me < NMe_3^+.
Ts = *p*-$Me{\cdot}C_6H_4{\cdot}SO_2$.

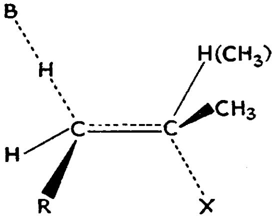
It is suggested that the bimolecular elimination proceeds through the transition states (XXV, XXVI).

In the absence of steric strain the reaction will proceed preferentially through the transition state (XXVI) to give the more alkylated of the two possible olefins (Saytzeff rule). With increasing steric requirements of either R or X (or both), steric strain will decrease the stability of this transition state. The alternative state (XXV) will be much less affected. Consequently there will occur an increased tendency for the reaction to proceed through transition state (XXV) to form the thermodynamically less stable 1-olefin. An increase in the steric requirements of the base, B, should also result in far greater strain in transition state (XXVI), where a secondary hydrogen must be removed, than in transition state (XXV), where a primary hydrogen is eliminated.

(XXV)



Transition state leading to 1-olefin



(XXVI)

Transition state leading to 2-olefin

This interpretation accounts in a simple manner for the observation that a shift from the more alkylated to the less alkylated olefin can be achieved by (1) an increase in the steric requirements of the alkyl groups on the incipient double bond, (2) an increase in the steric requirements of the leaving group, and (3) an increase in the steric requirements of the attacking base.

For simplicity the present discussion has been restricted to the reactions of 2-substituted derivatives, whose elimination reactions yield 1- or 2-olefins. Generalization to more complex examples appears to offer no difficulty.

The available data support the interpretation that elimination in accordance with the Saytzeff rule represents control by the hyperconjugative factor, whereas elimination in accordance with the Hofmann rule represents control by the steric factor.

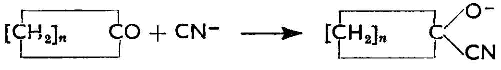
Steric effects also appear to be an important factor in the chemical behaviour of simple ring systems. Thus, in the small rings (3- and 4-membered) the *cyclo*alkyl halides, with a few exceptions, are unusually inert in typical substitution reactions.[16i] On the other hand, *cyclo*butanone is far more reactive than open-chain ketones.[16f]

Similar phenomena are observed in the common rings (5-, 6-, and 7-membered). Here *cyclo*pentyl and *cyclo*heptyl derivatives are quite reactive in substitution reactions, whereas the ketones are relatively inert. On the other hand, *cyclo*hexanone is very reactive and *cyclo*hexyl derivatives are inert.[16b, d]

The behaviour of the medium rings (8- to 12-membered) has been the subject of a thorough discussion in an earlier Centenary Lecture.[16g] Here also it is observed that the ketones and tetrahedral ring derivatives exhibit opposite reactivities. Thus the ring ketones in this range are highly inert in the usual ketone reactions, whereas the *cyclo*alkyl toluene-*p*-sulphonates [16e] or 1-chloro-1-methyl*cyclo*alkanes [16c] exhibit unusually high reactivities in solvolysis.

Thus the change in co-ordination number of a ring atom may be either favoured or not, depending upon the number of ring atoms. However, from the available data it appears to be a fairly general characteristic of these ring systems that in cases where the ring size favours a reaction which proceeds *via* a decrease in the co-ordination number, *e.g.*,

the opposite type of reaction



proceeds with relative difficulty.

[16] Chemistry of ring compounds: (*a*) Brown and Gerstein, *J. Amer. Chem. Soc.*, 1950, **72**, 2926; (*b*) Brown, Fletcher, and Johannesen, *ibid.*, 1951, **73**, 212; (*c*) Brown and Borkowski, *ibid.*, 1952, **74**, 1894; (*d*) Brown, Brewster, and Shechter, *ibid.*, 1954, **76**, 467; (*e*) Brown and Ham, *ibid.*, in the press; (*f*) Brown and Ichikawa, *ibid.*, in the press; (*g*) Prelog, *J.*, 1950, 420; (*h*) Bartlett, *Bull. Soc. chim. France*, 1951, c, 100; (*i*) Roberts and Chambers, *J. Amer. Chem. Soc.*, 1951, **73**, 5034; (*j*) Fierens and Verschelden, *Bull. Soc. chim. belges*, 1952, **61**, 427, 609; (*k*) Van Straten, Nicholls, and Winckler, *Canad. J. Res.*, 1951, **29**, 372; (*l*) Trotman-Dickenson and Steacie, *J. Chem. Phys.*, 1951, **19**, 329; (*m*) Overberger, Biletch, Finestone, Lilker, and Herbert, *J. Amer. Chem. Soc.*, 1953, **75**, 2078.

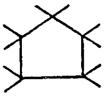
It has been proposed that this phenomenon is the result of changes in internal strain in these ring systems. Where a decrease in the co-ordination number of the ring atom (from 4 to 3, or sp^3 to sp^2) results in a decrease in internal strain, the reaction will be favoured; consequently, the opposite change (from 3 to 4, or from sp^2 to sp^3) will cause an increase in strain and the reaction will be hindered.[16b]

At the present time we recognize three sources of steric strains: (1) the compression of van der Waals radii, (2) the distortion of bond angles, and (3) bond opposition forces. For small rings, the distortion of bond angles appears to be the major source of strain. In *cyclo*pentane and *cyclo*heptane it is the bond opposition forces which are primarily responsible for the strains revealed in combustion studies, while in the medium rings it is probable that both bond opposition and compression of van der Waals radii are involved.

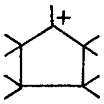
In 1-chloro-1-methyl*cyclo*butane the bond angle of the carbon atom is distorted from its preferred value of 109·5° to the 90° value established by the four-membered ring. The distortion is therefore 19·5°. In the solvolysis product, the carbonium ion, the preferred bond angle is believed to be 120°, whereas the actual angle must still be nearly 90°. This results in an increase of the distortion to 30°. It is suggested that such a reaction will be accompanied by an increase in angle strain and will therefore be resisted.

The identical arguments in opposite order apply to *cyclo*butanone. The reactions of this ketone should be accompanied by a decrease in angle strain and such reactions should be relatively fast.

In *cyclo*pentane angle strain is presumably small. Bond opposition forces are believed responsible for the large strain which is present. In the idealized planar model (XXVII) there will be 10 bond oppositions and approximately 10 kcal./mole strain. The removal of one atom will result in a decrease in the bond oppositions to 6 and a decrease in the estimated strain to 6 kcal./mole (XXVIII).



10 bond oppositions
10 kcal. strain
(XXVII)



6 bond oppositions
6 kcal. strain
(XXVIII)

In the actual molecule the strains are believed to be reduced by some 4 kcal. by some distortion of the bond angles and the assumption of a non-planar arrangement. Presumably similar distortion will occur in the carbonium ion so that the loss of one bond will still be accompanied by a considerable reduction in the internal strains.

*cyclo*Heptane is also strained because of bond opposition forces. Loss of one bond will also be accompanied by a decrease in internal strain.

*cyclo*Hexane, on the other hand, has all of its atoms in an ideally staggered arrangement. Loss of one atom results in a loss of this ideal arrangement and in the introduction of two bond oppositions. Consequently a change in co-ordination from 4 to 3 will be accompanied by an increase in internal strain and the reaction will be resisted.

Applying this interpretation to the corresponding ketones leads to the conclusion that *cyclo*hexanone should be relatively reactive, and *cyclo*pentanone and *cyclo*heptanone relatively inert.[16h]

In the middle rings the effects appear to be considerably larger with a maximum or minimum, depending upon the reaction type, observed in rings of 8- to 10-members.[16g, c] Because of the magnitude of the effect it is suggested that van der Waals deviations as well as bond oppositions are involved. Here again the strain will be relieved by loss of a bond. Consequently, reactions which proceed with a decrease in co-ordination number will be favoured; those which proceed with an increase in co-ordination number will be hindered.

The rate-determining step in free-radical reactions is usually the removal of a ring atom to form the free radical (change in co-ordination number from 4 to 3). The arguments used above should then apply to free radical reactions.[16l, m]

Bimolecular displacement reactions are more difficult. The pentaco-ordinate transition state will be similar to that involved in ionization reactions in having a 120° angle between the groups not involved in the displacement. Consequently, the effects on angle strain will be similar to that observed in ionization reactions. However, where bond opposition forces are involved the additional bond in the transition state may represent an additional factor in the opposite direction. Unfortunately, the experimental results for this type of reaction are relatively few. Those available suggest that the effects of ring size are similar to those observed in ionization reactions, but with smaller effects in the rings of 7 and 8 members than would be predicted from the results of ionization reactions. The available experimental results are summarized in Table 9.

TABLE 9. *Experimental data on the reactivity of ring compounds*: $[CH_2]_{n-1}\ C<$.

	S_N1		Ketone		S_N2			Free radical	
	Toluene-*p*-sulphonate	*tert*.-Chloride	Cyanohydrin formation K_{eq} (22—23°) [c]	Borohydride reduction	RI + I *	RBr + I^-		Decomp. of azonitriles	RH + CH_3
n	k_1 (70°) [a]	k_1 (25°) [b]		k_2 (0°) [d]	k_2 (25°) [e]	k_2 (25°) [f]	k_2 [g]	k_1 (80°) [h]	k_2 (182°)
3	—	—	—	—	—	no reaction (100°)		—	0·11
4	11·3	0·211	—	1·64	—	0·760	1·42 (90°)	0·0275	0·76
5	14·0	124	0·048	0·0435	—	161	5·68 (60°)	11·5	1·3
6	1·00	1·00	1·00	1·00	1·00	1·00	1·00 (90°)	1·00	1·00
7	25·4	108	0·0077	0·00634	140	98·5	—	194	—
8	191	286	0·0012	0·000485	33	19·1	—	1320	—
9	173	43·9	0·00059	0·000196	—	—	—	—	—
10	—	17·7	very small	0·000082	—	—	—	293	—
11	49·1	12·0	0·00089	0·000146					
12	3·25	—	0·0032	0·00113					
13	3·51	2·85	0·0039	0·00120					
14	1·32	—	0·017	—	—				
15	2·19	1·81	0·0091	0·00261					
16	—	—	0·011	—					
17	2·18	1·90	0·0083	0·00368					
18	—	—	0·010	—					
19	—	—	0·010	—					
20	—	—	0·014	—					

[a] Acetolysis in glacial acetic acid. First-order constant of *cyclo*hexyl ester at 70°, $k_1 = 2{\cdot}37 \times 10^{-5}$ sec.$^{-1}$. Ref. 16*e*. [b] Solvolysis of the 1-chloro-1-methyl*cyclo*alkanes in 80% ethanol. First-order constant of 1-chloro-1-methyl*cyclo*hexane at 25°, $k_1 = 0{\cdot}0106$ hr.$^{-1}$. Ref. 16*c*. [c] Equilibrium of the cyanohydrin formation in 96% ethanol. Calculated from the dissociation constants of cyanohydrins by Prelog and Kobelt. Dissociation constant of *cyclo*hexanone cyanohydrin at 22—23°: $K_{eq.} = [C_6H_{10}(OH){\cdot}CN]/[HCN][C_6H_{10}O] = 0{\cdot}1 \times 10^{-2}$. Ref. 16*g*. [d] Reduction of ketones with sodium borohydride in propan-2-ol. Second-order constants of *cyclo*hexanone at 0°: $k_2 = 161 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$. Ref. 16*f*. [e] Second-order constant of the reaction $RI + NaI^* \longrightarrow RI^* + NaI$ in ethanol. For *cyclo*hexyl iodide at 25°, $k_2 = 0{\cdot}0084 \times 10^{-2}$ c.c. mole^{-1} sec.$^{-1}$. Ref. 16*k*. [f] Second-order constant of the reaction, $RBr + LiI \longrightarrow RI + LiBr$, in acetone. For *cyclo*hexyl bromide at 25°, $k_2 = 0{\cdot}0129 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$. Ref. 16*j*. [g] Second-order constant of the reaction, $RBr + KI \longrightarrow RI + KBr$, in acetone. For *cyclo*hexyl bromide at 90°, $k_2 = 0{\cdot}0077$ l. mole^{-1} min.$^{-1}$. Ref. 16*i*. [h] Decomp. of azonitriles in toluene, $NC{\cdot}R{\cdot}N{:}N{\cdot}R{\cdot}CN \longrightarrow 2NC{\cdot}R{\cdot} + N_2$. First-order constant of the *cyclo*hexyl derivative at 80°, $k_1 = 0{\cdot}063 \times 10^{-4}$ sec.$^{-1}$. Ref. 16*m*. [i] Relative rates of the abstraction, by ${\cdot}CH_3$, of hydrogen atoms from *cyclo*alkanes, per active hydrogen. Ref. 16*l*.

It was pointed out that ring compounds contain strains arising from three different types of steric interaction. A change in co-ordination of a ring atom will greatly alter the magnitudes of each of these sources of strain. Ideally it would be desirable to be able to estimate each of these strains independently and to discuss each reaction in terms of its effects on each of these strains. Unfortunately, this is not possible at present. We can, however, estimate from both equilibrium and kinetic data the net change in internal strain accompanying the change in co-ordination of the ring atom. The term I-strain has been proposed as a convenient term for the sum total of the internal strains in ring systems arising from van der Waals compressions, bond-angles distortion, and bond opposition forces.

The results support the conclusion that I-strain is a very important factor in the reactions of ring compounds. It should, however, be understood that it cannot be the only factor. Obviously the use of a very bulky reagent will introduce F-strain effects which will vary with the ring size, and if sufficiently large might alter the order considerably from that predicted on the basis of I-strain. Similarly, if the change in co-ordination number of the ring atom is not involved in the rate-determining step, the I-strain theory cannot be applied to predict the effect of ring size on chemical reactivity. In spite of these limitations, the theory has proved very useful in systematizing the effects of ring size on chemical behaviour.

In conclusion I wish to point out that the Centenary Lecturer is requested to review the work of his research group in a given area. Needless to say the work I have presented has been made possible only by the co-operation of my very capable graduate students and associates. Moreover, in reviewing our own work, it has not been possible to pay adequate tribute to the numerous other workers who have, since 1940, completely altered the then prevailing opinion with regard to the importance of steric effects as a factor in chemical behaviour. In an effort to provide a proper perspective, the following outline of major developments in arriving at the present position is presented.

Outline of major developments in the study of steric effects.

I. Steric Forces.
    A. Atomic compressions : F. Kehrmann, 1889.
    B. Angle deformation : A. Baeyer, 1885.
    C. Bond oppositions : K. S. Pitzer, 1937; V. Shomaker, G. B. Kistiakowsky, 1939.

II. Steric Concepts.
    A. Steric hindrance : F. Kehrmann, 1889; V. Meyer, 1894.
    B. Steric assistance : H. C. Brown, 1946.

III. Application to Chemical Phenomena.
    A. Steric hindrance in aromatic substitution : A. F. Holleman, 1924; R. J. W. Le Fèvre, 1933.
    B. Hindered rotation in the diaryls : E. E. Turner and R. J. W. Le Fèvre, W. Mills, F. Bell, and J. Kenner, 1926.
    C. Steric hindrance in alkyl halides : M. Polanyi, 1932.
    D. Steric hindrance in *neo*pentyl derivatives : P. D. Bartlett, 1942; C. K. Ingold, 1946.
    E. Steric assistance in reactions of highly branched compounds : H. C. Brown, 1949.
    F. Angle strain in reactions of small rings : H. C. Brown, 1950.
    G. Bond oppositions in the chemistry of common rings : O. Hassell, 1942; K. S. Pitzer, 1945; P. D. Bartlett, 1951; H. C. Brown, 1951.
    H. Bond oppositions in the reactions of medium rings : V. Prelog, 1950.
    I. Bond oppositions in the reactions of steroids : D. H. R. Barton, 1950.
    J. Strain in the direction of elimination reactions : C. H. Schramm, 1950; H. C. Brown, 1953.

IV. Quantitative Approaches to Steric Effects.
    A. Activation energies in the racemization of diaryls : R. Adams, 1935.
    B. Dissociation of molecular addition compounds : H. C. Brown, 1944.
    C. Calculation of steric hindrance in *neo*pentyl derivatives : C. K. Ingold, 1946.
    D. Calculation of activation energy in diphenyl racemization : F. Westheimer, 1947.
    E. Quantitative treatment of rates : R. Taft, 1953.

It would be of little value to debate whether steric or polar effects are of greater importance to the organic chemist. Both factors are important and both factors must be utilized in developing a satisfactory understanding of the behaviour of organic substances.