QUARTERLY REVIEWS

QUANTITATIVE STUDY OF STERIC HINDRANCE.*

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BY the term " quantitative study ", as used in the title of this article, is meant the theoretical analysis of steric effects on reaction rate from first principles, in quantitative agreement with experimental determinations in a defined area, which could in principle be indefinitely extended. This is a distinct, and relatively new, phase in the study of steric hindrance, which started from purely qualitative ideas that were subsequently illustrated by many experimental measurements, but without any accompanying parallel in quantitative interpretation. A quantitative study succeeds only when observation and interpretation meet quantitatively. The transition from the qualitative to the quantitative study of steric hindrance was by no means a sudden process: it involved, and indeed depended largely on, a considerable intermediate development of chemical work and thought, the course of which will first be briefly outlined.

The general idea of steric hindrance, as an obstacle to reaction caused by the shielding of a reaction site by parts of the structure of a branched reactant, was established [1] in the 1890's. Thereafter, no advance was made towards greater precision of concept for more than 40 years. In retrospect one can see the reason for this long delay. Steric hindrance has to do with rate: it is a kinetic, not a thermodynamic, phenomenon. Therefore it must depend on reaction mechanism and not only on structure. And therefore its mode of operation could not be accurately described until reaction mechanisms had been sufficiently distinguished and defined.

During the 1930's, much of the necessary background knowledge of reaction mechanism was assembled. It became understood that any particular general reaction might have several available mechanisms, and that it would then use sometimes one and sometimes another, according to the structures of the reactants, and the conditions of reaction, particularly the electrochemical quality of the solvent medium. It was appreciated that steric conditions would affect alternative mechanisms very differently. And it became clear that steric effects on reaction rate would depend particularly

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[1] V. Meyer, *Ber.*, 1894, **27**, 510; 1895, **28**, 182, 1251, 2773, 3197; V. Meyer and J. J. Sudborough, *Ber.*, 1894, **27**, 1580, 3146.

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closely on the then unfamiliar geometry of transition states, and not alone on the well-understood geometry of normal molecules, in terms of which all previous attempts to consider steric hindrance had been made.

By 1940, a pattern in the incidence of steric hindrance was apparent.[2] The pattern depended partly on mechanism and partly on structure. Its broadest feature was related to mechanism, and was as follows.

It had been shown that a high proportion of the mechanisms used by the investigated general reactions of organic chemistry fall into either of two contrasting classes, called " unimolecular " and " bimolecular ", characterised respectively by dissociative and associative rate-controlling processes. These two types of mechanism tended to present themselves symmetrically. Thus nucleophilic substitution had two available mechanisms, one of each kind : the hydrolysis of carboxylic esters could proceed by any of six mechanisms, three of each kind ; and so on. Now whatever the reaction might be, these two classes of mechanism displayed a strong general distinction with respect to the exhibition of steric effects. The unimolecular mechanisms kinetically depend on dissociation. Hence the average density of matter in the neighbourhood of the reaction site must be decreased during the formation of the transition state. Therefore, there might be a local decrease of some pre-existing internal pressure ; and, even when we allow for the possible effect of geometrical changes accompanying the formation of the transition state, the average reduction of material density will secure that there can be no large net increase of pressure, or, more correctly, of potential energy due to pressure. Accordingly, unimolecular mechanisms, whilst they might show some degree of steric acceleration, cannot exhibit strong steric retardation. Bimolecular mechanisms, on the other hand, are rate-controlled by an associative process, in which the material density about the reaction site is increased in the transition state. It follows that bimolecular reactions will show a general susceptibility to substantial or large steric retardations.

Following this recognition of what was evidently the main feature of a pattern in the incidence of kinetic steric effects, survey work, mostly of a somewhat rapid and qualitative kind, designed to disclose the general character of the pattern more completely, was commenced, and has since been continued.

It has thus been found that, beneath the broad distinction, depending on the class of mechanism, finer but still notable differences arise, which are related to the type of molecular structure. For structure directly determines the geometry about the reaction centre in the initial state, whilst structure and mechanism together determine the corresponding geometry of the transition state ; and thus, for a given class of mechanism, the structural type of the substrate determines the geometrical alteration from the initial to the transition state, and so controls that rise or fall of internal pressure which produces the kinetic steric effect. For example, the reaction of nucleophilic substitution has essentially one unimolecular and one bi-

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[2] E. D. Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603 ; J. N. E. Day and C. K. Ingold, *ibid.*, p. 686.

molecular mechanism. In the unimolecular mechanism, the geometrical situations, and changes of situation, differ in the alkyl, aryl, and aralphyl series. And the differences make it possible to understand why, in the first two cases, closely situated groups may produce a mild acceleration,[3, 4] attributable to a net release of pressure on formation of the dissociative transition state; whereas in the third case, small retardations can be observed,[5] when the geometrical alternation produces new pressures overcompensating the dissociative pressure-release. Also in the bimolecular mechanism, the kinetically significant geometrical alterations are not the same in the alkyl, aryl, and aralphyl series.[5, 6, 7] And from the differences, we can understand why, although pronounced steric retardation is observed in all three cases, it is considerably stronger in the first case than in the others.

Such survey work is still being continued, because, even with restriction to the most important general reactions, available mechanisms, and structural types, the number of combinations requiring attention is quite large. Exploration over so wide a field is inevitably somewhat superficial and qualitative. But it constitutes indispensable preparation for the choice of particular local sites for that deeper penetration, which is to be illustrated in this article. There is no reason why, eventually, all the significantly different areas traversed by the survey should not be taken as sites for more intensive and more quantitative investigations. So far, however, only one small area has been thus exploited. This deeper type of study has been proceeding during the decade 1945—55, contemporaneously with extensions of the broad surface exploration mentioned already.

The chosen area was that of nucleophilic substitution by the bimolecular mechanism in alkyl structures, S_N2 alkyl substitutions, as we may call them for brevity. Long before this work was undertaken, a rough analysis of the relevant geometrical situation had led to certain surprising conclusions [7]—surprising in the sense that, whilst they were derived by disciplined reasoning, the old intuitive approach would describe them as nonsense. One such conclusion was that, in S_N2 alkyl substitutions, steric hindrance may increase when the seat of substitution is moved away from the branching-point of the structure, as on passing from a *tert.*-butyl to a *neo*pentyl halide, in contrast to Victor Meyer's experience with the esterification of *ortho*-substituted benzoic and phenylacetic acids. Another was that although steric hindrance would be highly dependent on the form of the alkyl group, it would be nearly independent of the size of the introduced group: a large group would go into a sterically restricted site about as easily as a small one. It may be doubted whether these predictions, which were recorded, were at all widely

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[3] F. Brown, T. D. Davies, I. Dostrovsky, O. J. Evans, and E. D. Hughes, *Nature*, 1951, **167**, 987.

[4] M. L. Crossley, R. H. Kienle, and C. H. Benbrook, *J. Amer. Chem. Soc.*, 1940, **62**, 1400.

[5] J. C. Charlton and E. D. Hughes, *J.*, 1956, 850, 855.

[6] H. Cohn, E. D. Hughes, M. H. Jones, and M. G. Peeling, *Nature*, 1952, **169**, 291.

[7] E. D. Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603; I. Dostrovsky and E. D. Hughes, *J.*, 1946, 157 *et seq.* (7 papers).

believed; but they have since been verified experimentally, and quantitatively rationalised theoretically. Moreover, investigation has disclosed several other equally non-intuitive, but rationally accountable phenomena, which were in principle foreseeable, but were actually unforeseen. Attention will be directed to these points as they arise.

The examples of substitution[8] employed were Finkelstein reactions of the form

$$Y^- + RX \longrightarrow RY + X^-$$

where X and Y are isotopically or chemically different halogens, and R is alkyl. Acetone was the solvent, because, for a number of combinations of halogens, it has adequate solvent properties, and also because, in acetone, the reactions use the bimolecular mechanism exclusively, or almost exclusively, over a wide range of alkyl structures.

An investigation of this type necessarily has the character of a pincer movement, dependent on converging experimental and theoretical attacks. We may notice first the experimental observations.

The range of these is indicated by the rate data in Table 1. Seven of the nine Finkelstein substitutions that involve chlorine, bromine, and iodine have been examined. With these reactions, the seven simplest alkyl groups that can provide complete series typifying α- and β-branching homology have been studied.

TABLE 1. *Range of observations on* S_N2 *Finkelstein exchanges in acetone*

α-Methylated branched-homologous series: Me, Et, Pr^i, Bu^t.
β-Methylated branched-homologous series: Et, Pr^n, Bu^i, *neo*Pe.
(The figures represent 10^5k_2 at 25°, with k_2 in sec.$^{-1}$ mole^{-1} l.)

Reactants. . .	Me	Et	Pr^i	Bu^t	Pr^n	Bu^i	*neo*Pe *
$Cl^- + RCl$	3·9	0·050	—	—	—	—	—
$Cl^- + RBr$	600	9·9	0·13	0·029	6·4	1·5	0·00026
$Cl^- + RI$.	470	42	1·3	—	25	1·6	0·00058
$Br^- + RBr$	13,000	170	1·8	0·51	110	5·7	0·0026
$Br^- + RI$.	27,000	1490	37	—	1050	32	—
$I^- + RBr$	25,000	170	1·3	0·10	140	6·0	0·0020
$I^- + RI$.	—	6000	53	18	—	—	0·11

* *neo*Pe = *neo*Pentyl

Every rate is in principle a product of two factors, as expressed in the Arrhenius equation, $k = Be^{-E/RT}$, or $\log_{10} k = \log_{10} B - E/4{\cdot}575T$. A frequency factor, alternatively called an entropy factor, B, is multiplied into an energy factor, $\exp(-E/RT)$, dependent on the activation energy, E. The next experimental task is, then, to split up each rate into its constituent factors in the well-known way, which uses the circumstance that only the energy factor contains the temperature explicitly.

Any consideration of structural effects on a measurable property has to

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[8] P. B. D. de la Mare, L. Fowden, E. D. Hughes, C. K. Ingold, and J. D. H. Mackie, *J.*, 1955, 3169 *et seq.* (8 papers).

be relative : we can discuss only the effects of changes of structure. Therefore, in order to consider structural effects on the rates and their separate factors, we have to choose a structural standard of reference. For these reactions, the convenient standard is that provided by the methyl case. Therefore, the experimental rate factors are treated on this basis.

As regards the energy factor, the convention involves subtracting the methyl activation energy from all the other activation energies for each reaction. One then obtains the series of energy excesses, ΔE, recorded in Table 2. They represent structural effects on activation energy, effects which it should be possible to discuss theoretically.

TABLE 2. *Observed increments* ΔE *of activation energy (kcal./mole) for* S_N2 *Finkelstein substitutions in acetone*

Reactants	Me	Et	$\mathrm{Pr^i}$	$\mathrm{Bu^t}$	$\mathrm{Pr^n}$	$\mathrm{Bu^i}$	*neo*Pe
$Cl^- + RCl$ . .	0·0	1·3	—	—	—	—	—
$Cl^- + RBr$ . .	0·0	1·9	2·9	5·3	2·1	2·6	6·0
$Cl^- + RI$ . .	0·0	1·2	1·6	—	1·4	1·8	5·0
$Br^- + RBr$ . .	0·0	1·7	3·9	6·0	1·7	3·1	6·2
$Br^- + RI$ . .	0·0	1·4	2·2	—	1·6	2·5	6·9
$I^- + RBr$ . .	0·0	2·6	4·2	6·9	2·7	3·6	7·9
$I^- + RI$ . .	0·0	1·7	3·7	5·7	—	—	6·5

It is to be observed that these experimental excesses of energy, ΔE, show irregular scatter, but no general trend, as smaller halogens are replaced by larger ones. On the other hand, they exhibit a common pattern of strong variation among the alkyl groups, rising throughout the α-methylated series, Me, Et, $\mathrm{Pr^i}$, $\mathrm{Bu^t}$, and rising also, but at first scarcely perceptibly, and then with progressively increasing steepness, along the β-methylated series, Et, $\mathrm{Pr^n}$, $\mathrm{Bu^i}$, *neo*Pe. The activation energies for *neo*Pe are a little higher than for $\mathrm{Bu^t}$.

Treating the frequency factor similarly, one subtracts the methyl values of $\log_{10} B$ from all the other values of that quantity, thus obtaining a series of experimental differences, which we call increments, although they are all negative apart from a few zero values. They are in Table 3. They represent structural effects on the logarithm of the frequency factor, or, what is the same thing apart from a scale change, on the activation entropy ; and it should be possible to treat them theoretically.

The general features of these figures also may be noted. First, they show some scatter, but no general trend, as smaller halogens are replaced by larger ones. Secondly, they show a pattern of variation among the alkyl groups, which is uniform, and is striking. For along the first three members of the α-methylated series, Me, Et, $\mathrm{Pr^i}$, $\mathrm{Bu^t}$, the figures progressively fall ; and then, in the last member, they return to, or nearly to, their starting value. In the β-methylated series, Et, $\mathrm{Pr^n}$, $\mathrm{Bu^i}$, *neo*Pe, the figures fall throughout. The frequency factors for *neo*Pe are thus lower than for $\mathrm{Bu^t}$.

This is as far as purely experimental work has proceeded in the development of its particular contribution to the investigation.

TABLE 3. *Observed increments $\Delta \log_{10} B$ in logarithms of frequency factors for S_N2 Finkelstein substitutions in acetone*

Reactants. . . .	Me	Et	Pr^i	Bu^t	Pr^n	Bu^i	*neo*Pe
Cl^- + RCl . .	0·0	− 0·8	—	—	—	—	—
Cl^- + RBr . .	0·0	− 0·4	− 1·4	− 0·4	− 0·7	− 0·9	− 1·9
Cl^- + RI . .	0·0	− 0·3	− 1·1	—	− 0·6	− 1·1	− 1·5
Br^- + RBr . .	0·0	− 0·6	− 1·0	± 0·0	− 0·9	− 1·1	− 2·1
Br^- + RI . .	0·0	− 0·3	− 1·2	—	− 0·6	− 1·1	− 1·3
I^- + RBr . .	0·0	− 0·4	− 1·2	− 0·3	− 0·6	− 1·1	− 1·2
I^- + RI . .	0·0	− 0·5	− 1·0	± 0·0	—	—	− 1·8

Theoretical study starts from the established model of the S_N2-alkyl transition state: the semi-ionic half-bonds, which hold the entering and departing groups to the seat of substitution in the transition state, extend outwards one on each side of a plane which contains those three bonds whose originally pyramidal configuration is to be inverted in the reaction. This is, of course, a general and qualitative model: it does not, at this stage, prescribe the exact configuration of any transition state.

Therefore the basic task of preparation for a theoretical treatment of kinetic structural effects on any of the reactions under consideration is to calculate, for a series of assumed atomic configurations believed to be near that of its transition state, the energy required to build each such configuration out of the reactants. For each adopted configuration one must calculate the energy needed to stretch the carbon–halogen bond to give the assumed atomic separation, the energy required to push the halide ion against the α-carbon atom to the assumed distance, that needed to push both halogens against the parts of the alkyl groups on which they must be pressing, that needed to bend certain bonds, and so on; and one must add the necessary items of energy together, so getting a total for the production of the assumed atomic configuration; and, after many such calculations, for various assumed configurations, the total as a function of configuration. With a wise choice of assumed configurations, a function will have been described which has an energy minimum at one particular configuration: this represents the transition state. In graphical terms, we may say that an " energy surface " has been constructed, the spatial and energy co-ordinates of the lowest point of which give the configuration and the energy of the transition state. Such a calculation must be carried through for each individual reaction, that is for each combination of halogens, and each alkyl group.

The mathematical apparatus consists only of three approximate but well-tested formulæ of the simplest possible type, one for bond-stretching, one for bond-bending, and one for non-bonding compression potentials. All the constants in these formulæ are either universal, or else are given by established values for certain mechanical, thermal, and optical properties of standard substances. No disposable constant is introduced at any point in the construction of these energy surfaces.

The simplest use to which one can put these surfaces is to read off from them the configurations and energies of the transition states. As an illustration of calculated transition-state configurations, the iodine positions in the transition states of the iodine exchange reaction are given in Table 4, in terms of the lengths and angular directions of the carbon–iodine bonds. All carbon–halogen bonds are stretched in the transition states, some more than others, because of the differing pressures of the different alkyl groups. Except in the methyl and *tert.*-butyl transition states, which are trigonally symmetrical about strictly linear halogen–carbon–halogen bonds, all carbon–halogen bonds are bent, those of *neo*pentyl transition states being bent quite strongly.

TABLE 4. *Calculated iodine positions in transition states of the reaction*
$I^- + RI \rightarrow IR + I^-$

R	Excess of length of each C · · · I half-bond (Å)	Bending angle of I · · · C · · · I bond
Me	0·36	0·0°
Et	0·37	3·8°
Pr^i	0·38	5·0°
Bu^t	0·40	0·0°
Pr^n	0·37	3·8°
Bu^i	0·39	5·0°
*neo*Pe	0·43	17·6°

The calculated energies of transition states in excess of that of the methyl transition state, or, in other words, the calculated steric increments of activation energy, which will be symbolised ΔW_s, are exemplified for the three exchange reactions with like halogens in Table 5. It will be observed that, as smaller halogens are replaced by larger ones, the calculated steric increments of energy are changed only slightly, and not always in the sense that might intuitively have been expected: some values become reduced. But as the alkyl groups are changed, the energies show a strong variation of uniform pattern. Throughout the α-methylated series the values rise. Along the β-methylated series they first remain constant, and then rise with progressively increasing steepness. The relations shown by these calculated values not only follow the lines of the early qualitative predictions, but also reproduce some of the general features of the activation energies later found by experiment.

TABLE 5. *Calculated steric contributions ΔW_s to energy of activation of S_N2 Finkelstein substitutions*

R	Me	Et	Pr^i	Bu^t	Pr^n	Bu^i	*neo*Pe
$Cl^- + RCl$	0·0	0·8	1·6	2·8	0·8	2·1	6·5
$Br^- + RBr$	0·0	0·8	1·6	2·5	0·8	2·3	7·3
$I^- + RI$	0·0	0·7	1·3	2·0	0·7	2·5	7·8

(The figures are in kcal./mole)

What has been calculated here is the steric increment of activation energy ΔW_s. As yet no practicable method has been devised for calculating from first principles the polar contribution ΔW_p. Therefore the only way forward from this point is by comparing the experimental values ΔE with the calculated values ΔW_s, and noting whether any differences that are left to represent ΔW_p fall into the correct pattern for a polar effect. It is found that they do, in two characteristic ways. First, the differences are exclusively correlated with α-alkyl substitution : β-alkyl substitution does not produce appreciable differences. This is the correct molecular distribution for a weak polar effect in an insulating system, and it would be incorrect for a steric effect. Secondly, the differences approximately obey an additive free-energy relation, such as is widely fulfilled by polar effects when they can be observed unmixed with steric effects. These two simplifying relations, together with the close electrochemical similarity of the halogens, make it possible to represent by a single rounded value, 1·0 kcal./mole, the energetic polar effect of any α-alkyl substituent in any alkyl group and for any Finkelstein substitution, and thus to compute, with this one empirical constant, the whole set of forty-nine ΔW_p values.

When the ΔW_s and ΔW_p values are added, totals are obtained which are in generally good agreement with the experimental ΔE values, though the agreement is only fair in the example of the *neo*pentyl group. The poorer concordance obtained in this last case can be understood, inasmuch as the calculation of ΔW_s is subject to a maximum of error here, and is expected to lead to high values. The numerical situation is illustrated in Table 6. The specific example given is the bromine-exchange reaction. A more general, but equally compact illustration is made possible by the close similarities, and absence of trend, among the calculated values, and equally among the observed values, when the halogens are changed ; and this

TABLE 6. *Calculated and observed effects of alkyl structure on energies of activation (kcal./mole) of* S_N2 *Finkelstein substitutions*

R	Me	Et	Pr^i	Bu^t	Pr^n	Bu^i	*neo*Pe
Reaction : $Br^- + RBr \longrightarrow BrR + Br^-$							
ΔW_s	0	0·8	1·6	2·5	0·8	2·3	7·3
ΔW_p	0	1·0	2·0	3·0	1·0	1·0	1·0
ΔE (calculated). .	0	1·8	3·6	5·5	1·8	3·3	8·3
ΔE (observed) . .	0	1·7	3·9	6·0	1·7	3·1	6·2
Differences . . .	0	+ 0·1	− 0·3	− 0·5	+ 0·1	+ 0·2	+ 2·1
Average of all investigated reactions							
ΔW_s	0	0·8	1·5	2·4	0·8	2·3	7·2
ΔW_p	0	1·0	2·0	3·0	1·0	1·0	1·0
ΔE (calculated) .	0	1·8	3·5	5·4	1·8	3·3	8·2
ΔE (observed . .	0	1·7	3·1	6·0	1·9	2·7	6·6
Differences . . .	0	+ 0·1	+ 0·4	− 0·6	− 0·1	+ 0·6	+ 1·6

illustration is given in the Table as a comparison of the averages of the calculated, with the averages of the observed values, for all the reactions studied.

The second use to which the computed energy surfaces have been put is in the calculation of the frequency factors of reaction rate. The logarithm of a frequency is the entropy of activation, except for possible (and optional) changes in the zero and the units of entropy ; and the entropy of the transition state depends fundamentally on these energy surfaces, but on their geometrical form rather than on their energetic height.

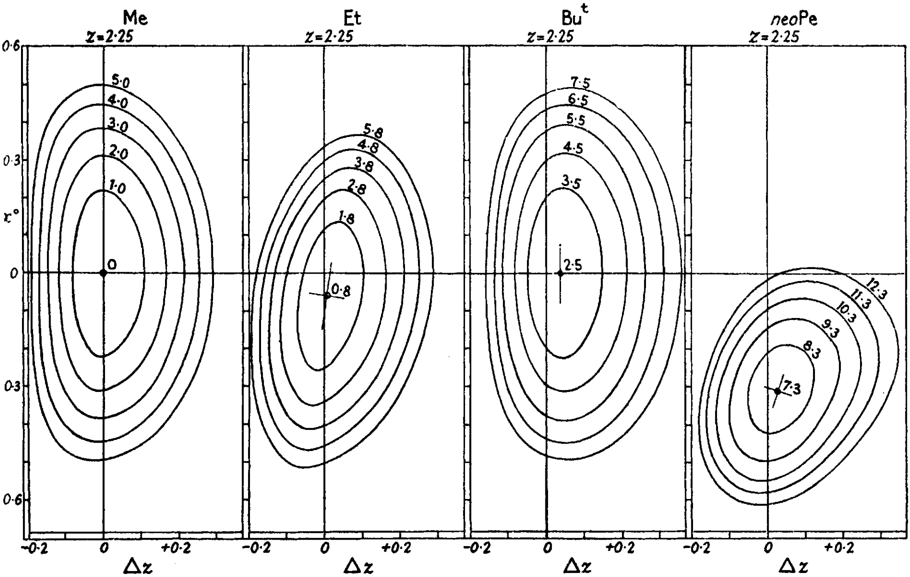

FIG. 1

Calculated Energy Surfaces for Reactions $Br^- + RBr \longrightarrow BrR + Br^-$.—The four basket-shaped surfaces are for R = Me, Et, Bu^t, and *neo*Pe. The figures against the contours are energies in kcal./mole, reckoned from the lowest point of the methyl surface as zero. The horizontal co-ordinate axis is the line through C_α normal to the plane of the three preserved C_α bonds in the transition state. The intersections of co-ordinates mark the calculated halogen positions in transition states in the absence of steric hindrance, and the dots their calculated positions in its presence. The relative heights of the bottoms of the energy baskets represent the steric contribution to energy of activation, and the relative widths of the baskets the steric contribution to the entropy of activation.

Each surface has the general form of a basket. To employ a simile, the reagent and the expelled group can be considered to be engaged in a game of basket-ball with these energy baskets. The lower the baskets are, and the wider they are, the more frequently they will be entered with production of a transition state. Their height, which represents energy, has been dealt with. The present question is that of their wideness, which represents entropy.

These basket-shaped surfaces are exemplified in Fig. 1, with reference to four alkyl groups in the bromine-exchange reaction. The groups are selected to illustrate the peculiar manner in which steric conditions influence the frequency factor of rate: the sign of the effect is largely conditioned by symmetry.

These contour diagrams obviously reflect the fact that the *tert.*-butyl transition state retains the axial symmetry of the methyl transition state, whereas the ethyl and *neo*pentyl transition states show progressive degrees of departure from such symmetry. Now it will be noted that the *tert.*-butyl basket is wider than the methyl basket, particularly in the axial direction (abscissæ), whereas the ethyl and *neo*pentyl baskets are narrower in successive degrees, particularly in the transverse direction. The reason why the *tert.*-butyl basket is wider is that steric pressure is here directly outwards, and that the forces in the bonds, thereby stretched, are weakened, with the result that the energy gradients become less steep, and the basket becomes shallower and more open. Uniquely in this case, there is no lateral pressure, and no bond-bending strain, to counter this effect by squeezing the sides of the basket together laterally. On the other hand, in the ethyl case, and still more in the *neo*pentyl case, the steric pressure is predominantly sideways; and thus the baskets are caught between such pressure on the one side and the steepening wall of a bending potential on the other, with the result that the sides become steeper, and the baskets narrower. Thus we see that steric pressure, according to its direction, may have either an accelerating or a decelerating effect on the frequency factor of rate. And the directional distribution of the effect is one which intuition would describe as absurd, inasmuch as a steric thrust which pushes the reagent directly away is accelerating, although one which only deflects it sideways is retarding.

For purposes of score-keeping, it is to be noted that this game of basketball is played, not under Newtonian rules, but under quantum rules; and so we have to estimate the wideness of our baskets, not by classical measurement, but by quantum counting. It is necessary to count the Boltzmann-weighted number of energy levels that the baskets contain; for it is this number which, under quantum rules, determines their receiving-capacity, which we express in the form of its logarithm as their entropy.

However, as soon as one begins to compute receiving-capacities in this way, one realises that they depend, not only on the geometry of the energy surfaces, but also on the masses and their distribution in the involved kinetic particles. As is well known, a given energy hollow will provide more energy levels for a heavy particle than for a light one, the increase representing a step towards the limit of an energy continuum at infinite mass, as is required by Bohr's correspondence principle. This simple consideration leads to the recognition of a class of structural effect on reaction rate which has not before been comprehensively considered. It is neither steric nor polar. It has been termed " ponderal ", because it depends on mass, independently of any space-filling qualities which the massive group may possess, and independently of any distribution of charge which it may carry. Neutrons, having mass but no bulk and no charge, added, as they could be, by an isotopic substitution, would produce a pure ponderal kinetic effect.

So structural kinetic effects have to be given a three-fold classification. The ponderal effect depends on the presence and distribution of mass, the steric effect on those of bulk, and the polar effect on those of charge. It cannot be doubted that appreciable ponderal effects on reactions have frequently passed unnoticed in admixtures with steric or polar effects.

In principle, ponderal, steric, and polar effects influence both the energy and the entropy factor of rate. But in the present problem, because the involved particles are relatively heavy, it is possible to neglect, as has been done, the ponderal effect on the energy factor. Also, because alkyl substituents are only weakly polar, it is permissible to neglect the polar effect on the entropy factor, and consider only the ponderal and steric contributions. The ponderal contribution is given by the energy levels which would be available in case steric pressure did not deform the energy surface. The total entropy effect depends on the energy levels actually available in the surface as deformed. But by calculating the ponderal contribution first, we isolate the steric effect, which was the original subject of study. The formulæ required for making these weighted counts of energy levels are simple and are standard in statistical mechanics.

These ponderal and steric contributions to the entropy of activation ΔS are illustrated for the bromine-exchange reaction in Table 7. For the moment the figures are presented in thermal units rather than in terms of frequency factors.

TABLE 7. *Calculated structural contributions* ΔS *to the entropy of activation of the reaction* $\mathrm{Br}^- + \mathrm{RBr} \rightarrow \mathrm{BrR} + \mathrm{Br}^-$

R	Me	Et	Pr^i	Bu^t	Pr^n	Bu^i	*neo*Pc
Ponderal . .	0·00	− 1·45	− 2·30	− 1·95	− 2·64	− 3·66	− 4·39
Steric . . .	0·00	− 0·66	− 1·52	+ 0·83	− 0·67	− 1·06	− 1·86
Total. . . .	0·00	− 2·11	− 3·82	− 1·12	− 3·31	− 4·72	− 6·25

(The figures are in cal. deg.$^{-1}$ mole^{-1})

The ponderal effect of an added mass is usually retarding, as the negative signs in the Table indicate. The ponderal effect might conceivably be mistaken for a steric effect in respect of this prevalent result of the presence of mass, but not in respect of the further regularity, now to be mentioned, which relates to the distribution of mass. As may be seen by comparing isomers, an added mass is usually more strongly retarding the further off it is from the reaction centre. Elementary intuition might have led one to the first of these rules, but certainly not to the second. Analytically, the approximate reason underlying the rules is that a given addition or separation of masses will produce a greater relative enrichment of the system of energy levels of the initial molecule than of the originally more inertial transition state ; but, actually, the effects of mass distribution are so complicated that the rules themselves are subject to exceptions.

As to the steric entropy effect, the figures confirm the qualitative deductions made from the shapes of the energy surfaces. As the single positive sign shows, this steric effect is accelerating for the *tert.*-butyl group, for which the steric thrust is outward, but retarding in all the other cases, in which it is predominantly sideways.

By adding the contributions, it is found that the total entropy effect is always retarding, least so for the *tert.*-butyl group, and most for the *neo*pentyl group.

The relation between entropy in thermal units and the frequency factor of rate is $\Delta \log_{10} B = \Delta S/4{\cdot}575$; and so, after this simple change of scale, comparison can be made with experiment. The comparison is illustrated in Table 8, first, specifically for the bromine-exchange reaction, and secondly, with the observed averages of all the reactions investigated.

TABLE 8. *Calculated and observed effects of structure on log$_{10}$ B for bimolecular Finkelstein substitutions*

	Me	Et	Pr^i	Bu^t	Pr^n	Bu^i	*neo*Pe
Obs. (Br exchange)	0·0	– 0·6	– 1·0	+ 0·0	– 0·9	– 1·1	– 2·1
Calc. (Br exchange)	0·0	– 0·46	– 0·84	– 0·24	– 0·72	– 1·03	– 1·37
Obs. (average) . .	0·0	– 0·5	– 1·1	– 0·2	– 0·7	– 1·1	– 1·6

It will be seen that the agreement is good in general. Indeed, except for the *neo*pentyl group, it is within the allowable error of the experimental determination of $\log_{10} B$, which could be as high as $\pm 0{\cdot}2$. Again the poorer agreement obtained for the *neo*pentyl group can be understood, inasmuch as the errors of calculation are considerably greater here than elsewhere, and are expected to produce a deviation in the observed direction. It should be noted that no disposable constant is introduced at any point in these entropy calculations : the formulæ used involve only independently established constants.

The final theoretical step is to combine the calculated energy and entropy factors, in order to see how well their combination matches the observed rates. This is done comprehensively by the diagram in Fig. 2, in which the vertical scales of ΔE, $\Delta \log B$, and $\Delta \log k$ (for 25°) are so adjusted as to show directly the relative importance of energy and entropy in the determination of rate : by subtracting the ordinates of the plot of ΔE from those for $\Delta \log B$, one obtains those for $\Delta \log k$. The lines for the α-methylated series (full), and for the β-methylated series (broken), are both theoretical in a dual sense : they join, first, points calculated for the bromine-exchange reaction, and secondly, mean points for all the reactions, since these are so close to the bromine-exchange points that they cannot be shown separately. The crosses mark the observed points for the bromine exchange, and the circles mark mean observed points for all the reactions. Except as regards the *neo*pentyl group, the pattern of observed effects is rather closely reproduced by the calculations, which, moreover, enable its principal features to be understood, for instance, the only slightly slower reactions of the *tert.*-butyl than of the *iso*propyl group, and the much slower reactions of the *neo*pentyl group than of any other group, even *tert.*-butyl.

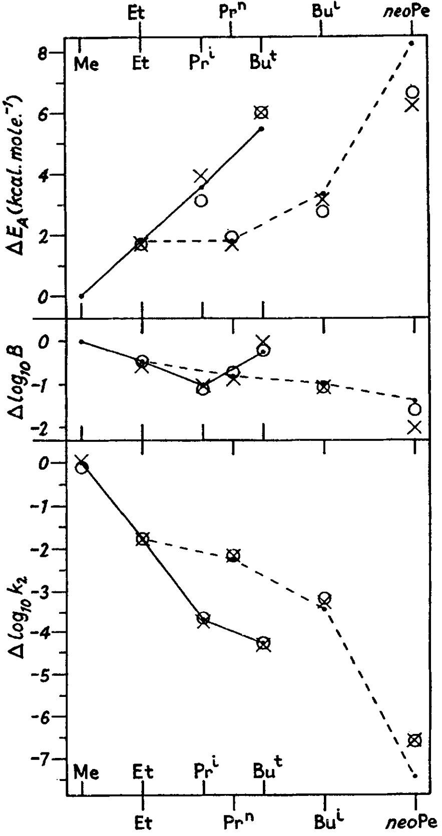

FIG. 2

Calculated and observed effects of alkyl structure on the energetic and entropic rate factors, and thence on the rates of Finkelstein substitutions. (For further explanation see the text.)

As a more numerical form of comparison, the observed and calculated rates for the bromine-exchange reaction are given in Table 9. Most of the calculated figures are good to within a factor of 2, though the *neo*pentyl factor is 5, which constitutes the limit of disagreement over the full rate-range of 5,000,000.

These comparisons show the extent to which the pincers have closed on this problem. Greater precision in the application of each of the complementary arms would be possible, but laborious. However, since a somewhat approximate analysis of the influence of structure on rate in a particular system has revealed so many general effects, which intuitive

Table 9. *Observed and calculated structural effects on rates at 25° of the reaction* $\mathrm{Br^- + RBr \longrightarrow BrR + Br^-}$ *in acetone*

	Me	Et	$\mathrm{Pr^i}$	$\mathrm{Bu^t}$	$\mathrm{Pr^n}$	$\mathrm{Bu^i}$	*neo*Pe
Obs.	1	0·013	0·00014	0·000039	0·0085	0·00044	0·00000020
Calc.	1	0·017	0·00035	0·000053	0·0090	0·00035	0·000000037

considerations would not have disclosed and would even have tended to conceal, it does seem that similarly approximate analyses for other types of structure, other reaction mechanisms, and other general reactions, would be more likely to produce a harvest in otherwise inaccessible conclusions of general interest, than would any attempt to secure markedly increased precision.