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EVALUATION OF THE EFFECT OF STRAIN UPON REACTIVITY

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CONTENTS

Ii. *Introduction and scope of the Report*

An old-fashioned veterinary treatment for deep gashes in the flesh of large farm animals, as reported in a popular autobiographical series,[1] involves packing the wound with iodine and then soaking it in turpentine. This produces a vigorous reaction[2] attributed to the exothermic process involving addition of iodine to the carbon–carbon double bond of α-pinene and subsequent rearrangement of the resulting cyclobutonium carbocation. Simple alkenes are, of course, inert to iodine.

This observation is typical of many thousands of anecdotal observations in the literature which purport to relate reactivity changes to the effects of strain, or more loosely, steric effects. It is the purpose of this report to review the attempts that have been made to make quantitative relationships between what will be called strain (defined below) and reactivity. "Reactivity" will be employed in the kinetic sense and hence the effect of "strain" is to be identified as an effect connected with the energy difference between the ground states of reagents and the transition state energy for the reaction under consideration. It is not a review of steric effects in general and in spite of the fact that very many reactivities have been carefully quantified by kineticists over many decades, very few comparisons have been made between systems for which strain energy differences are accurately known. The paucity of data is due to the lack of comparisons made between systems of known energy. Such energies are derived experimentally either from thermochemical measurements on the one hand, or from calculations on the other. The last two decades have seen substantial decline in the number of thermochemical determinations, but this decline has been complemented by a rapid increase in the calculation of energies of molecules or transition state models by molecular mechanics (empirical),[3,4] MNDO methods[5] or even *ab initio* (SCF)[6] methods.

A further restriction of the scope of this review imposed by the reporter is that effects which produce small changes in reactivity are in general neglected because of the difficulty of interpretation. For even simple molecules in solution, differences of solvation[7] may be responsible for differences in effective ground state energies of 1–2 kcal mol^{-1} and it is the reporter's firm belief that only substantial effects merit interpretation.

What emerges from a quantitative study of the relationship between strain and reactivity is either, on the one hand, an estimate of the nature of the transition state for the process or, on the other, identification of failure to accord with a relationship between strain and reactivity and hence the identification of processes occurring other than those considered when evaluating the relationship. The former approach has been particularly used by the reporter and his group using thermochemical strain energies in cyclic systems and relating the strain energies to the reactivities of such systems. The latter approach has been particularly used by Schleyer and his collaborators in, for example, the identification of the involvement of processes other than simple ionisation in solvolytic reactions. Molecular mechanics calculations can now be performed on certain types of system with great accuracy[8-10] and the prediction of reactivities in such systems is now becoming increasingly possible.

iii. *Background*

Comments in the literature relating to the obstruction of access of one reagent to another date back to Hoffmann[11,12] and "steric effects" are used like patriotism by a scoundrel as the last refuge of those who have difficulty in interpreting reactivities. The reason for this is not far to seek; there is a great lack of quantitative data on steric energies and hence guesses about the quantitative incursion of steric effects are difficult to criticise because critics lack a quantitative basis for comment. This situation is all the more disappointing because there is no doubt that, next to electron delocalisation, "steric effects", have the largest influence on the reactivity of organic substrates. Ten powers of ten is by no means the largest reactivity difference which can be directly ascribed to the effect of strain, and against this background therefore, small effects will be passed over with very brief mentions only.

The first serious studies of the quantitative effect of strain energy on reactivity were initiated nearly forty years ago on the experimental side by H. C. Brown's group at Wayne and Purdue[13] and by Ingold and his collaborators in London.[14] On the theoretical side, Westheimer,[15] at Harvard, made the first proper dissections of strain energy into its components and suggested how proper calculations of strain energies should be conducted.

In H. C. Brown's consideration of strain, particular attention was paid to three types of strain, the labels for which have passed into the qualitative vocabulary of steric effects. These are: F (forward) strains resulting directly from the interaction between two reagents or, in a dissociation (below), the interaction of *residuum*[16] and leaving group. The second, B (back) strain, is that which results from changes in the structure of a reagent when it enters into reaction, a typical example being the increased non-bonded interaction between alkyl groups in a tertiary amine upon quaternisation. The third type of strain, I (internal), is specific to ring systems and results from the strain engendered by hybridisation changes consequent upon reaction. Typical examples are nucleophilic substitution in cycloalkyl halides and the reduction of cyclic ketones.

The effects upon reactivity that were identified by Brown and his collaborators were quite substantial, spanning ranges of up to 10^6 in reactivity. Brown's data are nearly all in terms of relative reactivity and the energetics were generally not dissected into enthalpy and entropy components. Furthermore, there was no attempt to evaluate the energy change incurred on passing from ground state to the transition state with suitable models. Strain was clearly a very important factor in reactivity differences but the connection between strain energies and activation energies could not be made. Notwithstanding, Brown's work in this area has provided organic chemists with a qualitative language with which to discuss steric effects and a qualitative basis of comparison between systems.

At around the same time, Ingold and his collaborators[14] undertook the first calculations of the energies of transition states in nucleophilic substitution in simple aliphatic systems, and related the results to the reactivity of alkyl halides, putting on a quantitative basis for the first time the reactivity of, for example, neopentyl halides. These calculations were admittedly imprecise and restricted in their generality. The model for the activated complex was that in which nucleophile and leaving group were co-linear and covalent bond radii of the ligands attached to the penta-coordinate carbon in the transition state were used. The steric strains calculated in this way correlate broadly with the steric strains as determined experimentally by the difference in energy of activation increments from methyl in passing along the sequence methyl, ethyl, n-propyl, *iso*-butyl, neopentyl[15] (Table 1).

It is the development of such calculations, notably in the hands of Westheimer[15] and those who have followed after him that have put the calculation of steric effects on a proper basis and has been the foundation of modern connections between calculated quantities and experimental reactivities—Allinger's review[3] of the application of molecular mechanics to the predictions of reactivity particularly

Table 1. Steric strains and reactivities for the reaction: RBr + OEt → ROEt + Br

	R –				
	methyl	ethyl	n-propyl	*iso*-butyl	neopentyl
Relative rates at 55°	17.6	1	0.028	0.030	0.0000042
E_a (kcal mol $^{-1}$)	20.0	21.0		22.8	26.2
Steric strain (kcal mol $^{-1}$)	0.0	1.0	-	2.8	6.2
Calculated (with C—Br stretching)	0.0	0.7			11.7

in solvolyses, lactonisation, and nucleophilic substitution gives a useful survey of work in this area.

This report will also comment on the *absence* of steric strains upon reactivity. We shall see (below) that in many instances in which the influence of steric strains might be expected to be very marked, notably in cyclisation reactions, they are absent.

There have been very many reviews of strain, some dealing in a general way with strained molecules; notable recent examples are those of Greenberg,[17] Liebman[18a] and Tidwell.[18b] These, however, do not deal with the relationship between strain and reactivity. Likewise there have been many reviews of "steric effects" and their influence on reactivity, but without connecting reactivity with steric energies quantitatively.[19,20]

This review brings together those reports in which at least some quantitative connection is made between measured reactivities and strain energies derived either experimentally with identifiable assumptions, or from calculations.

Iiii. *Definition of strain*

It is important to define the term because the evaluation is affected by the definition. (For example cyclohexane may be referred to as "strainless".[20]) Strain can be regarded as a net unfavourable energy[21] but if the definition is "that energy, allowing for conformational mixing by which the molecule differs from the n-alkane, correcting for chain-branching" is applied,[22] then cyclohexane is strained by 1.35 kcal mol $^{-1}$ and values are temperature variable.[23] Strain is to be regarded as a composite of angle strain, torsional strain, bond extension strain, and non-bonded interactions. It is clear (below) that these factors may contribute to reactivity variations with very different weightings according to the natures of transition states. The definitions are the bases of calculations and connections between them are well made in a later review.[9] Similar summaries have been provided by Page.[24]

Iiv. *Calculations of molecular energies and evaluation of strain*

The overwhelming majority of calculations of molecular energy which are relevant to making the connection between strain and reactivity have emerged from molecular mechanics. It is not within the scope of this report to review in any detail the validity and assumptions of such calculations; recent reviews deal with the nature and bases of calculations.[9,25a] A comprehensive basis for force-field calculations has been provided.[8] Essentially, results for molecular energies are obtained by using a set of reference molecules whose energies are known from thermochemical data. The effects of perturbation of these reference structures in terms of bond lengths and angles is then calibrated from other thermochemical data and the information thus provided allows derivation of molecular energies of hydrocarbon and some oxygen-containing species. Superimposed upon these energies are the additional energies arising from angle deformation, torsion and non-bonded interactions. Results can be calibrated against thermochemical energies of molecules in ground states and energies of species differing in particular respects from the ground state can be derived. Particularly important, of course, are attempts to derive transition state energies from models with, for example, specific extensions of particular bonds, distortion of specific angles, and simulation of complex leaving groups with hydrogen atoms or methyl groups. Such calculations have proved particularly accurate in the hands of Schleyer and his collaborators and particularly in respect of solvolytic processes (below). These are particularly susceptible, because of their inherent simplicity, to calculation: reactivity comparisons of this nature. It is interesting to note the development of confidence in such calculations to the point where it is remarked "Quantitative calculations provide the best guide for the experimentalist who wishes to investigate a new system" and "Only quantitative calculational procedures will survive the rigours of extensive comparison with experimental results."[26]

The ability of such calculations to suggest or to identify that component of molecular energy that is significant in determining reactivity is striking. Obvious examples are seen in evaluation of strain involved in formation of a carbonium ion strained in its planar conformation which decides solvolytic reactivity (below), and in cyclobutane ring opening reactions (below) the sources of strain derived from calculations demonstrate the large differences from cyclopropanes notwithstanding their superficially similar energies.[27]

There are very substantial limitations on the types of structure for which accurate energies can be derived from molecular mechanics calculations. Heteroatoms other than oxygen cannot generally be included in, or attached to, hydrocarbon frameworks. Qualitative predictions of product distributions are possible by calculation of strain energies in transition states as, for example, in photolyses of bicyclic ketones[28] and this qualitative level of connection between strain and reactivity is typical of many reports that will not be specifically included on the basis of the definition of the scope of the report.

The force-field (molecular mechanics) method is based on empirical data. More refined calculations from more restricted data bases are, in principle, capable of obtaining more accurate energies. The necessary complexity of systems likely to be of interest in the connection between strain and reactivity, however, makes such calculations difficult. Dewar[29] has applied MNDO to calculations of transition state energies in homolytic rearrangements (below) but such bases for strain–reactivity correlations are rare.

Iv. *Empirical methods*

Ground-state energies of stable molecules are directly derivable from thermochemical measurements.[30a,30b] The information can be used as the data base for calibrating molecular mechanics calculations, or alternatively for giving energies of strained systems without the problems, in general, of complexity or atom variation. The response of activation parameters to such energies can then be used to draw conclusions about the nature of the transition states and hence the way in which strain is relieved. This approach has been employed in the reporter's group (below). It is particularly suitable for highly strained systems, notably small rings, when relief of strain is the dominant factor in reactivity. The essence of the method is to build up a data base of bond energy terms from measurements of heats of combustion, such bond energy terms being derived from "unstrained" (at least apparently) systems. Comparison of predicted and experimental energies then reveals discrepancies attributable, if in excess, to strain. Such excess enthalpies are not, of course, dissected into components as is possible with, for example, molecular mechanics calculations, but the assumptions contained in the results are clearly visible and recent work in the reporter's group has revealed very large discrepancies in the behaviour of systems with nominally similar strain energies expressed as excess enthalpies (below).

II. TYPES OF REACTIONS IN WHICH QUANTITATIVE REACTIVITY–STRAIN CORRELATIONS HAVE BEEN MADE

IIia. S_N1 *reactions*

Dissociations to form carbocations have provided the most comprehensive correlations of strain with reactivity. The pioneer work of Schleyer[4,31a] and Foote[31b] (the Foote–Schleyer correlation)[31c] in this field has enabled calculations of strain energies which can predict reactivities spanning factors of 10^{20} often within one power of ten.

It was recognized[31b] that the nature of the change in strain energy on dissociation was related to the change in stretching frequency of the corresponding ketones so that

$$\log k - \log k_{\text{cyclohexyl}} = -0.132\,(\nu_{C-O} - 1720)$$

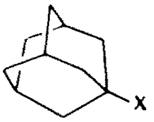
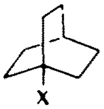
over ten powers of ten with $r = 0.97$. When, in addition to bond angle strain, changes reflected in carbonyl stretching frequencies, torsional and non-bonded interactions are considered, together with a structurally dependent inductive term, the more detailed equation is derived:[4]

$$\log k_{\text{rel}} = (1715 - \nu_{C=O})/8 + 1.32\,\Sigma\,(1 + 3\cos\phi_i) + (\text{GS} - \text{TS strain})/1.36 + \text{inductive term.}$$

This type of system is particularly suitable in that the reaction in its ideal form is inherently simple and the *residuum* is a hydrocarbon framework especially appropriate for calculations and often with well-defined geometry. As can be imagined, systems need choosing with great care as do the models for calculations. In terms of the reaction systems, it was important to be able to exclude, as far as possible, the intrusion of factors other than strain differences from the reactivity data. Solvolysis can often be very complex. Schleyer's group[21,32] has concentrated in most studies on tertiary and usually bridgehead derivatives. These systems are immune from the effects of neighbouring group participation, k_Δ, and solvent assistance k_s (as entry to the rear of the electrophile is obstructed), and give what are believed to be simple dissociation rate constants k_c. The calculations are then based on models in which the real leaving group, typically tosylate, or *p*-nitrobenzoate, is simulated, usually by hydrogen, although sometimes by methyl (below). The results obtained are astonishingly good[32] (Fig. 1); the pattern of bridgehead reactivities spanning more than 10^{18} involves approximations from substrates with varying leaving groups.

It had been concluded in earlier studies[33] that conformational strain was responsible for the low reactivity of bicyclo[2-2-2]octyl compounds, and that framework **4** was very much more rigid than **2** or **3**. Later work[34] demonstrates the lack of assistance from the cyclopropyl ring. Strain calculations have

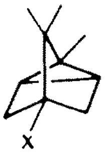
t-Bu-X

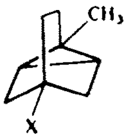




X = halogen or tosylate

k_{rel}	1	10^{-3}	2×10^{-6}	10^{-14}
	1	**2**	**3**	**4**

been able to predict the very high reactivity of manxyl chloride (**8**)[35] in which 6.8 kcal mol^{-1} of strain is *relieved* on carbocation formation. The observed rate is even faster than expected making this system one of the most reactive tertiary derivatives leading to a non-resonance stabilised carbocation. System

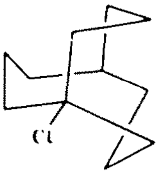




$X = OSO_2CF_3$

$RH \rightarrow R^+$	**5**	**6**	**7**
k_{rel}	1	2.84×10^4	5.5×10^7
ΔH_{strain}	31.3	25.4	19.1

9 gives a solvolysis rate[36] which fits on a strain–energy plot. Deviations have been observed for some bridgehead derivatives; solvolysis of tosylate **10**[37] is much slower than predicted from strain differential calculations. The abnormal behaviour is attributed to the electronic effect resulting from the



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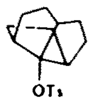

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difficulty of alignment of the developing vacant orbital with an anti-periplanar orbital in the cage framework.

For solvolysis of bridgehead derivatives, the strain calculations take into account the tendency of the residuum carbocation to adopt a planar conformation. It is the large force constants involved in deformation of the original tetrahedral structure that principally determine the increase in strain enthalpy and distinguishes between structures on the basis of their flexibility.[38,39]

In the examples above, selected from very many instances, departure of the leaving group leaves behind a structure in which strain increases because of the need to approach a planar conformation. Many examples are known, however, in which departure of the leaving group is associated with relief of

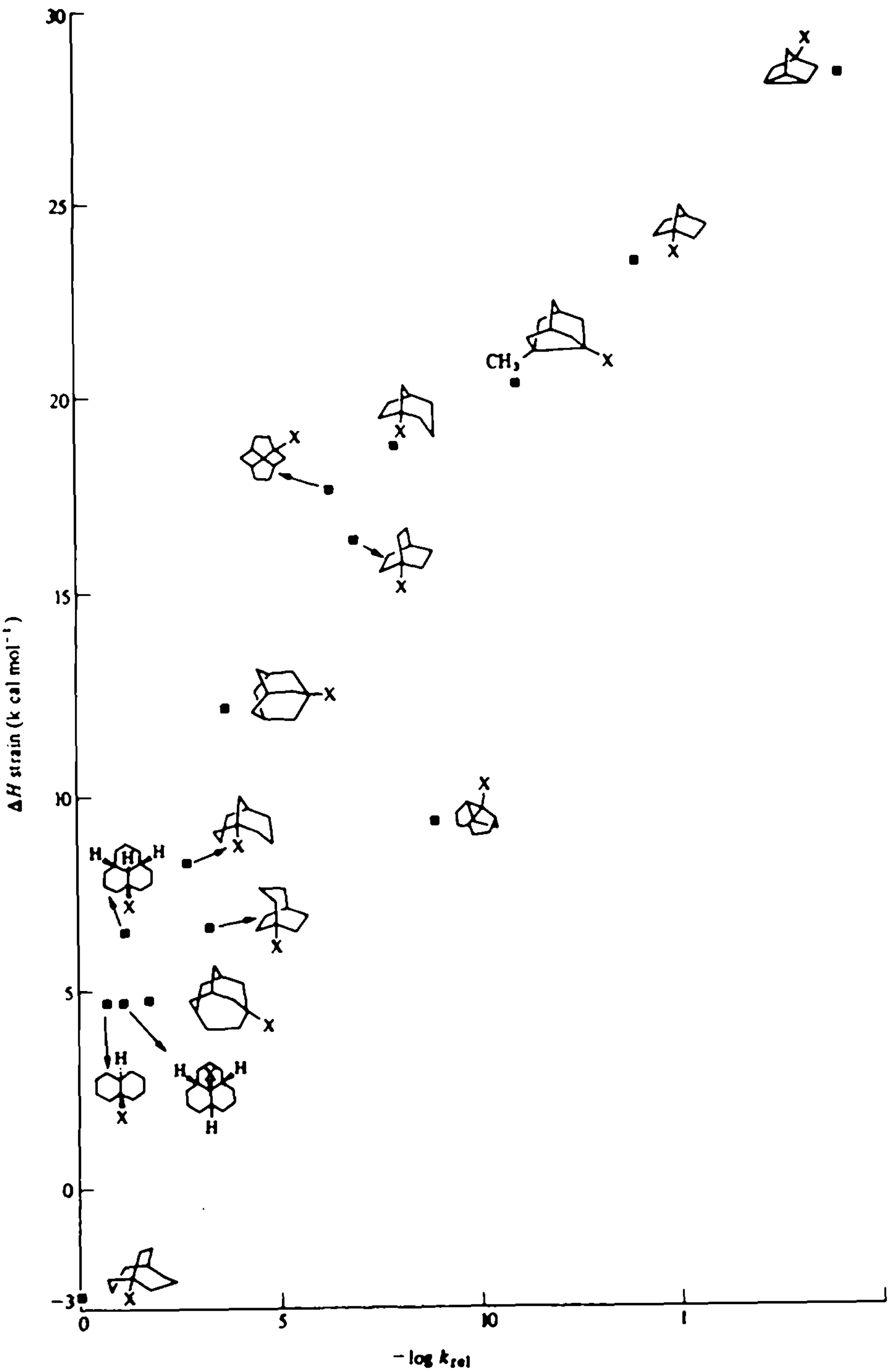
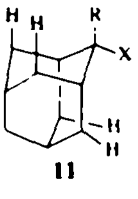


Fig. 1. Solvolysis of tosylates: ΔH_{strain} versus log k_{rel}.

ground-state strain. In the 2-alkyl-2-adamantyl system 11[40] with the bulky *p*-nitrobenzoate leaving group, rates of solvolysis increase dramatically (Fig. 2) as the size of the group R increases and the correlation with calculated strain energy is clear notwithstanding the bunching of points other than



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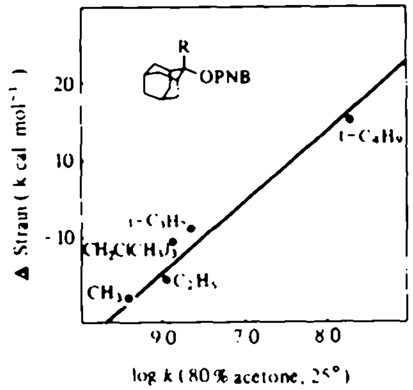


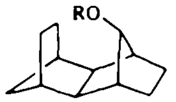
Fig. 2. Calculated hydrocarbon cation strain energy differences (Δ strain) plotted against log of the experimental rate constants (80% acetone, 25°) for a series of 2-alkyl-2-adamantyl-*p*-nitrobenzoates; least-squares fit: $\log k = 1.23\,\Delta\,\text{strain} - 6.93$. (Reproduced with permission from ref. 40. Copyright (1972) American Chemical Society.)

that for t-butyl. The line is defined by $\log k = 1.23\,\Delta\,\text{strain} - 6.93$. The activation parameters of Table 2 show clearly that it is enthalpy variation and not entropy that determines the trends. Strain in the ground state arises from non-bonded interaction with the R group in the axial position. Comparison, however, of the solvolysis of *p*-nitrobenzoates in this system, with acid catalysed dehydration[41a] shows that relief of front strain involving the leaving group is significant. For adamantanol dehydration, the slope of the ΔG^{*} versus Δ strain energy plot is 1.01 but for *p*-nitrobenzoate solvolysis is 1.77.[40] In strain energy calculations the *p*-nitrobenzoyl group cannot just be treated as a hydrogen atom. In later work,[41b] the same authors showed that strain energy calculations could deal with the greater steric demands of the *p*-nitrobenzoate leaving group if methyl and not hydrogen were employed as its surrogate. Similar results have been obtained[42] for tosylates when the correlation:

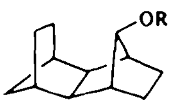
$$\log k = 0.63\ \Delta\ \text{strain} - 6.73$$

is obtained.

Cation-hydrocarbon strain energy differences can account[43] for the 10^3-fold greater reactivity of sulphonate **12** over **13**. In the former, the ester function is forced into proximity with the alkyl


R = $SO_2CH_2CF_3$

12


R = $SO_2CH_2CF_3$

13

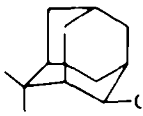
Table 2. Solvolysis rates and activation parameters for 2-alkyladamantyl-2-*p*-nitrobenzoates[40]

Substrate	k_{rel}	ΔH^{*} (kcal mol^{-1})	ΔS^{*} (cal mol^{-1} K^{-1})
t-BuOPNB	1	29.2	−7.1
R = Me	2.0	30.2	−2.2
R = Et	15.4	28.1	−5.3
R = neopentyl	20.0	29.0	−1.6
R = i-Pr	67.0	28.1	−2.4
R = t-Bu	450,000	21.6	−6.5

Table 3. Solvolyses of *p*-nitrobenzoates, R_3COPNB[45]

R_3	k_{rel}	R_3	k_{rel}
Me_3	1	t-Bu(Neopentyl)$_2$	68,000
(t-Bu)$_3$	13,000	(Neopentyl)$_3$	560
(t-Bu)$_2$Neopentyl	19,000		

substituents. Quite small differences can be accounted for in adamantyl systems. For tosylate **14**, solvolysis is 2.2 times faster than for **15**.[44] The calculated energy difference corresponding to strain relief in formation of the cation is 1-1.3 kcal mol^{-1}. When the leaving group is *p*-nitrobenzoate, the rate ratio is 350.



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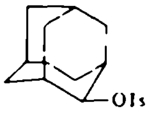

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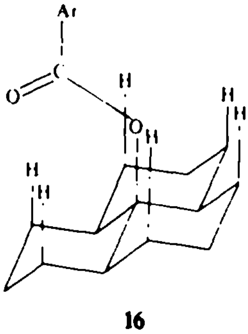
Several related examples of strain–reactivity correlations have been noted. In early work, Bartlett[45a] measured the rates of *p*-nitrobenzoate solvolyses for bulky alkyl groups (Table 3). B (back strain) is relieved by change from the tetrahedral to planar configuration. There was no correlation between solvolysis rate and rearrangement, and concerted assistance to ionisation was thought not to be important. There is a rough correlation of rates with the energies of repulsive interactions between non-geminal methyl groups. These amount to a maximum of about 7.7 kcal mol^{-1}. Collation[45b] of Bartlett's data[45a] with that of Dubois and Lomas[45c] gives an excellent correlation between ΔG^{*} solvolysis for R_3COPNB and Δ strain (R_3CMe-R_3C^+) with slope = 0.32. F (forward) strain involving the leaving group is seen[46] in reactions of compounds **16** and **17**. This is due to 1,5- and 1,6-interactions with the



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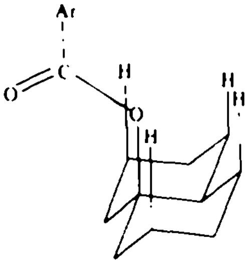

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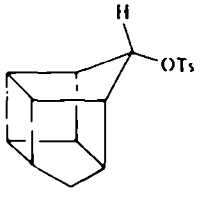
OPNB leaving group giving **16** a reactivity 2860 times greater than **17**. When the leaving group is chloride, however, the ratio is 1 : 12 for **16** : **17**. The F-strain derived for *p*-nitrobenzoates from this out-of-match amounts to 5.4 kcal mol^{-1}. Dubois and Lomas[46a] had shown earlier that relative rates of *p*-nitrobenzoate solvolysis and alcohol dehydration increase substantially with congestion at the leaving group.

For the reactivity–strain energy correlations described, systems have been carefully chosen so as to make simple, unassisted, dissociation the rate-determining process. Deviations from the well-behaved strain energy versus activation energy plots obtained can be used to detect processes other than simple dissociation. Good correlations between $\delta_{\text{strain energy}}$ $RH \rightarrow R^+$ and $\log k_{\text{solvolysis}}$ (k_c) are obtained when, in models for the transition state used in calculations, either H or Me are used to simulate the leaving group. When "assisted" substrates are included, the correlations break down.[47]

Examples of non-compliance with the Schleyer-Foote correlation[4,31b] and its later refinements are useful in suggesting details of the processes involved. Rates of solvolysis of homocubyl derivatives **18** and **19** both show[48] substantial positive deviations of *ca* 10^4 from calculated values. The accelerations are regarded as being consistent with σ-participation in ejection of the leaving group.



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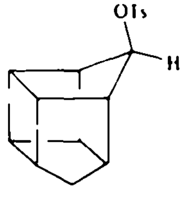

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Similarly, solvolyses of diadamantylmethyl and di-t-butylmethyl derivatives have been compared.[49a]

$(1\text{-Ad})_2CHX$ **20**	$t\text{-}Bu_2CHX$ **21**
$(1\text{-Ad})_2CMeX$ **22**	$t\text{-}Bu_2CMeX$ **23**

Strain energy differences calculated by molecular mechanics are very small either between

$$R_2\overset{\displaystyle H}{\overset{|}{C}}—H \text{ and } R_2\overset{+}{C}—H \text{ or between } R_2\overset{\displaystyle H}{\overset{|}{C}}—Me \text{ and } R_2\overset{+}{C}—Me$$

for both adamantyl and t-butyl series. They predict that solvolysis rates for **20** and **21** should be about the same; experimentally, diadamantyl derivatives **20** are more reactive by $10^{1.1}$–$10^{2.0}$. Likewise t-butyl derivatives **23** are predicted to be up to 10^1 faster than adamantyl derivatives **22**. They are slower by $10^{1.1}$ to $10^{1.4}$. Such deviations point to enhanced (and not allowed for) inductive and hyperconjugative contributions to the cation stabilities. This type of study, in view of the small energy differences involved, is to be regarded as the refined sector of strain–reactivity comparisons.[49b]

In solvolysis of cyclo-octyl tosylate,[50] relief of ground-state strain on dissociation provides a simple ionisation pathway k_c with which "assisted" pathways do not compete. The relief of strain on ionisation calculated for Me ≡ OTs is -3.06 kcal mol^{-1} and the k_c mechanism is confirmed by the linearity of the plots of log k for cyclo-octyl tosylate solvolysis and log k for 1-adamantyl bromide solvolysis in ethanol–water and trifluoroethanol–water mixtures of varying composition.[51] MM calculations were made of the strain energy difference between the methylcycloalkane as a model for the ester and the ketone as a model for the sp^2 hybridised transition state (using lowest energy conformers). Correlations of rates in ethanol with these strain energy differences are poor (Fig. 3) but with rates in TFE (no nucleophilic assistance) are good (Fig. 4).

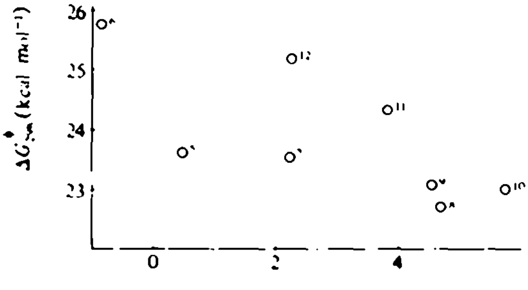


Fig. 3. Solvolysis rates in ethanol as a function of strain energy differences. Numbers refer to ring sizes (Reproduced with permission from ref. 51. Copyright (1980) American Chemical Society.)

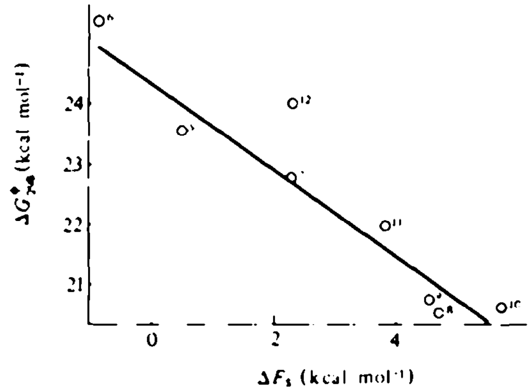


Fig. 4. Solvolysis rates in trifluoroethanol as a function of strain energy differences. Numbers refer to ring sizes. (Reproduced with permission from ref. 51. Copyright (1980) American Chemical Society.)

The observations fully support Brown's qualitative I-strain concept[52–54] in which internal strain is responsible for the differing reactivity of cycloalkyl halides induced by the change of hybridisation from sp^3 to sp^2. Brown[54] showed that cyclohexyl derivatives were least reactive because of bond opposition on ionisation and the medium-ring derivatives were most reactive because of loss of transannular interactions on dissociation.

Müller[55] and his colleagues have shown that for solvolysis of secondary tosylates in AcOH or TFE the free energies of activation correlate with strain differences between substrate and derived ketone obtained from MM calculations and with ΔG_{0t} for the equilibrium between ketone and cyclohexanol. Slopes are close to unity. The correlation is extensive; $\delta\Delta G^{\ddagger}$ covers *ca* 15 kcal mol^{-1} and the deviations are accountable on the basis of anchimeric or solvent assistance. When the carbocation formed is highly strained, the correlation breaks down. 7-Norbornyl shows a strong negative deviation while cyclobutyl correlates quite well; this is properly regarded as fortuitous. The carbonyl group as model probably leads to an underestimate of angle strain in the transition state and the rate for cyclobutyl is enhanced by other factors, notably anchimeric assistance.

IIb. *The norbornyl controversy*

A huge amount of work has been stimulated by the controversy over the structure of the species generated in the solvolysis of 2-norbornyl sulphonates and related compounds.[13,56,57] From the point of view of correlation of strain with reactivity, Schleyer[58] showed that *exo*-2-norbornyl tosylate solvolyses $10^{3.8}$ faster than can be accounted for by calculations which correlate rates for many other secondary tosylates. This was concluded to be compelling evidence for the formation of bridged carbocations, the *endo–exo* strain in norbornyl sulphonates being estimated[4,58] at 1.3 kcal mol^{-1} and the relative *exo* : *endo* rates after correction for internal return correspond to a $\Delta\Delta G^{\ddagger}$ of 4.5 kcal mol^{-1}. These values permit construction of the Goering–Schewene diagram (Fig. 5).[59] The question then arises: is $\Delta G^{\ddagger}_{exo}$ small because of bridging or is $\Delta G^{\ddagger}_{endo}$ large because of steric restraint upon nucleofuge departure? Calculations of energies to compare with reactivities have given variable results. As has been mentioned, the Foote-Schleyer correlation[4,47] of strain energies with solvolysis rates indicated that *exo*-reactivity was abnormally high and consistent with a non-classical ion. The Foote-Schleyer correlation does not however take into account the effect of differential strains in the transition state caused by the leaving group. Δ strain (TS) for leaving groups has been assumed to be zero. Substantial discrepancies between calculated and observed rates for *endo*-derivatives, in which Δ strain (TS) for the leaving group might be considered to be significant, forced the conclusion[60] that such correlations could not be decisive in dealing with the problem. The status of calculations in 1977 is reviewed by Schleyer.[56] That steric constraint on leaving group departure is important is suggested by the comparison[61] of acetolysis rates for **24**, **25** and **26** which are *not* matched by calculations which ignore the role of transition state strain for leaving groups. It is clear, however, that ground-state strain energy differences between *exo* and *endo* derivatives are small and as the intermediate carbocations are identical, it is the transition state energy differences which are responsible. Schleyer[56] doubts if leaving group departure can be the root of such differences and so does Grob.[57a]

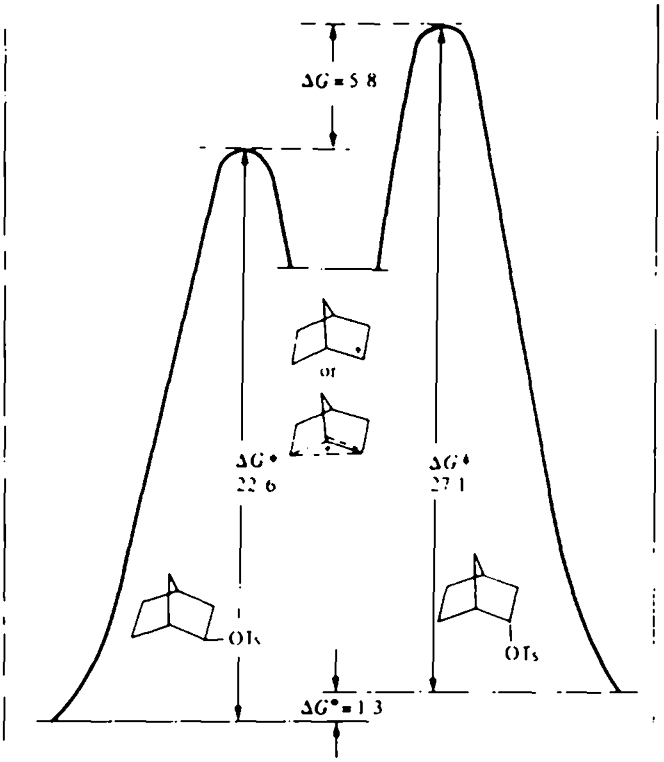
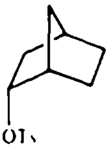
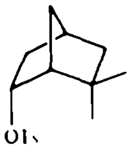
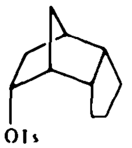


Fig. 5. Free-energy diagram for the acetolysis of *exo*- and *endo*-norbornyl tosylates. (Reproduced with permission of the authors and publishers of ref. 56.)

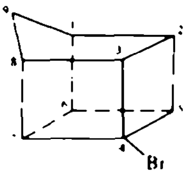
Thermochemical data on heats of ionisation, ΔH_i, show[62,63] that the tertiary–secondary differences in ΔH_i for RCMe$_2$Cl, 1-R-cyclopentyl-Cl and 2-R-norbornyl-Cl, in which R = Ph or H, vary rather little throughout the series. There is no controversy over the classical structure of the 2-Ph-norbornyl cation and the data does not, therefore reveal any special stabilisation of the 2-norbornyl cation. These

	ν_{C-O}	GSLG* strain	$10^8 k_c$	k_{rel} Calc	k_{rel} Obs
 **24**	1751	1.3	8.3	1	1
 **25**	1746	4.0	0.45	420	0.054
 **26**	1743	4.0	0.86	1000	0.10

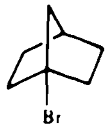
* Ground state leaving group strain.

data refer to complete ionisation. The Goering–Schewene diagrams for transition state energy differences show at least 6 kcal mol^{-1} between *exo*- and *endo*-substrates. The estimate for complete ionisation derived from partial transition state ionisation is reasonably put at 8 kcal mol^{-1}. This should show thermochemically if special stabilisation of the transition state for *exo*-norbornyl solvolysis is due to formation of a species other than a classical secondary carbocation.[64] It does not, but Arnett *et al.*[63] are non-committal on this point. Brown[57b,65] restates the thermochemical position and re-emphasises the missing extra stability of the 2-norbornyl cation. The latest calculations[66a,66b] show that there is a single minimum on the potential energy surface consistent with a non-classical structure also supported by ESCA spectra, NMR chemical shifts and by isotopic perturbation effects. Brown has oft-repeated the question "Why the *exo–endo* rate difference?" Grob[57a] suggests that *endo–exo* differences can be accounted for on the basis of control, by inductive effects, of the strength of bridging.

In connection with non-classical intermediates, the fact that 4-homocubyl bromide (**26a**) solvolyses very much more rapidly than 1-norbornyl bromide (**26b**) in hexafluoropropan-1-ol notwithstanding an increase of strain enthalpy of 66 kcal mol^{-1}, has led Rüchardt[66b] to suggest non-classical stabilisation of the homocubyl carbocation.



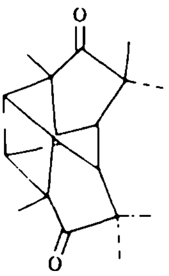
26a



26b

Strain effects in other situations related to solvolytic processes have been quantified; log k_{rel}, for solvolysis of tosylates and *p*-nitrobenzoates of small-ring derivatives,[67a] in which strain energy differences are insensitively expressed,[67b] show a rectilinear relationship with charge transfer frequencies for R – Ph → TCNE over 10^8 in k_{rel}. This implies that acceleration is due to $\sigma\pi$ conjugation of strained bonds with the adjacent carbocation centre.

As hinted at above, calculations are not always a safe guide to behaviour in spite of many striking successes. Isomerisation of **27**[68] in CF_3CO_2H gives **28** and not **29** or **30** in spite of the fact that MM calculations of their enthalpies give values 3–6 kcal mol^{-1} lower than that of **28**.



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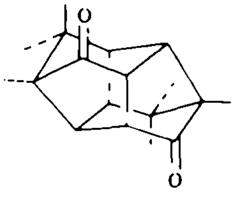

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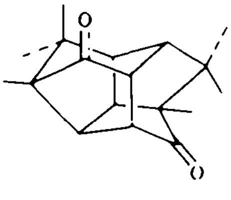

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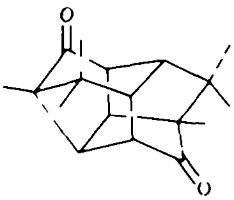

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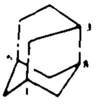
IIIc. *Bromination*

Force field calculations of hydrocarbon–cation strain energy differences allow prediction[69a,b] of the bromination site in, for example, protoadamantane **31** at C_6 to give **32**; its solvolysis rate is within a factor of three of the predicted value.



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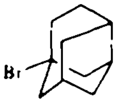

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Table 4. Observed and calculated ΔH^{*} values for alkyl bromides (RBr) in halogen exchange reactions[73]

R	$\Delta H^{*}_{R} - \Delta H^{*}_{Et}$	ΔSE (Calc $\Delta H^{*}_{R} - \Delta H^{*}_{Et}$)	log k^{calc}_{rel}	log k^{obs}_{rel}
Me	−2.42	−6.20	−1.77	−1.5
Et	0	0	0	0
n-Pr	0.28	0.04	0.20	0.4
i-Bu	1.99	1.87	1.46	1.5
Neopentyl	6.85	7.03	5.02	5.0
i-Pr	2.62	4.61	1.92	1.6
t-Bu	5.6	11.77	4.1	

*Source of data A. J. Streitwieser, *Chem. Rev.* **56**, 571 (1956), giving averages of experimental data from several sources.

IIIa. S_N2 *reactions*

In this section are lumped together those nucleophilic substitutions that cannot reasonably be described as dissociations—the emphasis of the report is more on strain than precise mechanistic definition. Some of the examples quoted may be better described as one-electron transfers which are becoming increasingly ubiquitous in this area.

Ingold[14] revealed the first *quantitative* relationship between strain ≡ "steric effects" and reactivity. Mechanisms of substitution reactions had been well defined at this time[70] and for halide ion–alkyl halide (Finkelstein) substitutions, changes in enthalpies and entropies of activation were calculated by what were essentially forerunners of molecular mechanics. Bond stretching, bending and non-bonded interactions gave rate values within factors of 5 over a reactivity range of 5×10^6 found for variation of alkyl group from methyl to neopentyl. Ingold remarked (prophetically for the content of this report) that "Calculations reveal conclusions which intuitive considerations would not have revealed, and would even have tended to conceal ... be more likely to produce a harvest in inaccessible conclusions of general interest than in precision." A generation later, Abraham *et al.*[71] have been able to reproduce experimental activation parameters for S_N2 halide exchange reactions without reference to polar effects of alkyl groups (used by Ingold but which have fallen into disrepute[72]) using flexible (one-bond) bending and plastic (two-bond bending) modes. DeTar[73] reviews hand-calculator attempts to derive activation parameters and obtains by MM methods good agreement between calculated and experimental log k_{rel} values for Me, Et n-Pr, i-Bu and neopentyl bromides in halogen exchange reactions. Calculated values are of enthalpy differences amounting to steric energy differences. Results are summarised in Table 4.

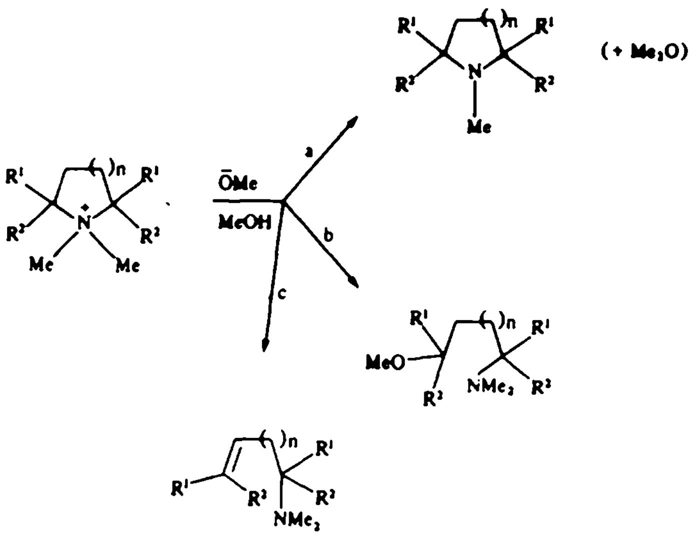
A different approach is to compare the reactivities of systems with strains known (or assumed) from thermochemical measurements. Much the most commonly used systems involved strained rings well known to be susceptible to nucleophilic ring opening.[74,75]

The most directly relevant work is that of the Rome group[76–78] on nucleophilic ring opening in cyclic ammonium salts (Scheme 1) whose data are collected in Table 5.

The competing reactions b and c are both affected by strain and for the nor-series ($R^1 = R^2 = H$) there is a broad correlation between δ strain (for cycloalkanes) and $\delta\Delta G^{*}$ whose slope suggests that around 20% of the strain energy is contributed to lowering of the transition state energy for substitution in the medium rings. Points for the 4 (most) and 5-ring systems deviate strongly. For the latter case the strain energy difference is small and the steric requirement in nucleophile orientation is significant.

The rates of *endo*-nucleophilic eliminative ring fission[79] also follow excess enthalpies of the rings, but with a maximum in rate at 8-members rather than 9. The effect of α-Me substitution is to cut S_N2 rate constants by *ca* 200 in agreement with general experience in open chain systems.[70] Recently, nucleophilic fission of strained oxa- and thia-ring systems has been quantified in the reporter's group.[80] Results for 3-, 4- and 5-ring systems are given in Table 6.

The reactivity of oxirans has been very widely investigated[81] but, surprisingly, few comparative studies on other ring systems have been carried out. Our results[80] on oxetan (4-ring) show a much larger 3 : 4 ratio than that found by Searles[82a] for thiosulphate reactions but similar to that found by Pritchard and Long[82b] for hydroxyl ion reactions. The 3 : 4 ratio is much larger, in terms of the strain differential, than the 4 : 5 ratio. We believe that strain in the 4-membered is differently distributed from that in the 3-



Scheme 1.

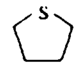
ring accounting, at least partially, for the very different behaviours of these systems. This point is taken up again in Section IIiii.

In nucleophilic attack at sulphur, trimethylene disulphide (33) is much more reactive than di-n-butyl disulphide (34) towards n-butylthiolate ion (Table 7).[83] The cyclic disulphide is strained[84] to the extent of 4 kcal mol^{-1} and it is odd that its high reactivity is largely due to a favourable entropy term.[85]

Table 5.

n	Ring size	R^1	R^2	k^{130° α S$_N$2 (reaction b)	k^{130° E (reaction c)	δ Strain energy (kcal mol^{-1})	δΔG* (kcal mol^{-1})
0	4	H	H	8.5	-		
0	4	Me	Me	-	1.19		—
0	4	H	Me	8.6×10^{-2}			-
1	5	H	H	3.14×10^{4}	4.18×10^{-6}	5.9	−3.9
1	5	H	Me	·	3.6×10^{-3}		..
1	5	Me	Me		3.68×10^{3}	—	
2	6	H	H	2.51×10^{-6}	7.29×10^{-6}	0	0
2	6	Me	Me	—	2.06×10^{-3}		—
3	7	H	H	6.04×10^{6}	3.08×10^{-4}	6.4	−0.7
4	8	H	H	1.64×10^{-5}	5.70×10^{-4}	10.1	−1.5
5	9	H	H	5.75×10^{-5}	5.31×10^{-4}	13.2	−2.5
7	11	H	H	4.08×10^{-5}	3.90×10^{-4}	12.4	−2.3
9	13	H	H	6.84×10^{-6}	7.61×10^{-5}	6.7	−0.8
12	16	H	H	4.6×10^{-6}	6.5×10^{-5}	4.1	−0.5
n-Bu$^+$NMe$_3$				2.94×10^{6}	4.33×10^{-5}	-	—

Table 6. Nucleophilic fission of strained saturated heterocycles[80]

			
k_{rel}* (120°)	1	5.4×10^{-4}	4.6×10^{-9}
Strain energy (kcal mol^{-1})	27.3	25.5	5.6
			
k_{rel}* (120°)	0.8	3.7×10^{5}	1.2×10^{-8}
Strain energy	19.8	19.6	5.8

*Reactions in sodium thiosulphate–water. Values for 3- and 4-rings extrapolated from values at *ca* 50°. 5-Rings measured at 120°.

Table 7.

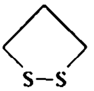
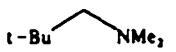
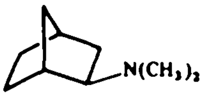
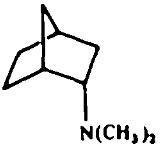
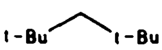
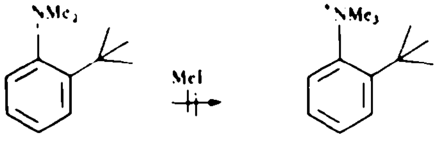
	 **33**	n-BuSSn-Bu **34**
k^{25} M^{-1} s^{-1}	1400	0.31
E_A (kcal mol^{-1})	13	14.2
$\Delta G^{\ddagger}$ (kcal mol^{-1})	13.6	18.1

Table 8.

	 **35**	n-BuNMe$_2$ **36**
$k^{\mathrm{MeI\,PhNO_2}}$	1	150
$\delta\Delta H^{\ddagger}$ (kcal mol^{-1})	2.8	0

	 **37**	 **38**	 **39**
$k^{\mathrm{MeI\text{-}PhNO_2}}$	51	1	

Brown[86] has also found moderate sensitivity ($\approx 50\%$) to build up of strain in alkylation of amines. Rates of methylation (MeI) of **35** and **36** are compared in Table 8. Compound **39** is a homomorph for the methylation product of **35** and the strain of 5.4 kcal mol^{-1} would suggest a rate depression of 10^3 to 10^4 if fully expressed. The different reactivities of **37** and **38** support a modest degree of steric inference in the cavity of **38**. In a much more highly oriented system **40**, with a much higher degree of strain (22 kcal mol^{-1}) in the homomorph **41**, methylation is not observed.[87]



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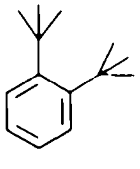

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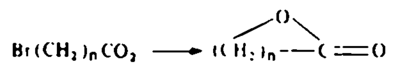
IIIb. *Intramolecular* S_N2 *reactions*

Strain energies of simple cyclic systems are well known from thermochemical measurements.[30,88] For this report, the relevant question in connection with intramolecular nucleophilic displacements is the extent to which these known strain energies are reflected in the free energies of activation for cyclisation. Intramolecular nucleophilic substitution[89] is a complex matter; formation of the most strained ring systems leads to the greatest deviations from expectation. In formation of 3- and of 5-membered rings, 3 : 5 rate ratios vary over 10^7 depending on the nucleophile, being $\ll 1$ for O and N nucleophiles and $\gg 1$ for carbon and sulphur nucleophiles.[90] The very high strain energies of small bridged ring systems do not prevent their (irreversible) formation by intramolecular substitution. Highly strained arylsulphonylbicyclobutanes, for example, are readily formed in one-pot reactions from β,γ-epoxy sulphones.[91]

Table 9. Lactonisation of ω-bromocarboxylates in 99% DMSO-H_2O


$Br(CH_2)_nCO_2 \longrightarrow (CH_2)_n$—$C$=O

Ring size	n	$k_{rel}^{50°}$	$\Delta H^{\neq}$ (kcal mol^{-1})	$\Delta S^{\neq}$ (cal mol^{-1} K^{-1})
3	1	21.7	22.0	−2.5
4	2	2.4×10^4	17.7	−4.9
5	3	2.8×10^6	15.9	5.6
6	4	2.6×10^4	17.2	4.2
7	5	97.3	17.4	13.6
8	6	1.00	21.8	−9.2
9	7	1.12	20.3	−13.9
10	8	3.35	17.4	20.5
11	9	8.51	16.4	−21.9
12	10	10.6	17.6	−17.6
13	11	32.2	15.3	22.5
14	12	41.9	14.8	23.6
15	13	45.1	16.1	−19.5
16	14	52.0	16.8	17.0
18	16	51.2	15.4	−21.2
23	21	60.4	14.5	−23.8

Activation parameters for four main types of system have been determined. References to reviews of quantitative work are given by DeTar.[92]

Lactones from ω-carboxyhalides. Illuminati, Mandolini and their collaborators[93a,b,c] have studied ring sizes from 3 to 23 members (Table 9).

The very low 3-ring/5-ring rate ratio is notable. For neither carbocycle nor heterocycle formation do enthalpies of activation suggest that ring strain is an important factor in determining rates of closure (below). In this case, however, the α-lactone formed by cyclisation of ω-bromo-propionic acid is undoubtedly very highly strained by incorporation within it of an sp^2-hybridised carbon atom. Formation of the 5-ring is fast but the effective molarity is very much lower than for cyclisation of ω-bromoalkylamines, alkoxides and phenolates. This is attributed[93a] to the imposition, for rings of less than nine members, of the *cis*-conformation of the ester function, less favourable than that of the *trans*, by 3.8 kcal mol^{-1}. The $\Delta H^{\neq}$ cyclisation *vs* ring size plot (Fig. 6) shows a jagged relationship. Not surprisingly $\Delta H^{\neq}$ 3-ring is high but only *ca* 8 kcal mol^{-1} higher than for the intermolecular analogue indicating a modest expression of ring strain in the inhibition of ring closure. Values for the 4, 5, and 6-rings show negligible dependence on ring strain in the product and the $\Delta S^{\neq}$ values differ remarkably little for formation of 3- to 6-membered rings. This information (as other information below) is not congruent with the Ruzicka[94] hypothesis that strain is necessarily an adverse factor in ring formation.

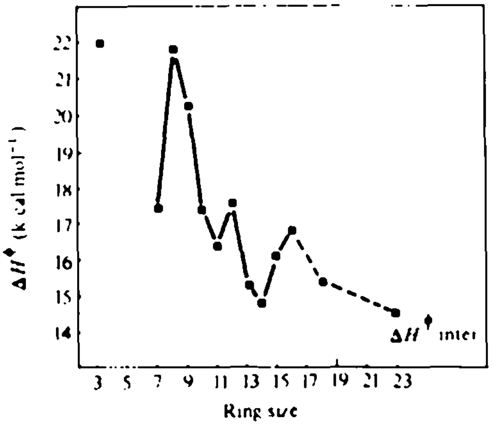
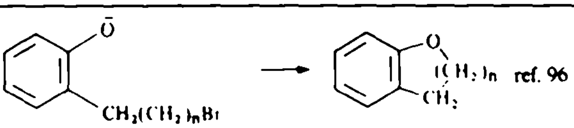


Fig. 6. Enthalpies of activation *vs* ring size for the formation of lactones. The $\Delta H^{\neq}$ value for the corresponding intermolecular reaction is also shown. (Reproduced with permission from ref. 93a. Copyright (1977) American Chemical Society.)

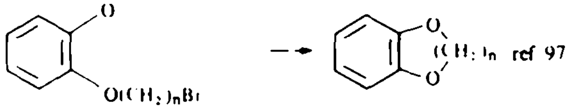
Table 10. Cyclisation of ω-halogenoalkylphenoxides

Series A



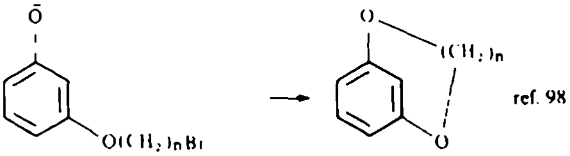
Ring size	5	6	7	8	9	10	Inter
$\Delta\Delta H^{\ddagger}$ (kcal mol^{-1})	0.0	2.3	2.1	5.3	5.3	4.3	1.0

Series B



Ring size	11	14	16	24
$\Delta\Delta H^{\ddagger}$ (kcal mol^{-1})	3.8	3.2	1.9	0

Series C



Ring size	13	14	15	17
$\Delta\Delta G^{\ddagger}$ (kcal mol^{-1})	1.40	0.43	0.36	0

Gem-dimethyl substitution is well known to accelerate cyclisation but the origins of the effect are controversial.[95] For lactonisation, values of k_{rel} as a function of ring size (in parentheses) are:[93b] (6) 38.5; (9) 6.62; (10) 1.13; (11) 0.61; (16) 1.22. These are small ratios by comparison with cyclopropane formation and fission (below). The adverse effect on rate of cyclisation to the 11-membered ring is to be attributed to the involvement of extra trans-annular effects.

Cyclisation of ω-substituted aryloxide ions. Cyclisation of phenoxide ions bearing remote leaving groups, usually bromide, has also been subjected to detailed and comprehensive study by the Rome group. Their results are given in Table 10.

Because values are not available, effects of strain energy differences in the products formed cannot generally be explored. Enthalpies of activation for the 8- and 9-membered rings compared with the strain-free intermolecular counterpart suggest strain energy differences of 3–4 kcal mol^{-1}. Accurate values of the strain energies of the products are not available for direct comparisons. As maximum excess enthalpies for medium ring carbocycles are in the region of 10–12 kcal mol^{-1} the results suggest a rather low, albeit consistent, response to strain energy developing in the transition state. Replacement of a methylene group by oxygen (series B) accelerates reactions, the acceleration being larger for the more strained rings. These effects are to be attributed to the reduction of the principal strain components of medium rings, namely, transannular and torsional interactions.

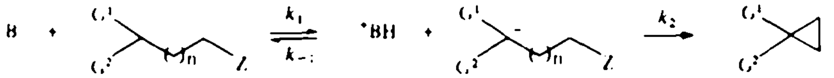
In the bis-oxygen series (C) rather small differences are seen in $\Delta\Delta G^{\ddagger}$ between medium and large ring systems and none in $\Delta\Delta G^{\ddagger}$ after 12 members. Again, direct comparisons of ground state and transition state energies are not possible. Effects are in any case small and origins complicated.

Formation of cycloalkanes. The first quantitative work[99] on formation of cyclopropanes from malonates followed synthetic application[100] eighty years later. The results were significant against the background of the Ruzicka hypothesis which contained the assumption that strain of a product, so evident for cyclopropanes, would be reflected in an adverse transition state enthalpy, albeit compensated by a favourable transition state entropy. Data are given in Table 11.

From the point of view of the effect of strain upon reactivity, the data of Table 11 are striking for the consistently high rates of cyclopropane and cyclopentane formation and the consistently low rates of cyclobutane and cyclohexane formation. These data are raw in respect of lack of breakdown between enthalpy and entropy terms. This notwithstanding, it is clear that strain in the product formed does not necessarily prevent a high rate of closure for 3-membered rings.

Data[102] on closure of ω-bromoalkylmalonate ions in DMSO give the first kinetic information on

Table 11. Cyclisation of ω-haloalkyl carbanions[a]



Series	Ring size 3	4	5	6	7
1 $G^1 = p\text{-tolylSO}_2$; $G^2 = H$,					
k_{rel}[b] (t-BuOK-t-BuOH)[i] Z = Br	1	1×10^{-4}[d]	0.01[d]	1×10^{-4}[d]	
2 $G^1 = G^2 = EtOCO$; Z = Cl					
k_{rel}[c] (t-BuOK-t-BuOH)[h]	1	1.5×10^{-6}	0.01	8×10^{-6}	
k_{rel}[e] (DMSO) Z = Br[f,e,j]		1	1.43×10^3	1.71	1.5×10^{-2}
3 $G^1 = PhCO$; $G^2 = H$					
k_{rel}[b] (NaOH 50:50 v/v Dioxan-H_2O) Z = Cl[k]	1	f,g	4.3×10^{-5}		
Z = Br[k]	1	f,g	2.0×10^{-3}		
4 $G^1 = G^2 = PhSO_2$, Z = Cl					
$k_{rel}^{25°}$ (EtONa-EtOH)[l]	1	6.7×10^{-6}	1.6×10^{-2}		

[a] All reactions involve rate-determining cyclisation except series 3.
[b] At 30°.
[c] At 55°.
[d] Maximum value.
[e] At 25°.
[f] Values for larger rings in Table 12.
[g] Rate-determining deprotonation.
[h] Ref. 99.
[i] Ref. 101.
[j] Ref. 102.
[k] Ref 103.
[l] Ref 104[a].

intramolecular substitutions relating to all of the categories of small, medium, and large rings (Table 12). The results for malonates in DMSO are remarkably similar to those obtained[101] for reactions in t-BuONa-t-BuOH and for bis-sulphones in EtONa-EtOH.[104a] They show conspicuous lack of sensitivity both to the nature of the carbanion-stabilizing group and to the medium. The conclusion that ring-strain is unimportant in effecting the formation of small rings is confirmed by the activation parameters recently determined for cyclisation of ω-halogeno bis-sulphones (Table 13).[104a]

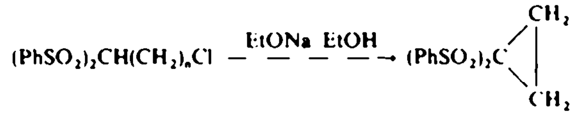
The activation enthalpies show that strain is of negligible importance. For the 3-ring the value is actually *lower* than for the 4-ring but, considering the ring strain energies, all of the values are remarkably similar. It is the entropies of activation that are responsible for the very large differences. It is to be concluded that an open-transition state is involved; solvent and leaving group effects are in accord with a considerable extent of leaving group separation.

Larger rings. For 6-membered or bigger rings, the Rome group have shown that in the cyclisation of ω-bromoalkylmalonates, the value of $\Delta H^{\ddagger}_{intra} - \Delta H^{\ddagger}_{inter}$ (Table 12) can be calculated from values of effective molarity and broadly correlate with cycloalkane ring strain values giving a zero intercept and slope of 0.45. They conclude that this degree of sensitivity to ring size indicates a close resemblance

Table 12. Cyclisation of ω-bromoalkylmalonate ions in DMSO[102]

Ring size	$k_{intramolecular}$ (s^{-1})	$\Delta H^{\ddagger}_{intra} - \Delta H^{\ddagger}_{inter}$
4	0.42	4.7
5	6×10^2	-0.9
6	0.72	1.7
7	6.3×10^{-3}	3.1
8	1.1×10^{-4}	4.2
9	1.2×10^{-5}	4.2
10	1.0×10^{-6}	5.6
11	2.1×10^{-6}	5.2
12	2.9×10^{-4}	2.3
13	5.3×10^{-4}	1.9
17	2.1×10^{-3}	1.1
21	3.1×10^{-3}	0.9

Table 13. Cyclisation of ω-chloroalkylbis-sulphones[a]



$$(PhSO_2)_2CH(CH_2)_nCl \xrightarrow{EtONa\ EtOH} (PhSO_2)_2C(CH_2)_2$$

Ring size	k_{rel}[b]	$\Delta H^{\neq}$ (kcal mol^{-1})	$\Delta S^{\neq}$ (cal mol^{-1} K^{-1})
3	1[c]	20.5	10
4	6.7×10^{-4}	21.8	9
5	1.6×10^{-2}	16.3	−12

[a] E1 anion mechanism

[b] At 25 .

[c] k_{obs} = 9.05×10^{-1} s^{-1}

between transition state and cyclic product and strain energies of medium and large rings turn out to be a valuable predictor of reactivity in their formation.

Formation of azacycloalkanes. In formation of 3- and of 5-membered rings, closure of ω-bromoalkylamines shows very different patterns of reactivity from those encountered in the formation of cycloalkanes. Results are given in Table 14. Large values (10^2–10^4) for the k_3/k_5 ratios in cycloalkane formation (Table 12) are now replaced by small ones (10^{-2}–10^{-3}).

In comparison of three- with five-membered ring formation, values of $\Delta H^{\neq}$ are more positive and values of $\Delta S^{\neq}$ more *negative* for the smaller ring. Again, this is contrary to the Ruzicka hypothesis; the situation is further complicated by the behaviour of the 4-ring system (8) which shows a substantially greater $\Delta H^{\neq}$ than either the 3-(7) or 6-(9) ring systems. The 4-ring system also fails to conform in the sulphonamide cyclisations **10**–**12**. Solvation is undoubtedly a serious complicating factor for activation parameters in these series; in this respect, carbanions (above) provide a more straightforward system.

DeTar and Luthra[92] have made a detailed quantitative study of halogeno-alkylamine cyclisation. Their results, which do not include 3-rings, are given in Tables 15 and 16.

Table 14. Formation of azacycloalkanes[90]

No.	Substrate	k_{rel}^{25}	$\Delta H^{\neq}$	$\Delta S^{\neq}$
1	$NH_2(CH_2)_2Cl^a$	5.3	19.3	−15
2	$NH_2(CH_2)_4Cl^a$	1777	16.5	−13
3	$PhNH(CH_2)_2Cl^a$	1	19.8	17
4	$PhNH(CH_2)_4Cl^a$	833	16.4	−15
5	$NH_2CH(Ph)CH_2Cl^a$	5.5	21.9	7
6	$NH_2CH(Ph)(CH_2)_3Cl^a$	1680	17.5	−10
		[a] 50% dioxan H_2O		
7	$PhNH(CH_2)_2Br^b$	1	19.4	−11
8	$PhNH(CH_2)_3Br^b$	0.019	21.7	−11
9	$PhNH(CH_2)_4Br^b$	9.55	16.2	−17
		[b] 60% EtOH H_2O K_2CO_3		
Azacycloalkanesulphonamides				
10	$TsNH(CH_2)_2Cl^c$	1	–	
11	$TsNH(CH_2)_3Cl^c$	0.01	.	
12	$TsNH(CH_2)_4Cl^c$	0.06		
		[c] NaOEt-EtOH		

Table 15. Ring closure of ω-bromoalkyldimethylamines[92]

	log k_{obs}[a]	log k_{calc}	$\Delta\Delta H^{\neq}_{rel}$	$\Delta\Delta S^{\neq}_{rel}$
$Me_2N(CH_2)_3Br$	−4.28	2.98	−0.26	24.1
$Me_2N(CH_2)_4Br$		0.28	6.77	21.2
$Me_2N(CH_2)_5Br$	−1.95	−1.95	−5.42	12.8
$Me_2N(CH_2)_6Br$	−4.77	−4.77	0.28	15.5
$Me_3N + EtBr$		4.55	−4.73	

[a] Conditions vary, see original paper.

Table 16 Ring closure of ω-bromoalkylamines[a][92]

No.	Substrate	log k_{obs}	log k_{calc}	$\Delta\Delta H^{\ddagger}_{rel}$[b]	$\Delta\Delta S^{\ddagger}_{rel}$[b]	SE (react)	SE(TS)[c]
1a	$H_2N(CH_2)_3Br$	−5.08	4.69	11.67	23.4	2.13	30.15
2a	$H_2N(CH_2)_4Br$	−0.06	−0.43	1.03	20.5	2.67	23.17
3a	$H_2N(CH_2)_5Br$	2.08	−2.29	1.08	12.1	3.11	23.90
4a	$H_2N(CH_2)_6Br$	4.60	−4.77	7.72	14.8	3.70	31.36
2b	$H_2NCMe_2(CH_2)_3Br$	0.24	0.43	0.49	23.3	4.60	24.29
2c	$H_2NCH_2CMe_2(CH_2)_2Br$	2.09	2.18	−3.31	23.3	7.22	23.11
2d	$H_2N(CH_2)_2CMe_2CH_2Br$	−0.84	0.22	1.89	23.3	6.26	27.35

[a] Conditions vary, see original paper

[b] To $EtNH_2 + n\text{-}PrBr$.

[c] Steric energy (force-field dependent)

The earlier experimental findings of slow formation of 4- and 7-rings are confirmed and the substantial effect of *gem*-dimethyl substitution – the Thorpe–Ingold effect – in some, compare 2c with 2b and 2c, but not all, 2d, systems (Table 16) is observed.

In the treatment of these data, values of $\Delta H^{\ddagger}$ are derived from MM calculations and of $\Delta S^{\ddagger}$ by analogy with $\delta\Delta S$ values in ring closure of open-chain alkanes to cycloalkanes. Correlations fail for the 4-membered ring (anomalous in every situation—see elsewhere in this report). In the medium-ring series, $\Delta G^{\ddagger}$ for bromo-amine cyclisation, as for lactonisation (above), shows the same peak in the 8- to 12-membered ring region. There is large entropic preference for the 4-ring, as against the intermolecular analogue, equivalent to $\delta\Delta G^{\ddagger}$ of 7 kcal mol^{-1} but the 4- *vs* 5-ring difference of only 0.9 kcal mol^{-1} is totally unrelated to ring strain energy differences. The authors emphasise that, as suspected from earlier work, product rings are *not* appropriate models of transition states. Formation of small rings is insensitive to ring strain. Similar conclusions had also been reached in earlier comparisons of cyclisations of ω-halogenocarbanions (above).

Quantitative treatment of the *gem*-dialkyl effect was not successful but it is almost entirely enthalpic in origin. The same conclusion was inferred from studies of eliminative ring fission (Section IIiii).

Cyclisation of ω-halogeno-sulphides. Intramolecular nucleophilic attack by two-coordinate sulphur in reactions of ω-halogenosulphides again occurs contrary to the Ruzicka hypothesis. The results of Table 17 show[104a] that in comparison of 3- with 5-ring formation, 3/5 ratios are > 1 and substantially so when the ring formed bears a phenyl substituent. Enthalpies of activation for 3-ring closure are *less* negative than for 5-ring closure, but entropies of activation behave in an erratic manner. The entropic situation is probably complicated by solvation of the developing positive charge; enthalpies, as for carbanion cyclisation to give small rings, do not indicate development of transition state strain.

It is appropriate to conclude this section with a remark of DeTar's,[104c] "It is clear that in such systems (closure of small rings) rate predictions based on classical explanations are of limited value".

IIiii. *Elimination reactions*

Although this type of reaction generally provides only rather few quantitative instances of the effect of strain on reactivity, recent work on eliminations from carbanions and oxy-anions has provided some direct quantitative connections showing very large effects.

Table 17. Formation of cyclic sulphonium salts[104b]

Substrate	k^{25}_{rel}[a]	Ring size	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
p-Tolyl$S(CH_2)_2Cl$	1	3	17.8	−24
p-Tolyl$S(CH_2)_4Cl$	0.53	5	19.4	−20
p-Tolyl$SCH_2CHPhCl$	5400	3	15.4	−13
p-Tolyl$S(CH_2)_3CHPhCl$	45	5	17.0	−19

[a] Reactions in 80% w/w EtOH H_2O at 25

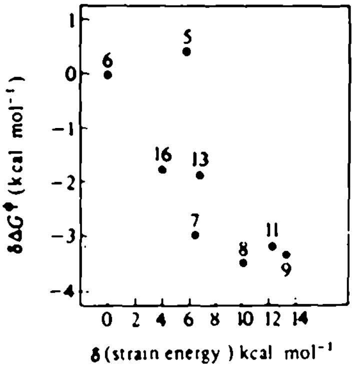


Fig. 7. $\Delta G^{\ddagger}$ changes for the ring-opening elimination vs the strain-energy changes of the cycloalkanes[76] (changes are relative to the six-membered ring) (Reproduced with permission from ref. 76. Copyright (1977) American Chemical Society.)

Early work on regiospecificity in alkene-forming eliminations[105] was controversial in respect of the importance of polar and steric effects leading to what are termed Hofmann or Saytseff orientations. Both effects were clearly variable in operation; small differences in regiospecificity often spoke of small differences in energies of activation, and strain differentials were unquantified.

E_1 *alkene-forming processes*. Dehydration (H_2SO_4) of 2-alkyladamantan-2-ols gives good correlation between Δ_{strain} and $\Delta\Delta G^{\ddagger}$.[41a] The slope of 1.01 shows that the effect of the 2-alkyl group is directly accountable in terms of (MM) strain energy differences. This is not so for the solvolysis of the *p*-nitrobenzoates unless an appropriate leaving group model is used (Section IIia).

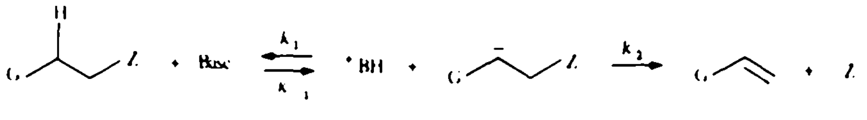
Dehydration of simple, strained cycloalkanols shows considerable strain-sensitivity.[106] 1-Methylcyclopentanol is at least 10^5 times more reactive in the same conditions as 1-methylcyclobutanol and crude calculations suggest that about 50% of the strain energy difference appears in reduction of $\Delta H^{\ddagger}$.

E_2 *alkene-forming reactions*. As mentioned above, very little relevant information is available because of the lack of quantification of strain differences between ground state and transition state. As a spin-off from the Rome group's work on nucleophilic substitution, in which the electrophile is a strained cyclic 'onium salt, information on *endo*-[79] nucleophilic eliminative ring fission is available[76] (Table 5).

The relationship between reactivity and strain energy for cyclo-alkanes is shown in Fig. 7. Effects are not large; the largest rate ratio of 136 is observed for 8- *vs* 5-membered rings. The slope of the plot of Fig. 7 suggests that about 20% of strain energy is expressed in $\Delta\Delta G^{\ddagger}$. The 5-ring deviates markedly from the general trend undergoing *endo*-elimination 1.7 times more *slowly* than its *less* strained 6-ring analogue. This is clearly due to the overshadowing of the (rather insensitively expressed) strain difference by the stereoelectronic demands of the anti-periplanar transition state.

E_1cB *reactions*. Recent work on alkene-forming eliminations has concentrated upon the effect of strain with particular reference to nucleofugality.

In carbanion forming eliminations of the type:



42 **43** **44**

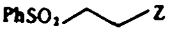
(G carbanion stabilising group. $PhSO_2$. CN. PhCO, etc.)

elimination of a wide variety of leaving groups, Z, from the carbanion **43** has been observed[107] and it has been demonstrated that expulsion of the leaving group (k_2) is rate-determining.

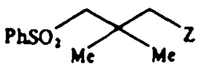
By quantifying the effect of the leaving group on the pre-equilibrium

$$\mathbf{42} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{43}$$

relative values of k_2 have been obtained. Values of $\Delta\log k_2$ are termed ranks and are equivalent to nucleofugality, the tendency for leaving group departure. It has been stressed[107] that these values, as for similar values obtained by similar treatment of data from 1,3-cyclopropane-forming eliminations[108] are not universal properties of groups; their magnitudes are reaction dependent. Values of ranks for leaving groups in 1,2-alkene forming (system **45**) and 1,3-cyclopropane forming (system **46**) eliminations are in Table 18.



45



46

Table 18. Ranks[a] for Groups Z, in elimination reactions[107,108]

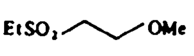
Z	Rank 1, 2	Rank 1, 3
OTs	[b]	10.4
Br	[b]	11.3
Cl	[b]	9.9
$PhSO_2$	8.7	3.5
PhS	8.7	0.4
PhO	8.9	−1.4
CMe_2NO_2	2.6	
$CMe(SO_2Et)_2$	−2.9	

[a] $\log k_{obs} - \log k_1 + 11$.

[b] $(E_1cB)_I$ or E_2 mechanism followed and therefore inappropriate for ranking.

Discussion of the magnitudes of these ranks lies outside the scope of this report, but particularly relevant for what follows are the ranks for the methoxy-group and the carbon leaving groups for which quantitative data on nucleofugality are available. Measurement of the effect of straining the bond connecting the leaving group in selected systems has been achieved[109] by incorporating the leaving group in a small ring of known strain energy (excess enthalpy). The first experiments were with the methoxy compound **47** and its ring-incorporated analogues **48**.[110] Results are given in Table 19.

It can be seen that incorporation of the leaving group in a three-membered ring accelerates elimination more than two million fold. Unfortunately, this degree of acceleration cannot be related to the degree of strain engendered in the leaving group connection; the mechanism of reaction is changed



47

48

a n = 0 **b** n = 2 **c** n = 3

Table 19. Eliminative ring fission of oxacycles[110]

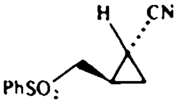
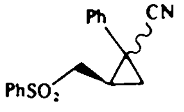
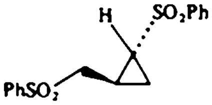
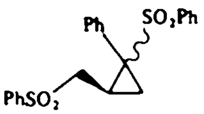
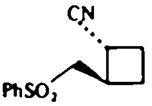
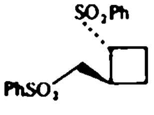
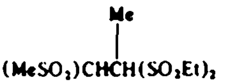
Substrate	k_{obs}[a]	Mechanism	$k^f_{H,D}$	Rank[b]	Strain energy
47	7.5×10^{-5}	$(E_1cB)_R$	[c]	6.1	·
48a	185	(E_2)	2.5	-	27.3
48b	1.39×10^{-3}	$(E_1cB)_R$	0.95	7.4	5.6
48c	2.0×10^{-3}	$(E_1cB)_R$	[c]	7.5	1.2

[a] $M^{-1}\,s^{-1}$; reactions in NaOEt EtOH at 25°.

[b] $\log k_{obs}$ $\log k_{deprotonation} + 11$ calc for Et=Ph; see original paper.

[c] $k_{H,D}$ exchange ≫ k_{obs}.

Table 20. Eliminative ring fission of cycloalkylmethyl sulphones

Substrate		k_{rel}[a]	DMSO pK_a MeCHRG	Leaving group rank[b]	$\Delta H^{\ddagger}$[e]	$\Delta S^{\ddagger}$[f]	Ref.
	**51**	0.4	32.6	8.4	24.4	12	111, 112
	**52**	510	23.0	10.9	17	0	111, 112
	**53**	1	31.1	8.8	17.7	−10	111, 112
	**54**	4.0	25.4	8.8	17.9	−6	111, 112
	**55**	8.3×10^{-5}	32.6	4.9	31.37	17	113
	**56**	1.7×10^{-5}	31.1	4.3	29.9[d]	9[d]	113
 $(MeSO_2)CHCH(Me)(SO_2Et)_2$	**50**	2.5×10^{-2}	14	−2.9			111

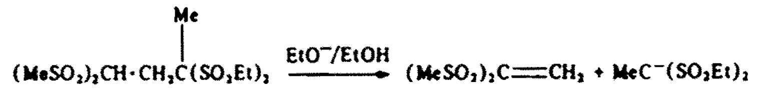
[a] Reactions in NaOEt-EtOH at 25°.
[b] See Table 18.
[c] Value not available.
[d] Values correct those in the original reference.
[e] kcal mol^{-1}.
[f] cal K^{-1} mol^{-1}.

by strain. Expulsion of the strained leaving group is so much accelerated that it is no longer the rate-determining step of the reaction. The primary deuterium isotope effect shows that leaving group loss is (probably) concerted with deprotonation. Consequently no rank value can be extracted from the data. When the ring size is 5, the degree of strain is small and acceleration over the open chain substrate **47** is correspondingly small. For both 5- and 6-ring systems, the mechanism involves, as for the open-chain system, rate-determining leaving group expulsion ($k^{\beta}_{H/D} = 1$). The small rate effects seen in the 5- and 6-ring systems are not solely due to strain; the less strained 6-ring system is actually slightly more reactive than the 5-ring system.

Table 18 shows that carbon leaving groups have very low ranks in alkene-forming eliminations and, in particular, substantially lower ranks than for example, methoxy. Incorporation of the carbon–carbon leaving group connection in a strained ring again offers a system for the direct examination of strain of nucleofugality. Substrates of general structure **49** have been compared with the open-chain analogue **50**. The results are given in Table 20.

The open-chain substrate is not a perfect match for the strained cyclic systems; the leaving group is doubly stabilised and the system is doubly activated in order to obtain a measurable elimination rate.

49



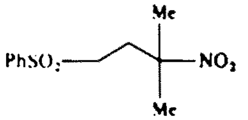
$(MeSO_2)_2CH\cdot CH_2\overset{Me}{C}(SO_2Et)_2 \xrightarrow{EtO^-/EtOH} (MeSO_2)_2C{=}CH_2 + MeC^-(SO_2Et)_2$

50

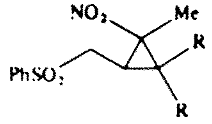
The bases of comparison are outlined in the original publications;[111,112] the simplest is with rank values. For cycloalkanes, the problem of change of mechanism between strained and unstrained systems does not generally arise. All reactions follow the $(E1cB)_R$ mechanism with loss of the leaving group in the rate-determining step; primary kinetic deuterium isotope effects are close to unity.

The rank values for **50** and **53** show a difference of 11.7 log units directly attributable to effect of the strain of the cyclopropane ring in lowering the energy of activation for ring fission.

The rank of the nitronate leaving group, $^-CMe_2NO_2$, has also been obtained[114] using, as before, phenylsulphonyl activation in substrate **57**. Comparison of reactivity of this open chain system with the strained analogues (**58**) is potentially capable of giving further quantitative evidence on the effect of strain on nucleofugality. Table 21 shows that incorporation of the leaving group in a cyclopropane produces accelerations of *ca* 4 × 10^{10}; unfortunately, for substrates **58a** and **58b**, the rank values show that in these cases deprotonation is slower than elimination and that the reactions are (probably) concerted. Direct evaluation of the effect of strain is not, therefore, possible.



57



58a R = H
58b R = Me

The questions then arise:

(i) How much is release of the strain of the ring expressed in acceleration of elimination?
(ii) What is the nature of the transition state for the process?
(iii) What is the comparison with other strained ring systems, notably cyclobutanes?
(iv) How do the derived values compare with other reactions?

Release of strain and transition state structure. The acceleration of $10^{11.7}$ for cyclopropane **53** (Table 20) corresponds to a reduction in free energy of activation of about 16 kcal mol^{-1} or about 60% of the strain energy (≡ to excess enthalpy of the ring). The effect of phenyl substitution **54** on the (strained) leaving group is very striking; notwithstanding the fact that the derived carbanion is stabilised by > 5 pK_a units, none of this stabilisation is reflected in an increased rate of ring cleavage. The activation

Table 21. Strained and unstrained nitronate leaving groups[114]

Substrate	k_{obs}[a]	Rank[b]
58a	61.7	+12.2
58b	5.3	+11.5
57	1.5×10^{-9}	+2.6

[a] Reactions in NaOEt EtOH at 25°; $M^{-1} s^{-1}$.
[b] $\log k_{obs}$ $\log k_{deprotonation} + 11$.

enthalpies for substrates **53** and **54** are remarkably similar. This evidence suggests a very small degree of ring fission in the transition state and that strain in a 3-membered ring decreases very sensitively with extension of a ring bond. The cyclopropanenitriles **51** and **52** show a different situation. The cyano-group is less effective than the phenylsulphonyl group in carbanion stabilisation; the leaving group rank for **51** is lower than that for **53**. Ring fission is more advanced in the transition state for the nitrile **51** than for sulphone **53**; $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are both more positive. This evidence is consistent with the greater mesomeric component of stabilisation by cyano than by sulphonyl groups.[115] A greater degree of charge transfer to the leaving group is required to benefit from cyano-stabilisation. Insertion of a phenyl group, as in cyclopropane **52**, produces a huge increase in rate which is accounted for by the much greater effect of a phenyl group in additionally stabilising cyano-stabilised rather than sulphonyl-stabilised carbanions.[115] The acceleration caused by both ring strain and leaving group stabilisation makes loss of leaving group competitive with (or concerted with) deprotonation and the mechanism is uncertain.

Comparison with cyclobutanes. It was an obvious extension of this work to examine four-membered rings with the same substitution pattern.[113] Results are in Table 20. Unfortunately, results for α-phenyl substituted substrates to calibrate transition-state structures, are not available because of synthetic difficulties. Comparison of cyclobutanes **55** and **56** with **51** and **52** show remarkably large 3-ring/4-ring ratios of 4840 and 57,600 respectively. The strain energy difference between cyclopropane and cyclobutane is 1.4 kcal mol^{-1} and, if expressed to the same extent as for cyclopropane fission, would give a rate ratio of around 6. The large rank differences of 3.5 and 4.5 respectively, speak of a different mode of strain release in the two systems. A simple calculation of ring strain as a function of bond extension to the strain-free open-chain structure for cyclopropane and cyclobutane respectively gives the plots of Fig. 8.

The differences between the two systems are accounted for by their different components of strain. In cyclopropane, 75% of the excess enthalpy is to be attributed to valence deformation (angle) strain and 25% to torsional strain. For cyclobutane, on the other hand, the contribution of 1,3-non-bonded interaction amounts to *ca* 50% of the total, the remainder being contributed, as for cyclopropane, by valence deformation and torsional strain.[27,116] It can be seen from Fig. 8 that except for very small bond extensions, the strain released for a given bond extension is less for cyclobutane than for cyclopropane. If the assumption is made that the *same* degree of bond extension to the leaving group is present in the transition states for fission of both systems, the rate ratio is reproduced with a degree of precision which is surprising when the simplicity of the calculations and the assumptions made are borne in mind.

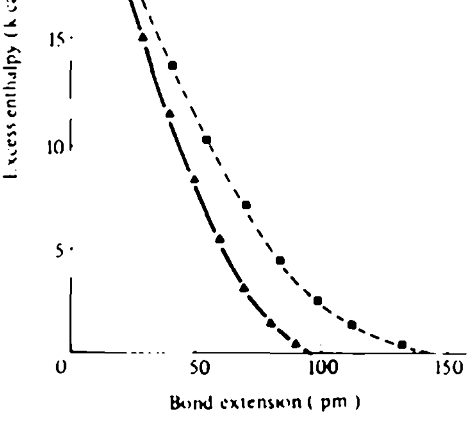
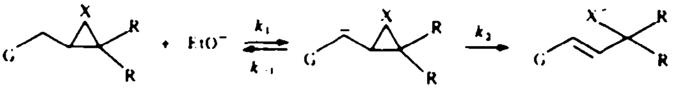


Fig. 8 Excess enthalpy as a function of bond extension for: ■, cyclobutane; ▲, cyclopropane.

Table 22. Nucleophilic eliminative cleavage of *gem*-dimethyl 3-ring systems[118]



Substrate		$k_{obs}^{a,b}$	$k_1^{a,b}$	$\Delta H^{\ddagger c}$	$\Delta S^{\ddagger d}$
48a	G = EtSO$_2$ X = O, R = H	185^e	2.5×10^{-1e}		
59	G = EtSO$_2$ X = O, R = Me	184	1.1×10^{-1}		
53	G = PhSO$_2$ X = CHSO$_2$Ph R = H(*trans*)	4.8×10^{-3f}	8.5×10^{-1f}	17.7^g	−10^g
60	G = PhSO$_2$ X = CHSO$_2$Ph R = Me(*cis*)	2.4×10^{-3}	3.8×10^{-1}	25.5	+15
61	G = PhSO$_2$ X = CHSO$_2$Ph R = Me(*trans*)	2.7×10^{-3}	3.8×10^{-1}	22.8	+7

[a] Reactions in EtONa EtOH.
[b] Units = $M^{-1} s^{-1}$ at 25°.
[c] Units = kcal mol^{-1}.
[d] cal $mol^{-1} K^{-1}$
[e] Value from ref. 110.
[f] Value from ref. 111.
[g] Value from ref. 112.

These observations pin-point the difficulty of generalising about the impact of strain differentials on reactivity even in very closely related systems. The problem is heightened by comparisons of reactivity in eliminations from oxy-anions (below).

Comparison of these results for heterolytic bond cleavage with those of homolytic cleavage is appropriate. Ruchardt and his collaborators[117a,117b] (Section IIvi) have compared free energies of activation for alkane homolysis with strain energies calculated by MM procedures. The slopes of the plots, when strain in the radicals is taken into account, indicate that 80–90% of the strain energy is expressed in reduction of $\Delta G^{\ddagger}$. This sensitivity is greater than for nucleophilic eliminative ring fission of cyclopropanes and is in contrast with results for S_N reactions on strained rings.

The gem-*dimethyl effect*. This effect has been discussed in Section IIii dealing with intramolecular nucleophilic substitution. The origins of the rate effects are controversial; recent work in the reporter's group has yielded quantitative results on its effect on ring cleavage. The systems of Table 20 lend themselves to modification with regard to the examination of structural effects on eliminative fission. We have examined cleavage of the three-membered rings. The results are given in Table 22.

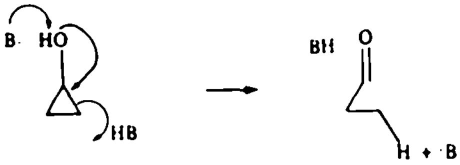
For the epoxides **48a** and **59**, *gem*-dimethyl substitution has a negligible effect on k_{obs} whose values are in any event well in excess of the calculated deprotonation rate constants. This indicates a concerted mechanism, which appears, surprisingly, to be unaffected by *gem*-dimethyl substitution.

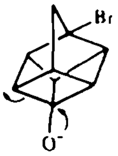
For cyclopropanes **53**, **60** and **61**, values of k_{obs} are closely similar. A *gem*-dimethyl effect is, however, apparent; the enthalpies of activation for cyclopropanes **60** and **61** are markedly greater than for **53**, implying a decrease in the strain contribution to acceleration of elimination. The differences of 5–8 kcal mol^{-1} are not expressed in the rate differentials because of compensation by more favourable entropy terms; were they to be fully expressed, k_{obs} values would be smaller by factors of 10^{3} to 10^{4}. These factors correspond broadly to the acceleration of ring *closure* by *gem*-dimethyl substitution discussed earlier. In ring cleavage, therefore, a *retro*-Thorpe–Ingold effect operates.

E1 *anion reactions: carbonyl-forming eliminative ring fission of oxy-anions*. Retro-aldol reactions usually proceed by sluggish approach to equilibrium whose position is extremely dependent on the structure of both carbanion and carbonyl components:

$$^{-}O{-}CR_2{-}R_3 \rightarrow O{=}CR_2 + {}^{-}R_3.$$

In the forward direction, the reaction is carbonyl-forming elimination of a carbon leaving group. By comparison with all other processes, carbonyl-forming elimination is insensitive to leaving group structure. This permits observation of the reaction in a wide range of structural situations. When the leaving group connection is strained by incorporation into a small ring, carbonyl forming elimination becomes rapid. Cyclopropanols have long been known to be unstable to bases:[79,119] and homocubyl alcohols, e.g. **62**, rapidly undergo eliminative ring fission in base.[120] It is not possible to obtain a direct evaluation of the role of strain in this reaction; the unstrained version – elimination of an ethyl carbanion – is not observable. Clearly the effect of strain is enormous. There is a mechanistic complication; Thibblin and Jencks[121] have shown that for the phenylcyclopropanol **63**, ring opening is subject to enforced acid catalysis. This implies that ring opening and attachment of the proton to the leaving group are concerted. Rates of ring cleavage of cyclobutanols **64** and **65** have been compared with the analogous cyclopropanols.[122] Results are given in Table 23.





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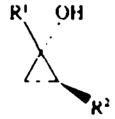

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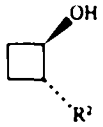

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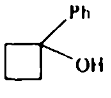
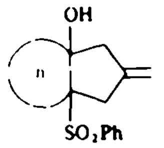


65

a R^1 = Ph, R^2 = H
b R^1 = H, R^2 = SPh
c R^2 = H
d R^2 = SPh

Clearly the main difference between the cyclopropanols and the cyclobutanols is in the impact of the respective and nearly identical ring strain energies upon the activation energy for ring fission. The explanations developed for the differentials seen above in cyclobutylmethyl anion cleavage cannot apply here. The factors are much too large. Either the transition states for ring cleavage are very different or there is an effect peculiar to cyclobutanes which inhibits ring opening. The latter explanation is preferred; it is tentatively postulated that a transannular interaction involving partial *bonding* between C_1 and C_3 of the cyclobutane ring is engendered by the relatively high electron density at C_1 in the anion. This is highly speculative and both calculations and experimental work are in progress with a view to understanding these very large effects better.

In connection with eliminative fission of cyclobutanols, the reaction has received considerable attention from synthetic chemists and their slow fission has been remarked upon.[123] Bicyclic alcohols **66** undergo fission as a function of the totality of strain:



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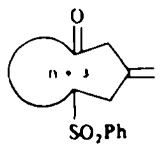


67

Table 23. Ring cleavage of cycloalkanols[122]

Substrate	k_{rel}[a]	Substrate	k_{rel}
63a	1	**63b**	110
64c	2.6×10^{-10}[b]	**64d**	1.4×10^{-5}
65	7.8×10^{-10}[b]		

[a] Reactions at 25° in aqueous M NaOH.
[b] Values by extrapolation from runs at 180°.

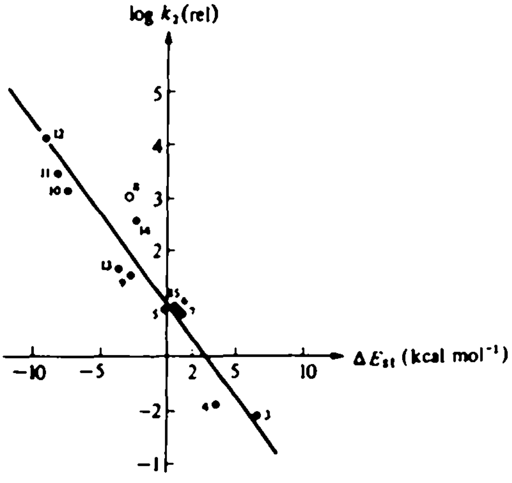


Fig. 9. Correlation of log k vs ΔE_{st} (ketone – ROH). Slope −0.34, intercept 0.89, r = 0.9717 (○ excluded). (Reproduced with permission from *Helvetica Chimica Acta.*)

with n = 6 and n = 7 the reactions are 6 kcal mol^{-1} endothermic and thermoneutral, respectively, and fission does not occur. For n = 8–12 reactions are exothermic by 5–9 kcal mol^{-1} and give the monocyclic systems **67**.[124]

Oxidative carbonyl-forming elimination in cyclic systems. Synthesis of cyclic ketones by chromic acid oxidation of cyclic secondary alcohols has been studied with respect to strain by Müller.[125,126a] Rates of oxidation of bi- and polycyclic secondary alcohols correlate with strain energy differences (from the Allinger MM1 programme) between alcohol and ketone. Correlations are obtained whether or not OH is simulated by Me in the strain energy calculations (Fig. 9). Reactivities span 10^5 and the correlation demonstrates that there is a high degree of cleavage to the chromate leaving group and that the carbonyl group is a good transition state model. The slope of the $\Delta H^{\neq}$ vs ΔE_{strain} plot is 0.47 showing that calculations on a simple sp^3–sp^2 model overestimate the strain energy change between ground and transition state. Correlation of $\Delta G_{oxidation}$ with the calculated (MM) strain energy differences between $R_2C{=}O$ and $R_2CH{-}Me$ gives a slope of 1.2. When the OH group itself is used in calculations the slope is 0.8 showing that the calculations with OH are not ideally accurate.[125]

Surprisingly, in this connection, cyclobutanol is oxidised by Cr(IV) slightly *faster* than cyclohexanol.[127] It would be expected that incorporation of an sp^2 hybridised carbon atom in an already strained ring would militate against ready oxidation. It turns out that from thermochemical measurements cyclobutanol is actually slightly *more* strained than cyclobutanone.

IIiv. *Additions to alkenes and alkynes*

There has been remarkably little correlation between the reactivity of alkenes and their degree of strain. On the one hand, the strain energies of a wide variety of (especially) bridgehead alkenes have been calculated by the MM1 programme[26] and are known from thermochemical measurements.[30] On the other hand many kinetic studies have been made of alkene and alkyne reactivity. It is not altogether clear therefore why so little connection has been made between the two collections of data.

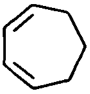
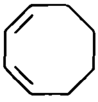
The most familiar types of strained alkenes are those in which the carbon–carbon double bond is constrained within a small ring or is of the E configuration within a medium ring.

Hydration of simple alkenes shows[106] negligible response to strain; relative rates of hydration of 2-methylpropene, 1-methylcyclopentene, 1-methylcyclobutene, and methylenecyclobutene are 1 : 2.29 : 0.2 : 0.6. The difference in strain energy between cyclopentene and cyclobutene is about 20 kcal mol^{-1}. The clear conclusion is that little change in alkene structure has occurred at the transition state and no appreciable covalent bonding of the water molecule has occurred.

Particularly familiar amongst strained medium ring alkenes are "Bredt" alkenes in which the double bond is at a bridgehead. Their chemistry has been reviewed[128,129] and they have been shown to undergo a variety of reactions not observed for their unstrained counterparts. The observations are qualitative; connections between strain and reactivity have, in general, not been made.

Electrophilic additions which permit rearrangement with relief of strain resulting in a strongly

Table 24. Hydration[a] of cyclic dienes in relation to their strain energies

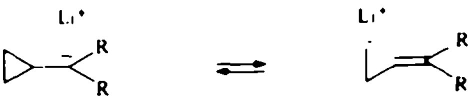
Diene	k_{rel}	Strain energy[b]	$\Delta H^{\circ}_{hydration}$[c]
	200	0.8	
	2000	−1.2	16.5
	4	1.4	
	1	3.8	19.0

[a] 1.05 M H_2SO_4–H_2O at 80°.
[b] Calculated from ref. 133
[c] kcal mol^{-1}.

exothermic reaction, have been referred to.[2] Recent work on electrophilic additions of sulphenyl halides to alkenes shows that norbornene derivatives are more reactive than unstrained alkenes but the rate ratios are not large. Norbornene is almost one hundred times more reactive than cyclohexene.[130] The alkene–alkane strain energy difference[131] for norbornene is 5.72 kcal mol^{-1} while that for cyclohexene is 0.86 kcal mol^{-1}, so the response to strain, even if this were the sole factor in reactivity, is about 50%.

Electrophilic hydration of cyclic 1,3-dienes actually shows[132] *inverse* correlation with strain energy[133] (Table 24), the slope of the plot of log k_{rel} *vs* strain energy is −0.9. The factor determining reactivity in these systems is the ground state conjugative stabilisation. This is absent[133] in cyclohexadiene. By comparison with an S_N1 dissociative process involving nearly complete conversion of sp^3 to sp^2 hybridisation, addition to alkenes is expected to be rather insensitive to strain elements because two sp^2 hybridised atoms in the ground state go to one sp^2 hybridised and one partly sp^3 hybridised atoms in the transition state.

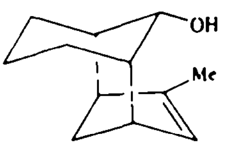
Results on nucleophilic addition are likewise qualitative and most evidence comes from intramolecular processes. The eliminative ring fission[79] **68** ⇌ **69** has been shown[134] to be reversible;



68 **69**

$t_{1/2}$ for equilibration, when R = H, is 30 hr at 27°. This is, *prima facie*, a doubly surprising result; unactivated nucleophilic addition to a non-polarised alkene is an unfavourable process and a highly strained cyclopropane ring is formed. Formation of a highly strained product has been seen to be of little significance in connection with rates of cyclisation by intramolecular nucleophilic substitution (Section IIiib) and addition of nucleophiles to unpolarised alkenes is seen below in strain-favoured situations. The equilibrium **68** ⇌ **69** is easily perturbed; when R = H, the equilibrium favours **69** essentially exclusively. With R = Ph, **68** is stable in THF but opens to **69** on addition of ether to the solution.

Interesting work by Ganter[135] has shown that addition of the hydroxyl group of **70** to the carbon–carbon double bond is enforced by strain to give **71** with the expected regiospecificity. The



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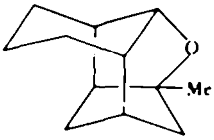

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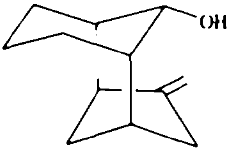
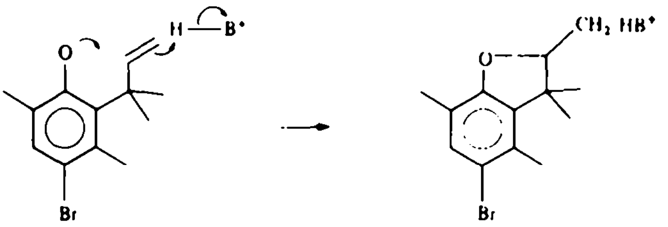


72

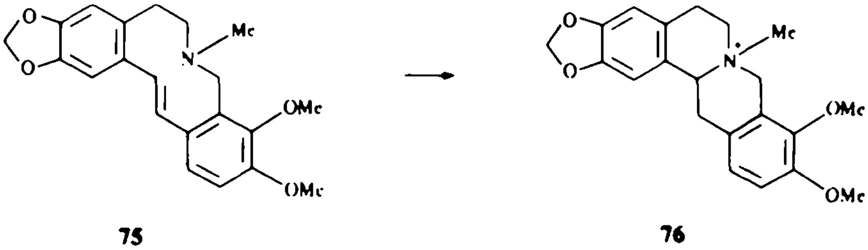
other regioisomer is proven to be stable in the reaction conditions. Deuterium labelling experiments and reactions with **72** show **72** to lie on the pathway between **70** and **71**. A very similar system showing strong hydrogen bonding between the hydroxyl group and the carbon–carbon double bond has been described by Grob.[136] In neither investigation, however, were strain energies known.

Intramolecular addition of phenolic hydroxyl to an unactivated alkene has been reported by Evans and Kirby;[137] **73** gives **74** probably by enforced acid catalysis.[138]



73 74

Similarly, Kirby and Logan[139] have demonstrated strain-enforced reversal **75** → **76** of Hofmann-type elimination of an 'onium group, a system closely related to others recently reported.[140,141]



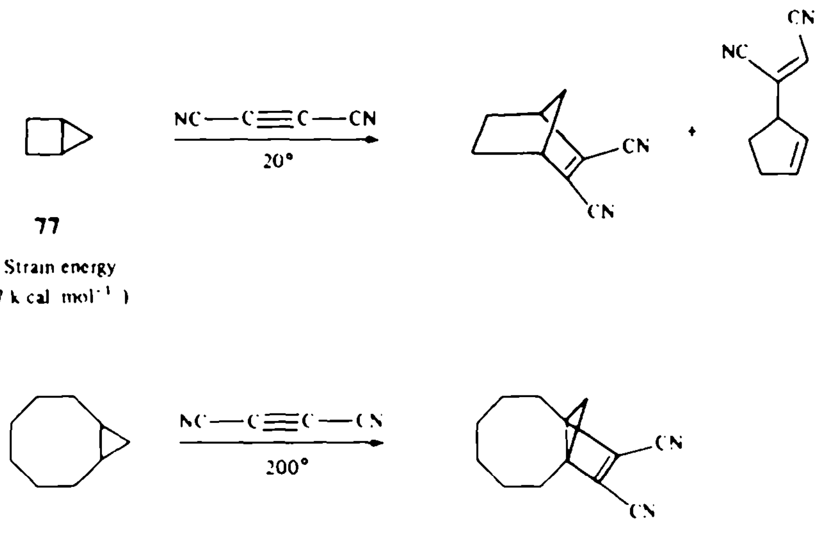
75 76

No direct strain–reactivity correlations in these interesting reactions are possible.

Cyclo-additions. Again, in all cases, accurate connection between reactivity and strain is impossible, but a scatter of numerical values gives some impression of strain effects.

Reactivities of the bicycloalkanes **77** and **78** with dicyanoacetylene are indicated in Scheme 2.[142] It could be very roughly estimated that k_{rel} is 10^5, $\Delta\Delta G^{\neq}$ is 7 kcal mol^{-1} or 50% expression of strain energy difference. The very small solvent effect suggests that diradicals may be involved.

The very high reactivities of cycloalkynes, including benzyne have been extensively described,[143] but relationships between reactivity and strain have not been quantitatively examined. Reactivity of



77

(Strain energy
47 k cal mol^{-1})

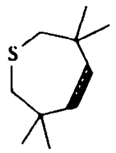
78

(Strain energy
≈ 33 k cal mol^{-1})

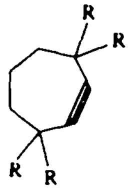
Scheme 2.

cycloalkynes increases rapidly as ring size is reduced; $t_{1/2}$ values are roughly days at 25° for C_8, 1 hr at $-75°$ for C_7 and seconds at $-110°$ for C_6.

Krebs and Kimling[144] have examined the reactivity of cycloalkynes **79** and **80**.



79



80a R = H
80b R = Me

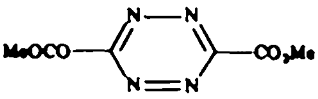
79 is stable at 140° whereas for **80a**, $t_{1/2}$ in 0.016 M solution in CH_2Cl_2 is < 60 s at $-25°$. Remarkably, for **80b**, $t_{1/2}$ for a 0.2 M solution in CCl_4 at 25° is 1 day, and **80b** dimerises 10^8 times more slowly than **80a**, corresponding to an activation energy difference of 10–11 kcal mol^{-1}. Presumably, this is another manifestation of *gem*-dimethyl stabilisation of cyclic systems noted earlier in Sections IIiib and IIiii.

Huisgen[145] has correlated rates of 1,3-dipolar addition of phenylazide to alkenes with the infrared stretching frequencies of the carbon–carbon double bonds. The norbornene : cyclohexene ratio of 5700 is very much larger than for sulphenyl halide additions (above). If the alkenes are compared on the basis of their alkene less alkane strain energy differences, the $\delta\Delta$ strain energy value is 4.86 kcal mol^{-1} and the reactivity response to strain differential is very high. Huisgen and his co-workers[146] have also compared reactivities of norbornene and cyclohexene in reactions with phenylisocyanate and diazomethane. Similar ratios of 6100 and 5400 were found.

Reactivities of cycloalkenes towards dipolarophiles **81** and **82** have also been compared[147] (Table 25).

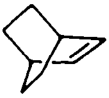
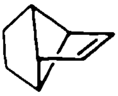
$PhC\equiv\overset{+}{N}-\bar{O}$

81



82

Table 25. Reactivities of cycloalkenes towards dipolarophiles

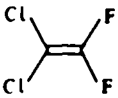
Alkene	δ Strain[a]	k^b (81)	k^b (82)
	−0.15	1.2	1.27
	−4.74	3150	11,700
	−0.51	5.7	113
	−9.96	2280	-
	−8.91	2300	5370

[a] Strain energy difference between cycloalkene and cycloalkane; n.b. values vary somewhat with source (below), general conclusions are unaffected (kcal mol^{-1}).

[b] 10^6 M^{-1} s^{-1} at 25° in CCl_4.

Since the relationship between log k and δ strain is not rectilinear the reactivity differences can only be attributed in part to strain released in the transition state. The authors estimate that 27–49% of $\Delta\Delta G^{\neq}$ is due to strain release; the remainder may be due to what is termed "non-equivalent orbital extension".

Bredt alkenes have been shown[148] to be highly reactive in 2 + 2 cycloadditions with alkene **83**. Typically, **84** reacts in 30 hr at 80°, norbornene requires 3 days at 120° and 1-methyl-*cis*-cyclo-octene, 15 days at 150°. The olefinic strain energy for norbornene is 5.72 kcal mol^{-1} [131] while that for **84** is 15.2 kcal mol^{-1}.[26] A crude calculation suggests a rate ratio of 100 so olefinic strain is only insensitively expressed.



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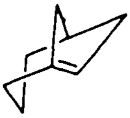
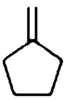


84

Table 26. Additions of PhN$_3$ to alkenes

					
k_{rel}	0.005	0.23	1	101	580
Strain relieved on hydrogenation (kcal mol^{-1})	−0.9	13	−0.3	9.6	26

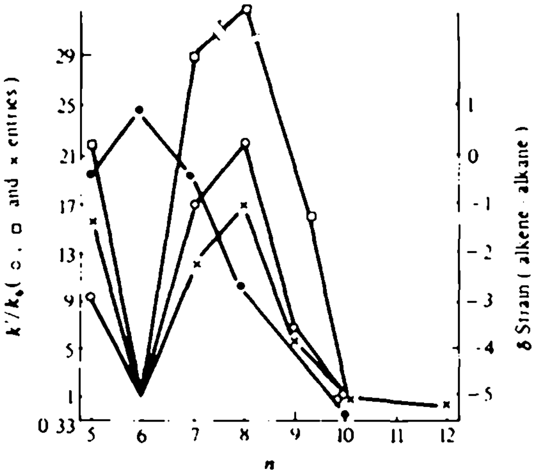


Fig. 10 Relative rates (k_n/k_6) of diethylaluminium hydride addition at 78° (○), hexachlorocyclopentadiene addition at 78° (□), and diimide reduction (×) at 80° of *cis*-cycloalkenes as a function of ring size, n. δ strain (alkene–alkane) kcal mol^{-1} (●).

Aue and Helwig[149,150] estimate that in additions of phenylazide to alkenes about 20–25% of strain is released at the transition state. Results are given in Table 26; terminal alkenes are evidently inherently less reactive.

Addition of hexachlorocyclopentadiene to *cis*-cycloalkenes[151] shows 70-fold rate variation from C_4 to C_{11} (Fig. 10). In this plot of reactivity versus ring size, the olefinic strain energy is superimposed and it is clear that no simple relationship exists between the two sets of data.

4-Centre reactions. In di-imide reductions of alkenes,[152] k_{rel} values (Fig. 10) again do *not* follow either the ground-state strain energies of the cycloalkenes or the differences between reactant and product strains. It is suggested that the transition state is early and that π-bond orders are still large; small parallel deflections are envisaged. The high reactivities of norbornene and cyclopentene are due to the relief, in the transition state, of valence angle distortion and torsion in the vicinity of the carbon–carbon double bond. Smaller effects are seen in the additions of Et_2AlH to *cis*-cycloalkenes (Fig. 10).[153]

Complex-formation. Cyclopropene forms an argentic complex with a formation constant, roughly 10^8 times that of cyclopentene, corresponding to a $\Delta\Delta G°$ value of 11 kcal mol^{-1}.[154] This indicates that 20–30% of the strain energy is expressed. The deformation of the π-orbital enhances complex formation and, with smaller energies involved, the same effect is seen in argentic complexation of the C_5, C_6 and C_7 cycloalkenes (Table 27).[155]

Again, the $\Delta\Delta H°$ versus strain response is about 30%. This is clearly not a general phenomenon, however. Bach and Richter[156] have shown a lack of general correlation between rates of oxymercuration and equilibrium constants for argentic complex formation on the one hand and strain energies of alkenes or even alkene–alkane strain energy differences on the other (Table 28).

It is clear that relief of strain in the rate determining step is not appreciable. Steric hindrance is a major factor as demonstrated by the low formation constants of complexes with 1-methylcyclohexene and *trans*-1,2-di-t-butylethene.

Table 27. Formation of argentic complexes of cycloalkenes

Cycloalkene	ΔH_0[a]	Δ Ring strain[a]	Δ Strain[a] alkene–alkane
C_5	−7.03	4.4[b,c]	1.46[b,d]
C_6	−5.58	0[b,c]	0[b,d]
C_7	−6.61	4.1[b,c]	1.55[b,d]

[a] kcal mol^{-1} at 25°

[b] Relative to cyclohexene.

[c] Calc from heats of formation.

[d] Alkene alkane strain energy difference.

Table 28. Oxymercuration and argentic complex formation in alkenes

Alkene	Hg^{2+} k_{rel}	Ag^{+} k_{rel}	Cycloalkene strain energy*	Δ strain (alkene–alkane)*
Norbornadiene	27.0	8.5	31.59	7.97
trans-Cyclo-octene	10.1	7300	17.85	6.33
Norbornene	4.5	13	23.62	5.72
1-Methylcyclohexene	2.2	0.07	2.68	
Cyclohexene	1.0	1.0	1.61	0.86
Cyclobutene	0.40	0.76	28	2
trans-1,2-Di-t-butylethene		0.026	6.01	−0.54
Bicyclo[2,2,2]octene	0.030	1.1	15.99	4.30
cis-Cyclo-octene	0.004	3.04	8.81	−2.71
cis-Di-t-butylethene		1.0	16.37	9.82

* kcal mol^{-1}.

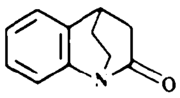
IIv. *Ac and related reactions*

Ac reactions. There is an enormous literature in this field with very many kinetic studies. Reactions are often mechanistically complex and identification of structural effects on rate determining steps is not always possible. Again, notwithstanding the large amount of quantitative work, connections of reactivity with strain have been sparse.

Ester hydrolysis and related reactions. The fact that the hydrolysis rate of maleic anhydride is about 10 times that of succinic anhydride has been attributed[157] to strain differentials. Such a small effect is undoubtedly complicated by electronic factors and the effect of the carbon–carbon double bond is unquantified.

Eberson[158] has shown that hydrolysis rates of fused 5-ring anhydrides vary over $10^{1.2}$ according to the size of the fused ring and the configuration of the ring junction. No clear relationship with strain energies is apparent.

In amide hydrolysis, very substantial neighbouring group effects have been observed[159] but quantitative correlations with experimental or calculated strain differentials are not possible. A more direct comparison emerges from interesting work of Blackburn's[160a] group in which the lactam **85** reacts 10^7 times more rapidly than the unstrained analogue **86**. In this case, the "strain energy" can be equated with a loss of resonance energy, amounting to 17 kcal mol^{-1}, in the amide function. This loss arises from the enforced uncoupling of the p–π interaction. The acceleration corresponds to a $\Delta\Delta G^{\neq}$ of about 10 kcal mol^{-1} which implies that slightly more than half of the strain energy is relieved at the transition state of hydrolysis.



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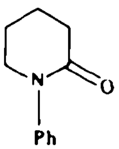
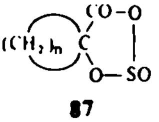


86

Page and his group[160b] have demonstrated the unimportance of strain in acceleration of the alkaline hydrolysis of β-lactams; they conclude that the rate-limiting step involves little or no ring fission.

For alkaline hydrolysis of simple lactones[161] with 4- to 7-membered rings, the rate order is 6 > 4 > 5 > 7 > open chain, with rates spanning $10^{2.3}$. The β-lactone has the *highest* $\Delta H^{\neq}$ value and clearly there is not a direct connection between ring-strain and reactivity. The rate determining step, however, is addition to the carbonyl group and hence relief of ring strain by ring cleavage should have insignificant effects on activation energies. Clearly, bending at the intracyclic C-1 angle, change in torsional strain, and loss of resonance energy contribute in different respects according to the lactone, but the differentials are so far unquantified.

In polymerisation of spiroanhydrosulphites (87),[162] rates follow the order of ring size 4 > 7 > 5



87

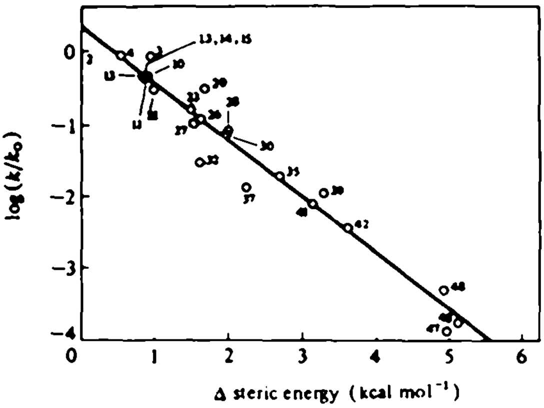


Fig. 11. Linear free energy correlation of E_S(= log k_{rel}) for acid-catalyzed hydrolysis of esters *vs* ΔSE (= steric energy for ortho acid–steric energy for acid). The numbers correspond to Taft's table (ref. 166). (Reproduced with permission from ref. 165 Copyright (1976) American Chemical Society.)

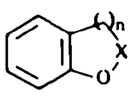
> 6. Values of E_A are 4-, 17.5; 5-, 28.5; 6, 32.6; and 7-, 28.7 kcal mol^{-1}, respectively, for reactions in nitrobenzene. The spirocarbocyclic ring is not opened in the polymerisation but the 4- and 7-membered ring systems are substantially more reactive than the bis-alkyl (non-spiro) analogues. The effect of the spiro linkage is probably to increase strain in the heterocyclic ring but, again, effects are not large and contributions to strain are not readily discernible.

Steric effects in acyl transfer reactions have been analysed by DeTar.[163–165] Steric effects of groups were quantified on an empirical basis many years ago by Taft[166a] who compared rates of acid hydrolysis of esters RCO_2Et with that of CH_3CO_2Et. His E_S values have not, however, been related quantitatively to other physico-chemical parameters, notably van der Waals radii. DeTar[164] has successfully related these E_S values to the strain energy difference between $RCH(CH_3)_2$ representing RCO_2Et and $RC(CH_3)_3$ representing $RC(OH)_2OEt$, the tetrahedral intermediate. The strain energy differences were obtained by molecular mechanics[9,22] giving ΔH_f values which include not only steric energies but also base values dependent on group increment terms and statistical mechanical corrections inserted to take account of real conformer populations. A linear relationship between $\Delta\Delta H_f$ and log k_{rel} for acid hydrolysis is obtained, so E_S values are derivable by calculation, $E_S = 4.419 + 0.552\ \Delta\Delta H_f$. Substantially deviant points are found for R = tBuMeCH, neopentyl(CH_3)CH, and 4- and 5-membered cycloalkanecarboxylates. In the former cases, the model for the ester is notably imperfect and in the latter the alkanes are highly hindered. The success of such a correlation shows, incidentally, that strain effects on free energies of activation are primarily to be related to the enthalpy term.

DeTar[165] has refined this treatment by selection of RCO_2H to represent the ester and $RC(OH)_3$ to represent the tetrahedral intermediate in the force field calculations. As before, ΔH_f values, the sums of several components including steric energy, were obtained. The plot of log k_{rel} for acid hydrolysis *vs* ΔSE is in Fig. 11 giving log k_{rel} = 0.34 − 0.789SE.

Predictions of relative rates spanning 800,000 have been made, and real confidence is expressed that E_S values do measure steric effects of alkyl groups. In this connection, F-strain effects on reactivity have been discussed.[166b] Plots of E_S *vs* the front strain parameter $\mathscr{T}_f$ give similar slopes but different intercepts.

In comparison of alkaline hydrolysis of 5- and 6-ring sultones and lactones **88**[167] only rather small (< 10) 5:6 ratios are found for lactones. For sultones, however, values of 5:6 ratios are 10^4 and $\Delta\Delta H^c_{hydrolysis}$ 5-ring–6-ring is 23.4 kcal mol^{-1}. Clearly this enthalpy difference is only insensitively

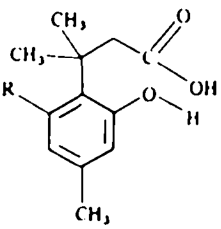


X = CO or SO_2, n = 1 or 2

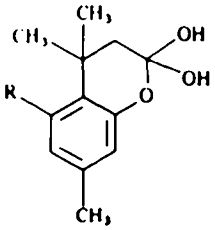
88

mirrored in the transition state $\Delta\Delta G^{*}$ but the reactivity difference is attributed to the (unquantified) ring strain difference as well as other possible factors.

Lactonisation. Very large effects of structure on lactonisation rates have been observed, the most striking being the "trimethyl lock" **89**.[168a] For **89b** lactonisation is 5.1×10^{10} faster than for **89a**

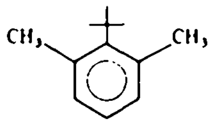


89a R = H
89b R = Me



90a R = H
90b R = Me

corresponding to $\Delta\Delta G^{*} \simeq -15$ kcal mol^{-1}. It was concluded that the acceleration was due to an increase in the population of conformers with geometries appropriate for cyclisation and no strain factors were invoked. Winans and Wilcox,[168b] however, have interpreted these results on the basis of conventional relief of ground-state strain. They carried out MM calculations using, additionally, homomorphic (Section IIiia) representations of starting materials **91** and products **92**. The



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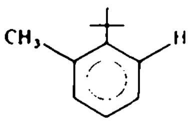
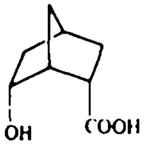


92

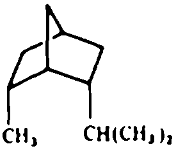
homomorphs suggested an acceleration of 10^{12}–10^{14} to be reasonable and certainly to accommodate the acceleration of lactonisation which was claimed. Calculations on **89a** and **90** showed that the difference in relief of strain energy between lactonisation of **89a** and **89b** to give **90a** and **90b** respectively was 10.34 kcal mol^{-1} corresponding to rate difference of $> 10^{7}$. Further refinement[168b] to give full thermodynamic results suggest $\Delta\Delta G^{\circ}_{298}$ of 14.25 kcal mol^{-1} and a rate ratio of about 3×10^{10}. The dominant contribution is assigned to a conventional steric interaction which raises the ground state energy. If the "locking" contribution is purely entropic (both systems having the same ground state energy) then the acceleration due to this effect is *ca* 10^{3}. The most recent work on this topic[169a,b] shows, however, that earlier work had overestimated the reactivity. Further analysis by DeTar[170] reduces the real reactivity ratio to 4×10^{3} bearing in mind the lesser degree of strain relief for formation of the tetrahedral intermediate in lactonisation. Relative reactivities estimated from strain differences suggest, therefore, that only a fraction of ground state strain is relieved at the transition state.

Storm and Koshland[171] have dissected acid-catalysed lactonisation rates spanning a range of 10^{6} in k_{rel}. Corrections ($< 10^{2}$ in k_{rel}) were made for torsional effects in reduction of rate as well as estimations of strain in, for example, the very reactive hydroxy acid **93**. This acid is $> 10^{4}$ times as reactive as γ-hydroxybutanoic acid. As rates of alkaline hydrolysis are very similar, ring strain effects are dismissed and 'orbital steering' into the required alignment for bond formation is invoked.



93

DeTar[172] is able to reproduce by MM calculations on hydrocarbon models **94** and **95** (representing the starting material and the tetrahedral intermediate, respectively) relative lactonisation rates of hydroxy-acids such as **93** with fair accuracy. His results suggest that it is not necessary to invoke the special trajectories involved in orbital steering.



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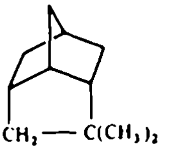

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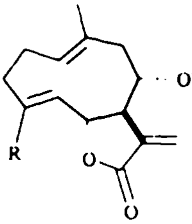
In lactone isomerisation, it is possible to predict (successfully) from MM calculations[173] that **96** will rearrange to **97**.



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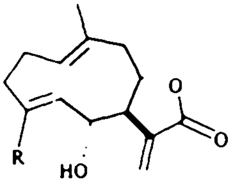
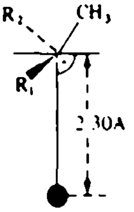


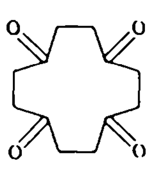
97

Additions to carbonyl groups. For reductions of ketones with sodium borohydride, Perlberger and Müller[174,175] have calculated strain energy differences between the carbonyl compound and **98** as a model of the transition state. The methyl group simulates the forming hydroxyl group and the perpendicular approach angle is adopted for simplicity. The bond length of 2.30 Å was adopted in order to reproduce the isomer proportions obtained experimentally from camphor. Epimer distributions were reproduced within 10% and rates over $10^{8\pm1}$.

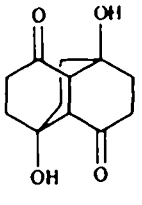


98

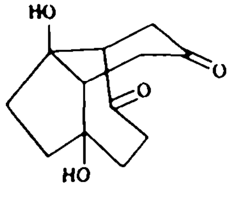
Osawa[176] and his collaborators have used molecular mechanics calculations (Allinger MM1 and MM2) to evaluate strain in the candidate products of acid-catalysed aldol-type cyclisation of the tetraone **99**. The outcome is predicted to be **100** which has an enthalpy 10–20 kcal mol^{-1} below other candidates except **101** for which the difference is 1.5 kcal mol^{-1}.



99

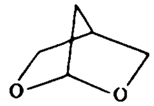
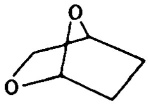
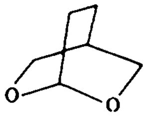
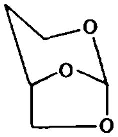


100



101

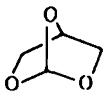
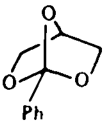
Table 29. Acid-catalysed hydrolysis of cyclic acetals[179]

Substrate	k_{rel}
 **102**	6.9×10^5
 **103**	2.5×10^4
 **104**	2.5×10^3
 **105**	7.7
$(MeO)_2CH_2$	1

IIvi. *Hydrolysis of acetals and orthoesters*

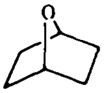
Hall[177–180] and a number of collaborators have compared rates of acid catalysed hydrolysis of cyclic acetals and orthoesters with acyclic analogues presumed to have little or no strain. Results are given in Tables 29 and 30.

Table 30. Acid-catalysed hydrolysis of orthoesters[177]

Orthoester	k_{rel}
 **106**	1.63
 **107**	15.7
$(MeO)_3CH$	1

While no values for strain energies are available, it is reasonable to ascribe[179] the substantial rate ratios in Table 29 to strain differentials coupled with the anomeric effect of the oxygen atoms adjacent to the reaction site. The lower reactivity of **105** by comparison with **102**, **103** and **104** is ascribed to lesser operation of the anomeric effect[180] and it is in any event substantially less strained. The real significance of strain is not clear in these systems.

For hydrolysis of orthoesters[177] (Table 30) the absence of rate enhancement over acyclic orthoesters is striking. The ring systems are undoubtedly strained but not to the same extent as their hydrocarbon analogues. The mono-oxa compound **108**, for example, is 3.6 kcal mol^{-1} less strained than norbornane. The transition state for oxygen–carbon heterolysis is probably early with little ring opening and consequent strain relief. The higher reactivity of **107** is consistent with rate determining formation of an intermediate carbocation.



108

IIvii. *Radical reactions*

The relationship between strain and reactivity in homolytic processes has been particularly explored in three principal processes, (i) the simplest of all reaction types—homolytic dissociation of alkanes, (ii) in the eliminative ring fission of cycloalkylmethyl radicals and (iii) in ring opening of cycloalkyl radicals. It is particularly in types (i) and (ii) that direct connections can be made between reactivity and strain and that comparisons can be drawn with analogous heterolytic processes.

Homolytic dissociation of alkanes. Rüchardt and his group have examined many different types of alkane and have derived values of $\Delta G^{\ddagger}$ for thermolysis. These $\Delta G^{\ddagger}$ values have been compared[117] with strain energies of the alkanes calculated by MM methods and typical plots of $\Delta G^{\ddagger}$ *vs* calculated values of alkane ground state strain energy, H_{sp} are given in Fig. 12. Rüchardt's extensive data, together with some from other laboratories, are summarised in Table 31.

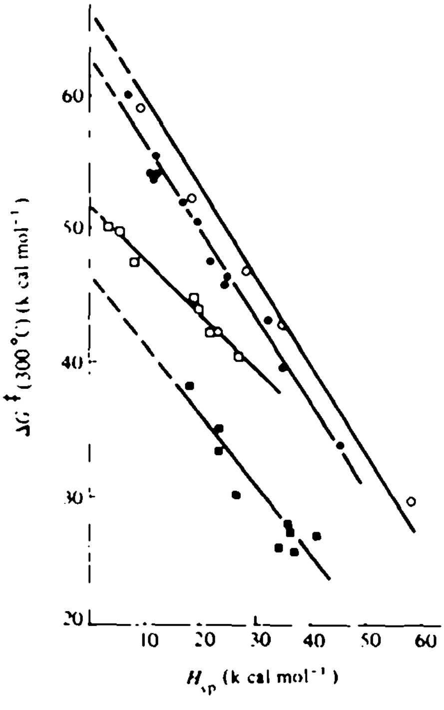


Fig. 12. Correlation between the free energy of activation, $\Delta G^{\ddagger}$ (300°), for thermolysis and the ground state strain enthalpy for hydrocarbons. The correlation lines yield the following equations (see text): ○ $\Delta G^{\ddagger} = 66.9\,(\pm 1.0) - 0.65\,(\pm 0.04)\,H_{sp}$ kcal mol^{-1} (tertiary–tertiary); ● $\Delta G^{\ddagger} = 62.2\,(\pm 0.7) - 0.62\,(\pm 0.03)\,H_{sp}$ kcal mol^{-1} (quaternary quaternary); ☐ $\Delta G^{\ddagger} = 51.4\,(\pm 1.4) - 0.48\,(\pm 0.11)\,H_{sp}$ kcal mol^{-1} (α-phenyl-t-tertiary); ■ $\Delta G^{\ddagger} = 43.3\,(\pm 2.3) - 0.64\,(\pm 0.11)\,H_{sp}$ kcal mol^{-1} (α-phenyl–q-quaternary). Standard deviations in parentheses.

Table 31. Thermolysis of alkanes and related compounds

Entry	System	Slope $\Delta G^{\neq}$ *vs* H_{sp}[a]	Slope $\Delta G^{\neq}$ *vs* D_{sp}[b]	Ref.
1	R^1R^2CH t-Bu	-0.70 ± 0.07	–	181
2	$R^1R^2R^3C$ t-Bu	-0.67 ± 0.02	-0.91[c]	181
3	$R^1R^2R^3C$–$CR^1R^2R^3$	-0.62 ± 0.03	–	117, 182
4	R^1R^2CH–CHR^1R^2	-0.65 ± 0.04	-0.79	183
5	PhR^1R^2C CR^1R^2Ph	-0.64 ± 0.01	-0.77	184
6	$R^1C(CN)_2$ t-Bu	-0.81 ± 0.17		185
7	$R_1R^2C(CN)$–$C(CN)R^1R^2$	-0.77 ± 0.17	-0.88	186
8	$PhR^1(OMe)C$ $C(OMe)R^1Ph$	-0.60		187
9	$R^1R^2C(OH)$- t-Bu	—	$-1.09\ (\pm 0.12)$	188

[a] Calculated ground state strain energy of the hydrocarbon.

[b] Calculated change in strain enthalpy on dissociation (i.e. strain in product radicals allowed for).

[c] Mean of quaternary quaternary and tertiary–quaternary systems.

Values of the strain energies of the hydrocarbons, H_{sp}, do not take into account the strain energies of the radicals produced and slopes are substantially less than the value of unity that would be expected for dissociation into strainless fragments. Alternatively, however, the strain energies of the radicals, $R^{\cdot}$, produced can be calculated by a force field for radicals developed in Rüchardt's laboratories, or equated with those of the hydrocarbons, R—H. When these are subtracted from values of strain energies of the thermolysis substrates, values of strain energy differences, D_{sp}, are obtained. The correlations of these D_{sp} values with values of $\Delta G^{\neq}_{400}$ are even better than those between $\Delta G^{\neq}_{300}$ and H_{sp}. Slopes of $\Delta G^{\neq}$ *vs* D_{sp} are substantially greater (Table 31) reflecting the release of roughly 90% of the strain energy difference between substrate and initial thermolysis products (entries 2, 7 and 9). The "missing" 10% is to be attributed to the lack of precise compensation between $\Delta H^{\neq}$ and $T\Delta S^{\neq}$ terms and/or the fact that strained alkyl radicals may pass a small activation barrier to recombination.

Incorporation of an α-phenyl group (entry 5) again gives a good linear correlation (slope -0.64) between $\Delta G^{\neq}_{300}$ and H_{sp} rising to -0.77 when the correlation is *vs* D_{sp}. The intercept on the $\Delta G^{\neq}_{300}$ axis allows derivation of a value for the resonance stabilisation of the α-phenyl substituted radicals of *ca* 9 kcal mol^{-1} in good agreement with the literature value.

The symmetrical (entry 7) and unsymmetrical dinitriles (entry 8) show substantially larger slopes for the H_{sp} correlation than for other systems studied; this change is attributed to the small size of the cyano group and hence the smaller strain energy of the radical produced. The correlation with D_{sp} (for symmetrical dinitriles, entry 7) again gives a larger slope. The intercepts produce values of resonance stabilisation energies amounting to 5.5 and 9.1 kcal mol^{-1} respectively for radicals $NC\dot{C}R_2$ and $(NC)_2\dot{C}R$. Similar considerations give resonance stabilisation energies of 1.5–2.0 kcal mol^{-1} for α-methoxyalkyl radicals. Results for pyrolysis of 1,1′-diadamantane show that there is little strain energy difference between the 1-adamantyl radical and the parent hydrocarbon. The conclusions are confirmed by force field calculations. A generally higher flexibility of bond angles to carbon radical centres is characteristic of these species[189a] and contrasts with their much more rigid carbocation counterparts.[32] The strain enthalpy of 1,1′-diadamantane is 6.7 kcal mol^{-1}.

The large reactivity range for thermolysis of bis-α-phenylcycloalkanes is attributed both to I-strain effects and in, for example, the nine-membered ring, relief of non-bonded repulsion terms.[189b]

α-Hydroxyalkyl radicals are produced by pyrolysis of tertiary alcohols[188] and again, values of $\Delta G^{\neq}$ correlate with MM2 calculations in which C—OH is simulated by CHOH. Stabilisation by α-OH of an alkyl radical is estimated at 2.8–4.7 kcal mol^{-1} in fair agreement with estimates from other sources (2.6–5.0 kcal mol^{-1}). This work has recently been extended to formation of bi- and tricyclic radicals. In $R^1R^2R^2C$—$OH \rightarrow R^2R^2COH + R^{3\cdot}$, 1-adamantyl and octyl are ejected more easily than norbornyl.[190a] Strain energies in radicals, $C^{\cdot}$, are slightly greater than in the alkanes, C—H, for adamantyl, bicyclo(2,2,2)octyl and norbornyl by 2.2, 3.5 and 3.8 kcal mol^{-1} respectively.

Some relevant work has also been carried out on thermolysis of azoalkanes, $R^1R^2R^3C$—N=N—$CR^1R^2R^3$.[190b] It was found[191] that $\Delta H^{\neq}_{dissoc}$ broadly correlated with calculated strain energies (Table 32). The very close agreement between Δ strain energy and $\Delta\Delta H^{\neq}$ suggests a ground state effect. A concerted two-bond cleavage is indicated by $\Delta\Delta H^{\neq}$ for systems 1 and 3; the value for single bond cleavage would be *ca* 5 kcal mol^{-1}. Also the fact that system 2 shows an

Table 32. Thermolysis of azoalkanes, $R^1—N{=}N{=}R^2$

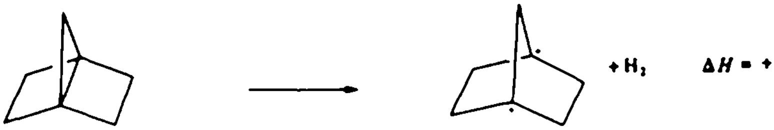
No.	R^1	R^2	$\Delta H^{\ddagger}$	Δ strain energy (calc)
1	t-Bu	t-Bu	42.2	0
2	t-Bu	t-$BuCH_2CMe_2$	38.1	4.6
3	t-$BuCH_2CMe_2$	t-$BuCH_2CMe_2$	31.7	10.7

intermediate value of $\Delta H^{\ddagger}$ is consistent with cleavage of carbon–nitrogen bonds simultaneously. The more unsymmetrical the azo-compound, however, the more unsymmetrical is its cleavage, and a continuum of mechanisms appears to exist.[190b]

Linear correlations have been found between log k values for thermolysis of azoalkanes and solvolysis of the corresponding tertiary *p*-nitrobenzoates.[192] The *p*-nitrobenzoates with linear side chains give a steeper slope (0.93) *vs* thermolyses than those with branched side chains (0.63). The difference is put down to solvation effects in the esters.

Wiberg and Walker[193] have calculated values for enthalpies of "intramolecular" dissociation in tricycloalkanes (**109**, **110** and **111**). The strain energies of all three *tri*cyclic compounds are equal but

109



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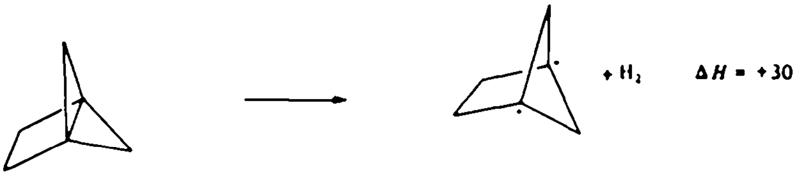

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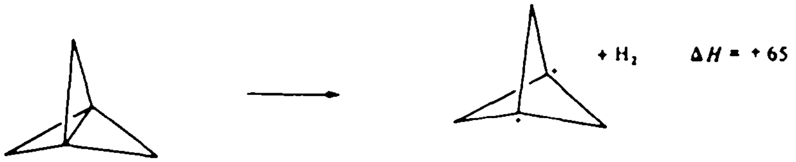
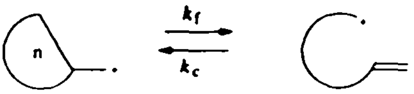


those of the *bi*cycloalkanes are markedly different, suggesting that the reverse (ring closure) to propellanes should occur much more easily for **111** than for **109** and **110**.

Homolytic eliminative ring fission. Eliminative ring fission of carbanions was discussed earlier (Section IIiii) and very large accelerations of elimination of oxygen and carbon leaving groups have been recorded. Homolytic analogues of those reactions have been widely reported; again most of the work is qualitative. This type of reaction is one of many rearrangements recently reviewed by Beckwith and Ingold.[194] The general scheme of reaction is:

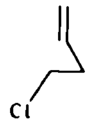


Reaction k_f is a thermochemical compromise between cleavage of a (weak) σ-bond adjacent to a radical centre and release of strain energy *vs* formation of a π in place of a σ-bond. Unsurprisingly, the left-hand side of the equilibrium is disfavoured for 3- and 4-rings while the balance is much more even for 5- and 6-rings.

Some qualitative examples from many reported illustrate the general pattern of behaviour.

Homolytic chlorination of methylcyclopropane gives[195] **112** and **113**. For radical **114** therefore, there is competition between direct reaction with chlorine to give **112** and eliminative ring fission, to **115**, with subsequent formation of **113**. Rearrangement of **115** to give the cyclobutyl radical precursor of **116** is not detectable. Formation of 4-rings is known to be slow (Section IIiib). By contrast, rapid interconversion of **117** and **118** is observable[196] and occurs faster than abstraction of a hydrogen atom from triethyltin hydride. Strain in the 3-ring of **117** is clearly little of a barrier to rapid intramolecular addition.

112



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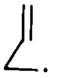
114



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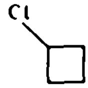
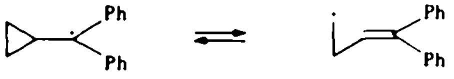
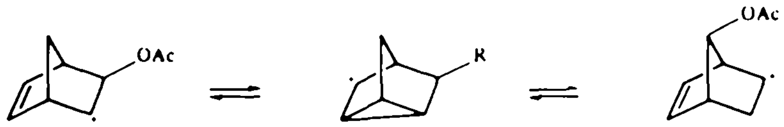


116



117 **118**

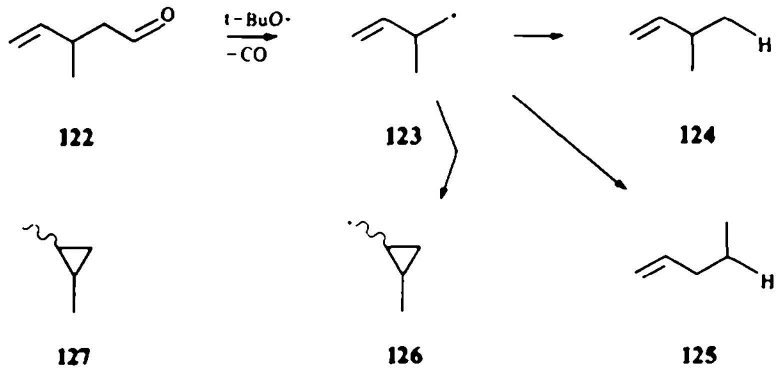
The same conclusion emerges from consideration of the bridged radicals **119**, **120a** and **121**. The trapping products from **120a** and **121** are obtained in ratios close to unity and the rate constant for conversion of **121** to **120a** (4×10^7 s^{-1} at 25°) is therefore closely matched by that in the reverse direction.[197] Radical **120b** can be trapped in pentane[198] before isomerisation to **119**.



a R = OAc. **b** R = H

119 **120** **121**

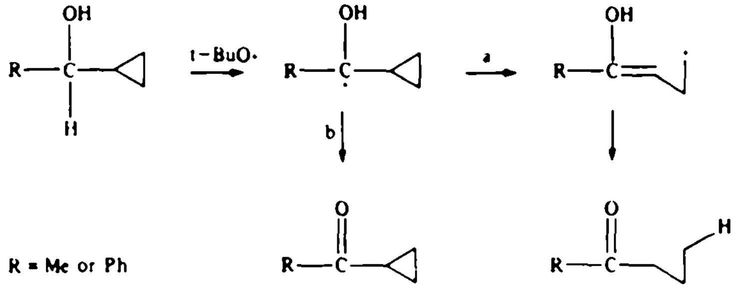
Decarbonylation of aldehyde **122** gives radical[199,200] **123** from which the normal **124** and rearranged **125** open-chain alkenes are derived. Furthermore, the formation of traces of the cyclopropanes **127** demonstrates that the strain energy difference between **123** and **126** is remarkably small.



122 **123** **124**

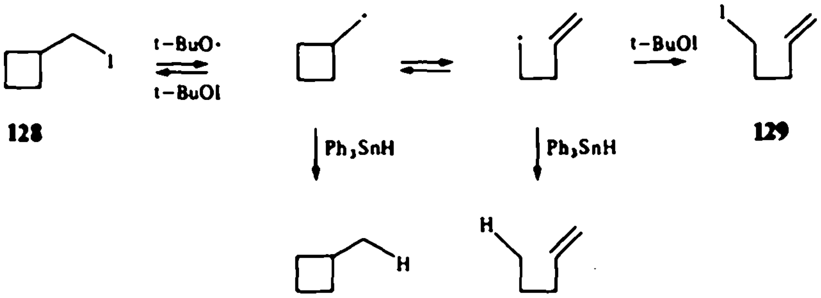
127 **126** **125**

α-Hydroxy-radicals similarly undergo eliminative fission.[201]

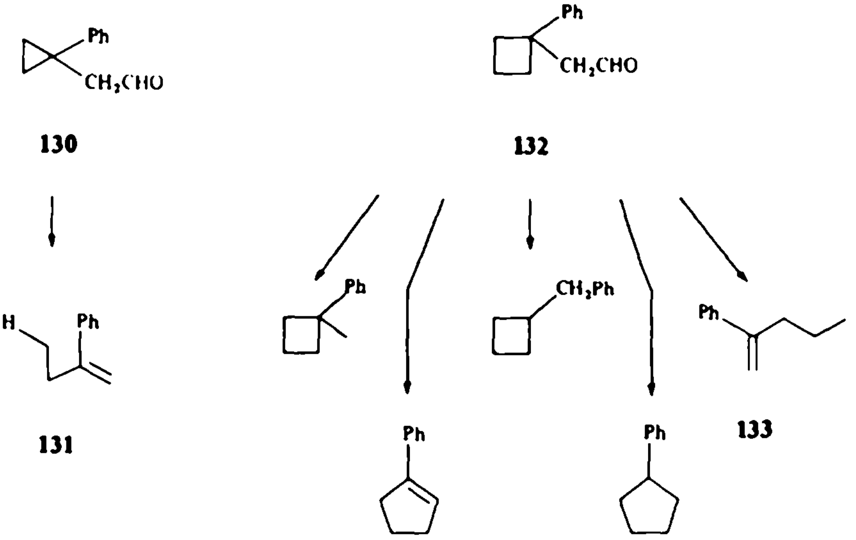


For R = Me, the eliminative pathway (a) is a rapid intramolecular process. For the more stable hydroxy-radical (R = Ph), there is time for (intermolecular) dehydrogenation to cyclopropyl ketone (pathway b) as a competing reaction. Related results have been obtained by Davies and Muggleton[202] who have also examined cleavage of α-hydroxyaziridinyl radicals.

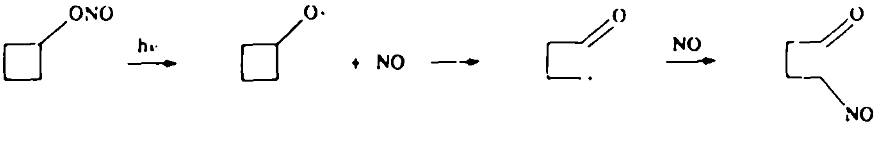
Four-membered rings are also observed to undergo eliminative ring fission readily. Reaction of cyclobutylmethyl iodide **128** with t-butoxy radicals gives[203] a 2 : 1 (equilibrium) mixture of ring-fission product **129** and starting material, and ring fission can be intercepted [contrast diphenylmethyl cyclopropyl[196] (above)], with a tin hydride.



Decarbonylation of the cyclopropaneacetaldehyde **130** gives[204] the ring-fission product **131** as sole product but the 4-ring analogue **132** gives only a small proportion of ring-fission product **133**.

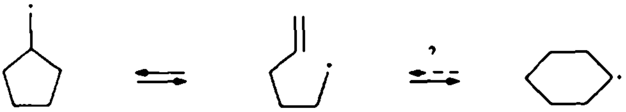


α-Hydroxycyclobutylmethyl radicals undergo fission to butyl ketones[205] and photolysis of cyclobutyl nitrite produces[206] the ring-fission–combination product **134**.



134

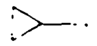
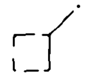
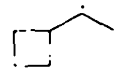
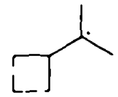
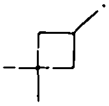
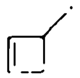
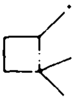
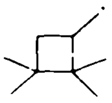
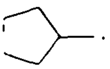
When the ring is 5-membered, equilibration between open-chain and cyclic radicals is observed[207,208] and both *exo-* and *endo*-addition, the latter giving the 6-ring, are found.[209]



Qualitatively, therefore, the role of strain in determining the stability of radicals is much as expected but with clear indications that fission of 4-rings is slower than 3-rings to an extent not predictable simply from overall strain energy differences.

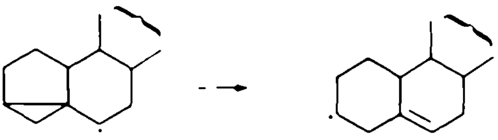
Considerable quantitative data are available from the work of Ingold[208,210,211] and Beckwith[212] (Tables 33 and 34).

Table 33. Activation parameters for eliminative ring fission of cycloalkylmethyl radicals

No.	System	E_A[a]	Ring strain[a]	$\Delta H^\ddagger$[a]	$\Delta S^\ddagger$[b]	ΔH°[c]	Ref.
114		5.9	27.6			−5.9	211
135		11.9	26.2	9.1	15.4	−4.5	211 212
136				9.2	14.9		212
137		13.9	–	-	·	−2.6	211
138				10.5	18.5	-	212
139		-		6.3	18.2	-	212
140		10.1	29.8			−22.8	211
141				7.0	18.9		212
142		23.3	6.3			+15.5	211

[a] kcal mol^{-1}.
[b] cal mol^{-1} K^{-1}.
[c] Reaction enthalpy.

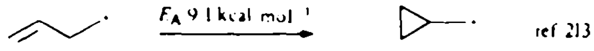
Table 34.

System	k^{25}_{open} (s^{-1})	Ref.
	1.3×10^{8}	208
	5×10^{3}	212
	2.25×10^{8}•	210

• at 30°C

Ring fission of cyclopropylmethyl radicals is very rapid and the data reveal the absence of direct correlation between ring strain and activation energy for ring fission. The 3-ring/4-ring comparison is again striking, the ratio ($\approx 10^5$) being similar to that found for carbanions (Section IIiii) and unrelated to the small ring-strain energy difference.

Quantitative information for the reverse reaction—cyclopropane ring *formation*—has been obtained for radicals **143** and **144**:



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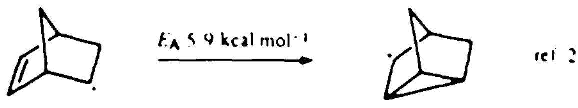


144

The difference in the activation energies is reasonably ascribed to the already strained ground state of **144** leading to a reduced ground state–transition state difference.

Ring strain energy is not the only factor involved in determining energies of activation for ring fission. The strengths of the bonds broken clearly must also have an effect. In strained cycloalkanes, C—H bonds are stronger and C—C bonds therefore probably weaker than in open-chain alkanes. C—H bond strengthening can be regarded as a measure of that component of C—C bond weakening unconnected with ring strain. When ring strain energies are added to ΔD(C—H) between cycloalkane and the secondary C—H value for an open-chain alkane and the *sum* is compared with E_A for ring fission a remarkably good correlation is obtained (Fig. 13).[211]

Of considerable interest in this connection, however, is the finding[215] that $\log k_{rel}$ for abstraction of hydrogen atoms from strained benzocycloalkenes gives a very insensitive (slope −0.082) correlation with strain energy. The dominant factor is, of course, benzylic stabilisation of the radical produced.

The results of Table 33 show that, as expected, the energy of activation for ring fission of a primary radical **135** is substantially lower than that for the more stable tertiary radical **137**. Ring substituents vary in their effect on reactivity; *gem*-dimethyl substitution **138** adjacent to the open radical centre raises the activation enthalpy consistently with operation of a *retro*-Thorpe–Ingold effect (Section IIiii) but when the *gem*-dimethyl substitution is *at* the radical centre **140**, the effect on stability of the

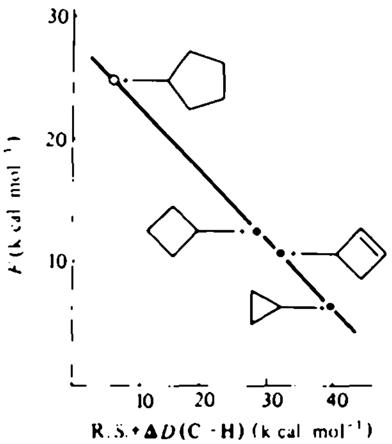
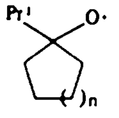


Fig. 13. Correlation of the sum of ring strain and ΔD(C—H) with the activation energies for ring fission in cycloalkylmethyl radicals.

rearranged radical is evident and E_A decreases. ΔH^* decreases when *gem*-dimethyl substituents are present at both positions **141**. Cleavage of the cyclobutenylmethyl radical **139** is slightly more favourable than that of the cyclobutylmethyl radical **135**; the strain energies of cyclobutane and cyclobutene are very similar but in **139** the open chain radical is delocalised. In the cyclopentylmethyl radical **142** the very much lower ring strain energy does give rise to a higher barrier for ring fission.

In carbonyl-forming homolytic eliminative ring fission of **145** the effect of strain is seen[216] in the competition between ring fission and loss of a propyl radical.



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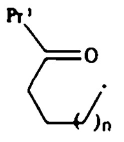

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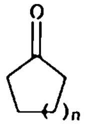
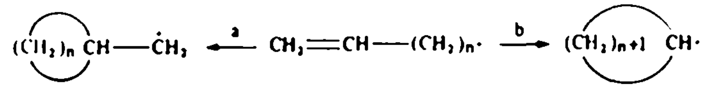


147

For n = 1 (5-ring) the **146**:**147** ratio is 14:1 and for n = 2 (6-ring) is 1:11 suggesting a substantial proportion of strain release at the transition state for cleavage.

Several sets of calculations on homolytic eliminative ring fission have been reported.[29,217,218] For conversion of the cyclopropylmethyl radical to the but-3-enyl radical, values of, $E_A = 8.7$ for the forward and 17.3 kcal mol^{-1} for the reverse (ring-forming) reaction have been derived.[217] Dewar[29] predicts conversion of but-3-enyl to cyclopropylmethyl to be much easier than for conversion to but-1-enyl or cyclobutyl, and obtains a value for the activation barrier of 12.9 kcal mol^{-1}. For cyclisation to cyclobutyl, the activation barrier is calculated to be 17.1 kcal mol^{-1} higher. This very much larger barrier is attributed to the energetic price of distortions enforced by the geometry and electronic requirements of the system. Bischof[218] also predicts from calculations that in cyclisation of radicals **148**, pathway a will be preferred to pathway b for values of n < 4.



$$(CH_2)_n\,CH—\dot{C}H_2 \xleftarrow{a} CH_2{=}CH—(CH_2)_n\cdot \xrightarrow{b} (CH_2)_{n+1}\,CH\cdot$$

148

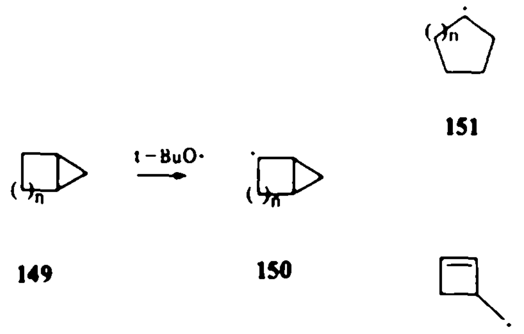
Table 35. Fission of bicyclo[n.1.0]alk-2-yl radicals[219] [a]

Radical (149)	RS[a](150) − RS(151)	Radical formed	RS[a](150) − RS(152)
n = 0	37.1	**151**	13.4
n = 1	49.3	**151**	25.6
n = 2	31.3	**152**	26.8
n = 3	23.4	**152**	27.5
n = 4	23.7	**152**	24.4
n = 5	21.3	**152**	25.1

[a] Ring strain, kcal mol^{-1}.

For n = 2, ΔH_a^* is 52 kcal mol^{-1} and ΔS_a^* is -34 cal mol^{-1} K^{-1} but for n = 3, ΔH_a^* is calculated to be 77 kcal mol^{-1} and ΔS_a^* -48 cal mol^{-1} K^{-1}.

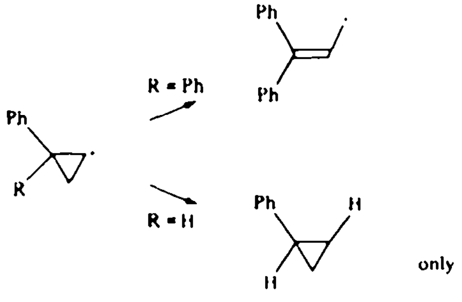
In bicyclic systems **149** abstraction of the (more weakly bound) cyclobutyl methylene hydrogen atom gives **150** and reaction can proceed by fission either of an internal (**151**) or an external (**152**) bond.[219] Results are given in Table 35.



149 **150** **151** **152**

When n = 0 the product is cyclobutene and clearly for radicals **149** (n = 0 and 1) the much larger ring strain difference on rearrangement to **151** outweighs the unfavourable stereoelectronic factor in which the semi-occupied molecular orbital (SOMO) and internal bond are orthogonal. For the remainder, the ring strain difference is insufficient to outweigh the stereoelectronic factor; consequently, radical **152** is produced.

Ring opening in cycloalkyl radicals. Cyclopropyl radicals have been reported[220,221] *not* to open in spite of favourable energetics, but E_A for the reaction, 19.1 kcal mol^{-1} has been measured.[222] In solution two phenyl groups stabilising the open radical, are required for fission.[223,224]

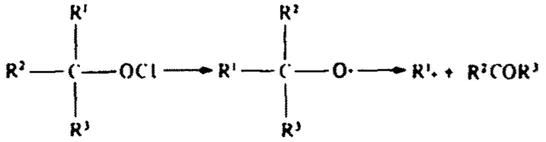


Ring opening competes with radical abstraction and the product distribution can be used to calibrate hydrogen atom donor capability of solvents.

Critical threshold energies for ring opening of cycloalkyl radicals have been obtained by Stein and Rabinovitch[225] with values for cyclopropyl ≈ 20; cyclobutyl ≈ 29; and cyclopentyl ≈ 34 kcal mol^{-1}, respectively. For cyclopropylmethyl the value is ≈ 16, significantly different from cyclobutyl in view of the very similar enthalpies (-5.5 kcal mol^{-1}) for the rearrangements of the radicals.

The reluctance of cyclopropyl radicals to rearrange in spite of considerable energetic assistance from strain is to be attributed to the difficulty of achieving an eclipsed conformation of the semi-occupied molecular orbital (SOMO) with respect to the bond about to break.[194]

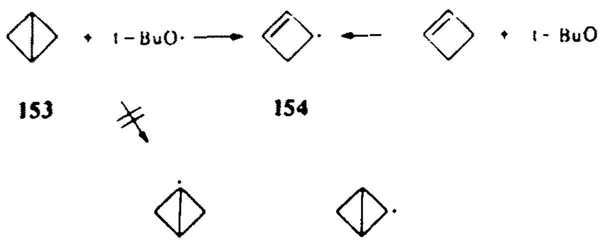
Radical displacement on strained cycloalkanes causes ring-opening.[226,227] Chlorination of cyclopropane gives cyclopropyl chloride and 1,3-dichloropropane[228,229] but bromination gives only open-chain dibromide[229] and the reaction is regiospecific. Walling[228] has shown that abstraction of hydrogen from cyclobutane occurs *ca* 7 times more rapidly than from cyclopropane but the product is exclusively cyclobutyl chloride. There is no displacement reaction. Once again the cyclobutyl structure reveals itself to be much more stable than the analogous cyclopropyl structure while the reactions which occur do so only by virtue of the considerable but closely similar ring strains. The greater stability of the cyclobutyl radical also emerges from work[230] on the decomposition of t-alkyl hypochlorites.



$$R^2-\overset{\displaystyle R^1}{\underset{\displaystyle R^3}{C}}-OCl \longrightarrow R^1-\overset{\displaystyle R^2}{\underset{\displaystyle R^3}{C}}-O\cdot \longrightarrow R^1\cdot + R^2COR^3$$

The most stable radical, $R^1\cdot$, is ejected with formation of a ketone and by this criterion the stability order is cyclobutyl > methyl > cyclopropyl. Products from unrearranged cyclobutyl radicals are obtained.

In the much more highly strained bicyclobutanes **153**, abstraction of hydrogen from the bridgehead

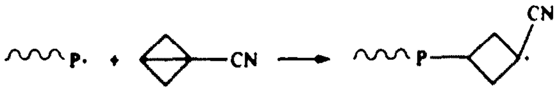


153 **154**

155

is *not* detectable; instead removal of a methylene hydrogen atom to give **155** occurs. Subsequent intramolecular eliminative fission produces **154** identical with that from t-butoxy radical reaction with cyclobutene.[231a] In this case the SOMO and the breaking bond are orthogonal but much greater relief of strain is achieved than by breaking an external bond.

With polystyryl radicals, for example, attack is at the bridgehead and for bicyclobutanecarbonitrile



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156 the reactivity ratio, compared to styrene, of 0.71 demonstrates the great lability of this highly strained system which behaves essentially as a vinyl monomer.[231b]

Abstraction. The very small effect of ring strain on rates of hydrogen abstraction from cycloalkenes has been referred to above.[215] Relief of *peri*-interactive strain is responsible for the substantial differences in rates of autoxidation of phenols **157**.[232]

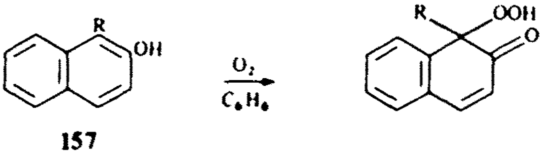

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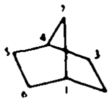
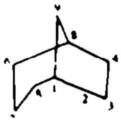
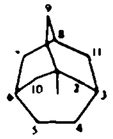
Table 36. Abstraction of hydrogen from polycyclic alkanes[233]

	Bridgehead		Secondary	
Alkane	$k/k_{\mathrm{ad}-1}$[a]	$\Delta\Delta H$[b]	$k/k_{\mathrm{ad}-1}$[a]	$\Delta\Delta H$[b]
	no reaction	+6.032	0.668	−2.417
	1.112	+0.487	1.919	−4.042
	15.976	3.696		−4.002
	40.306	−4.367	0.049	−1.139
	1.000	0	1.000	0
	Slope −0.327		Slope −0.537	

[a] 1-Adamantyl.
[b] kcal mol^{-1}.

Values of $t_{1/2}$ for 1/2 mole O_2 per mole of **157** are : R = Me, no reaction in 3 days under standard conditions ; R = i-Pr, 4 hr ; R = t-Bu, 10 min ; 1,8-dimethyl-2-naphthol, 3 hr.

Rates of hydrogen abstraction from strained alkanes have been correlated with (calculated) strain energies.[233] Results are given in Table 36.

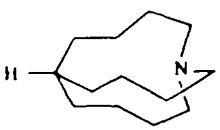
Homolytic additions. The addition of ethyl cyanoacetate to strained cycloalkenes with 5–12-membered rings has been studied. Rates correlate[234] with MM calculations of strain energies but effects are small and cover a range of only a factor of 6.

In later work, correlation[235] was obtained with Fukui delocalisabilities, but rate constants varied only within one order of magnitude for carbon radicals in irreversible reactions.

IIviii. *Miscellaneous*

This section comprises several general situations not readily classified under earlier headings.

Proton transfer equilibria. Steric effects on proton transfers are familiar[236] but quantitative relationships between rates and equilibria on the one hand and strain energies on the other have seldom been established. A particularly interesting recent example is seen in the work of Alder and his colleagues[237] on the protonation of bicyclic amines, compounds **158** and **159**.



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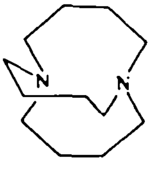

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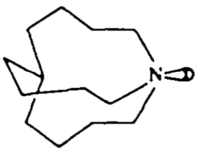
The proton affinity of **158** is 20 kcal mol^{-1} lower than that of n-Bu$_3$N. Force field calculations show a strain energy penalty of 17 kcal mol^{-1} incumbent upon the (accessible) *out*-protonation as in **160**.

This agrees well with the difference of 11 pK_a units between **158** with its remarkable pK_a of +0.6, and n-Bu$_3$N, In the related diamine **159** a similar situation obtains; pK_a^1 is 6.5 and pK_a^2, is -3.25. *Some* strain is induced upon *out*-protonation of the first nitrogen atom as the pK_a^1 is substantially smaller than that of n-Bu$_3$N but the second nitrogen atom confers greater flexibility on the structure giving pK_a^1 **159** $\gg$ pK_a for **160**. The price is paid on the *second* proton transfer.



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Enzyme systems. Mechanistic aspects of enzymic processes have frequently been reviewed[238] and the effect of strain is specifically referred to.[239] *Quantitative* evidence is, not surprisingly, unavailable. Fersht and Kirby[240] conclude that enzyme–substrate binding is not responsible for the induction of rate-enhancing strain in small substrates.

In studies [241] of cycloamylose complexation, use of partially methylated cycloamyloses produced only very small changes in dissociation of *p*-nitrophenol used as a monitor of complexation. The possibility was rejected that release of ring strain upon binding was a significant factor.

Conformational transmission. Barton[242,243] and his collaborators observed that rates of formation of benzylidine derivatives of 3-keto-steroids were affected by distal substituents. Rate effects were subtle, spanning at most two powers of ten, and were attributed to "progressively varied angle strain throughout the molecule". They were significant, however, in terms of synthetic applications. Allinger and Lane[244] have carried out force field calculations of steric energies of 3-ketosteroids related to the series studied by Barton. They are able to correlate steric energies with rates (correlation coefficient 0.83) and to obtain relative values of ΔG^{*} with a standard deviation of 0.28 kcal mol^{-1}.

Ozonisation of cycloalkanes. Popov and his collaborators[245] have found a dependence of ozonisation rates on cycloalkane excess enthalpy, showing that log $(k/k_{6\text{-ring}}) = 1.22$ (excess enthalpy)$^{0\ 5}$ for the series C_5 to C_{12} with rates spanning a factor of 40.

IIix. *Conclusions*

It is clear from the wide range of work collected in this report that quantitative correlations between strain and reactivity are now feasible for many reactions. These correlations provide valuable information both on the nature of transition states and the manner in which strain is either generated or released as the transition state is reached. A valuable review of the application of strain–reactivity correlations in transition state localisation has recently appeared.[246] The correlations allow predictive use of MM calculations for reactivities in a series with important synthetic repurcussions. Examination of the correlations of total strain energies with molecular reactivities, particularly of small ring systems, point to substantially different distributions of enthalpy in such systems. These investigations are focusing attention on the nature of "strain" and in particular upon its distribution within the molecular framework. The unravelling and quantification of these very large and differently distributed effects on reactivity offers an exciting prospect.

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