SOME QUANTITATIVE EFFECTS OF STRAIN ON REACTIVITY

Charles J M Stirling

Department of Chemistry, University College of North Wales, Bangor,
Gwynedd LL57 2UW

Abstract — Evaluation has been made of the effect of strain in three
types of reaction involving small rings:
(i)   nucleophilic substitutive ring fission of saturated heterocycles
(ii) eliminative ring fission in oxa- and carbocycles
(iii) intramolecular nucleophilic substitution by carbanions.

The impact of strain varies considerably from reaction to reaction and the
significance of these variations is discussed.

In a popular autobiographical series, James Herriot (1) describes the veterinary treatment
for large wounds in the flesh of farm animals which consists of packing the wound with
iodine and pouring on turpentine. This produces a strongly exothermic reaction which is
desirable from the veterinarian's point of view in that iodine is driven deep into the
wound and is regarded as good value by the farmer because it produces a spectacular cloud
of purple iodine vapour – a sure sign, as with total eclipses of the sun, that something
magical is occurring. The exothermicity of the reaction is due to the addition of iodine
across the double bond of α-pinene, the major constituent of turpentine, with generation
of a cyclobutonium ion which rearranges with release of strain. This observation is
typical of many anecdotal connections which have been made between strain and reactivity;
it is however striking that, in terms of *quantitative* relationships between strain and
reactivity, remarkably few direct connections have been made, partly because of the lack
of appropriate choices of system and partly because, until the widespread advent of
appropriate programmes for the calculation of molecular energies, values of strain
energies were not available for comparison with kinetic data.

A recent review (2) summarises the evidence that is available for quantitative connection
between strain and reactivity, and it is evident that two main approaches have been
adopted.   The first is to calculate the strain energy difference between ground state and
transition state and then to compare this value with that of the experimentally observed
free energy of activation.   From this comparison emerged deductions, usually about either
the validity of the calculations or the appropriateness of the model of the transition
state which has been adopted in the calculations.   This approach has been adopted by
Schleyer (3), whose work in this field has provided the background for most quantitative
comparisons that have been made between strain and reactivity.   Strain calculations have
been derived from the Allinger molecular mechanics programmes (4) and these have been
widely used by later workers, notably DeTar (5), Müller (6), Rüchardt (7) and Lomas (8).

The approach is typified by results of Schleyer (9), presented in Figure 1, dealing with
the effect of strain on the solvolysis of bridgehead tosylates.   The carbocation is the
model for the transition state and the rectilinear relationship between log k_{rel} and the
calculated strain energy difference was obtained over many powers of 10 in reactivity.
Related results have been obtained by Müller (6) on rates of oxidation of alcohols, for
which the strain energy difference between the sp^2 and sp^3 hybridised states is
calculated, and by Rüchardt (7) for the thermolysis of strained hydrocarbons in which
again differences in free energy of activation for the thermolysis are directly related to
calculated strain differentials.

The second approach, and that employed by the author and his group, is to make comparisons
between the reactivities of systems of known thermodynamic strain energy difference and
hence to deduce, first, the sensitivity of the system to strain and hence the nature of
the transition state;   second, in the transition state of inferred structure how strain
exerts its influence.   This approach is, of course, a very simple one in not requiring
access to calculated strain energies and uses instead thermodynamic data which, for ring
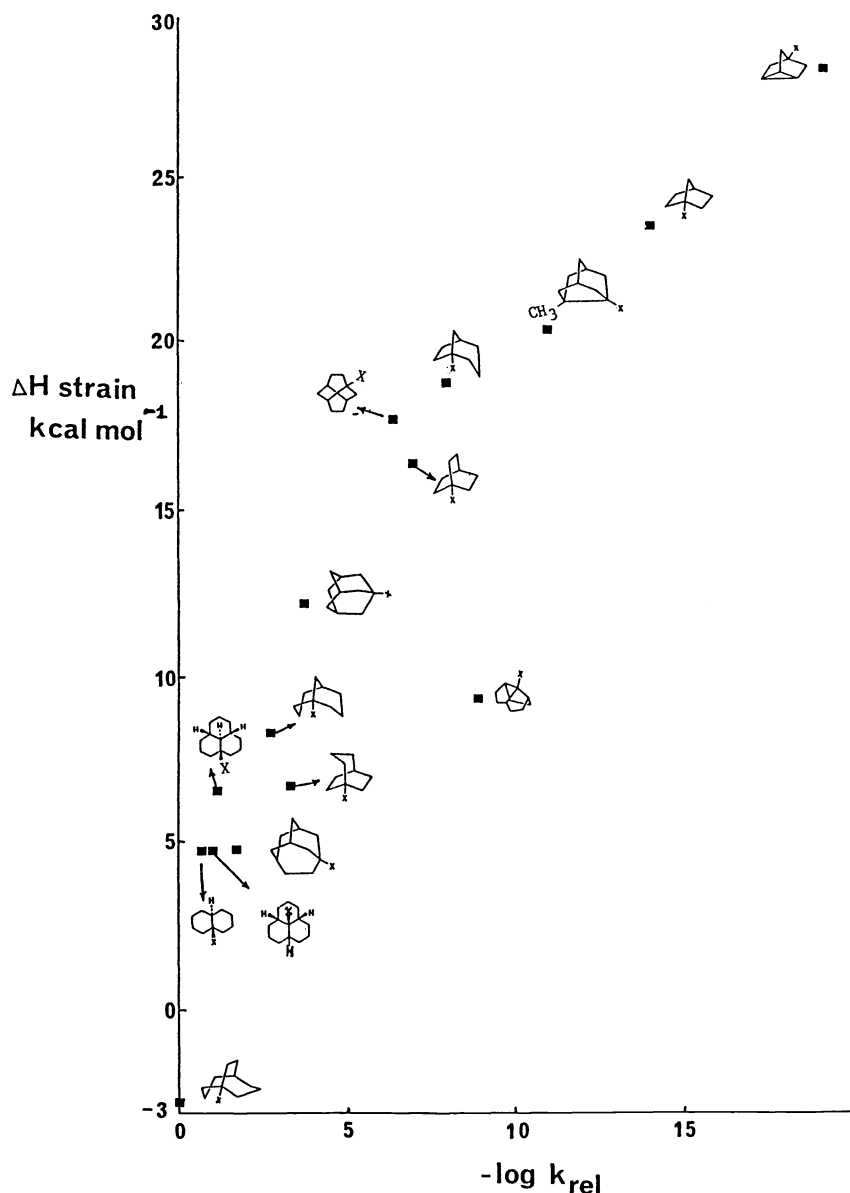systems, is particularly plentiful.   The assumptions about the natures of transition

Fig. 1. Solvolysis rates of bridgehead tosylates

states necessary in the first approach are avoided; the assumption is made in the second approach that the effect of substituents upon the strain energies of cyclic systems are small by comparison with the strain energies of those systems. In this second approach, there is an obvious requirement for the careful design of systems. The systems used require that comparison of systems of known strain differential be made and that the comparison is made between reactions of known mechanism. In these comparisons an obvious advantage is to be able to exclude minor effects by concentration on very large effects, and this is generally true of the results discussed in this article. Bearing in mind the availability of a recent review (2), work from the author's laboratories will be concentrated upon herein, and attention will be focussed on three main types of system: 1) nucleophilic substitutive ring fission of small ring heterocycles; 2) nucleophilic eliminative ring fission of small ring systems; 3) cyclisation of carbanions.

Nucleophilic substitutive cleavage in small ring heterocycles
This is an extremely familiar reaction for epoxides, but almost unknown, and certainly not quantified, for any other ring size. The comparison of strained and unstrained systems is, however, difficult for this type of reaction. Scheme 1 illustrates the problem:
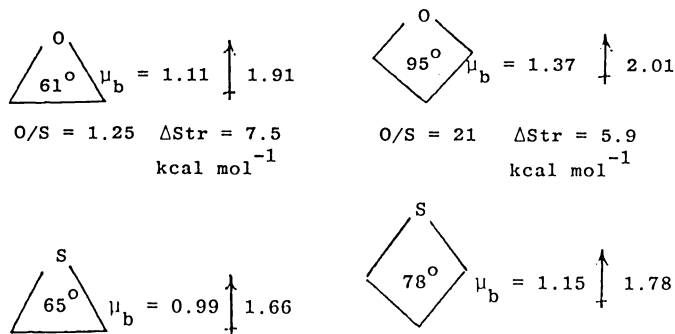
Nu: + (epoxide) $\longrightarrow$ Nu$\diagup\!\!\diagdown$O$^-$ familiar

Nu: + MeOEt $\longrightarrow$ NuMe + $^-$OEt   unknown

Nu: + (cyclopropane with G) $\longrightarrow$ Nu$\diagup\!\!\diagdown$G   known but G must be
                                                     CN, CO_2Et, RSO_2 etc.

Nu: + MeCH$_2$G $\longrightarrow$ NuMe + $^-$CH$_2$G   unknown

SCHEME 1.   Strain in concerted displacements

The trouble is that epoxides are rendered susceptible to nucleophilic displacement of alkoxide ion from sp^3 carbon by strain in the ring, but the reaction is unknown for unstrained systems.   Likewise, nucleophilic substitution on substituted cyclopropanes is a familiar reaction provided that the carbanion leaving group is appropriately stabilised, but the reaction is not seen in unstrained analogues.   Our work in this area has concentrated on comparing the reactivity towards nucleophiles of ring systems of known ring strain.   These strain energies for the systems that we have studied are summarised (10) in Table 1.

TABLE 1.   Ring strain energies (kcal mol^{-1})

$$\left(\begin{array}{c} (CH_2)_n \\ X \end{array} \right)$$

No of ring atoms	X = C	S	O
3	27.4	19.8	27.3
4	26.0	19.6	25.5
5	6.1	5.8	5.6

The general reaction is then shown as in Scheme 2.

Nu: (ring with Z, n) $\longrightarrow$ Nu —— (Nu—Z ring)

Nu = $S_2O_3^{--}$;   Z = O or S;   n = 3, 4 or 5

SCHEME 2.   Reactivities in nucleophilic ring fission

The results of Table 2 show clearly that, as expected, strain is a very important factor in reactivity.   Highly strained three-membered rings are much the most reactive and the five-ring systems with a low degree of ring strain are very unreactive.   The results for the five-membered ring systems are not accurate; there are always quantitative problems in comparing systems which differ by huge reactivity ratios and the results obtained for the three- and four-membered ring systems at lower temperatures have been extrapolated to 120°, the conditions used for the five-ring systems.   The results show clearly, however, that the relationship between strain and reactivity is not a simple one.   Strain energies of three- and four-membered ring systems differ only to a small extent (Table 1).   Even if this strain energy difference were to be fully expressed in the differences between free energy of activation, the rate ratios would be of the order of 5 instead of 10^4 to 10^5.   Clearly, either the three-membered ring systems are much more reactive, or the four-membered ring systems are very much less reactive than they should be when their strain energies are taken into account.   We believe that it is the four-membered ring systems which are anomalous and this aspect will be returned to later.   The results of Table 2 also show clearly however, that the ring systems containing sulphur behave differently from those containing oxygen.   The small rate ratio of oxiran to thiiran is magnified nearly twenty-fold in the four-membered ring systems although the strain energy difference is substantially smaller.   This may be due to differences in bond

TABLE 2.   Relative reactivities[*] in nucleophilic ring fission (11)

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

[*]S_2O_3/H_2O at 50°C (5 rings at 120° and estimated)

polarisation; in oxiran, the C–O bond moment is 1.11 debye units and the C–S bond moment in thiiran, 0.99 debye units. As a result of the much narrower CSC angle in thietan, the C–S bond moment in thietan is 1.15 debye units compared with 1.37 for C–O in oxetan. As will be seen later, bond polarisation is clearly the most important single factor in determining nucleofugality and the striking, albeit modest, difference in reactivity between the oxygen and sulphur systems may be attributed to this source (Scheme 3).

O/S = 1.25   ΔStr = 7.5 kcal mol^{-1}

O/S = 21   ΔStr = 5.9 kcal mol^{-1}

$\mu_b = 1.11$ 1.91

$\mu_b = 1.37$ 2.01

$\mu_b = 0.99$ 1.66

$\mu_b = 1.15$ 1.78

SCHEME 3.   Bond polarisation in small-ring heterocycles

Elimination from carbanions

Extensive studies by several groups have been undertaken during the last fifteen years or so on the ejection of leaving groups from carbanions with formation of alkenes, sulphenes, ketenes and a number of other functions. This type of ElcB reaction, once thought to be a special case, is now quite clearly the normal mode of elimination and processes in which deprotonation and leaving group ejection are concerted are to be regarded as rarities.

The general scheme for ElcB alkene–forming elimination is in equation 1.

$$G \diagup\diagdown Z + B: \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} BH + G \diagup\diagdown Z^- \overset{k_2}{\longrightarrow} G \diagup\diagdown + :Z \quad \ldots\ldots\ldots (1)$$
$$(\underline{1})$$
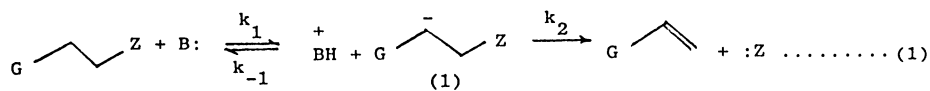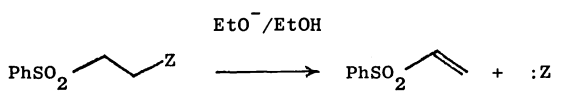
There are several variations on the ElcB theme whose incursion is determined by the relative values of the rate constants involved. The only type of mechanism of interest from the point of view of evaluating the effects of strain on reactivity, is that in which the process with rate constant, k_2, is rate–determining. The advantage of this system is that a very wide range of leaving groups, Z, can be studied, whereas for nucleophilic displacements the range of leaving groups is extremely limited. Additionally, by judicious manipulation of activating group, G, a constant mechanism is accessible and appropriate analysis of the kinetic data then yields relative values of k_2 which reflect

the nucleofugality of the leaving group, Z, from the carbanion ($\underline{1}$). These relative values are termed ranks (12). There is a final further advantage; the bond connecting the leaving group Z to the substrate can readily be strained by incorporation of it within a small ring of known strain energy. The way is therefore made clear for the determination of the effect of strain upon nucleofugality.

Nucleofugalities of a wide range of leaving groups have been determined in the author's laboratories (12) using, in the main, cyano- and phenylsulphonyl-activated alkene forming elimination reactions. These two activating groups are particularly advantageous in that the stabilised carbanions are reprotonated very rapidly. This circumstance permits the process with rate constant, k_2, to be rate determining in more instances than for other activating groups. Ranks (equivalent to nucleofugalities) for a few leaving groups, Z, are in Table 3.

TABLE 3.   Reactivity data and ranks (12)

$$\text{PhSO}_2\diagup\diagdown\diagup^Z \quad \xrightarrow{\text{EtO}^-/\text{EtOH}} \quad \text{PhSO}_2\diagup\diagdown\!\!\!= \quad + \quad :Z$$

Z	k_{obs}^{rel}	Rank*
PhS^+Me_2	1,800,000	9.8
PhSO_2	3	8.7
PhO	1	8.9
MeO	4.3×10^{-5}	6.1
CMe_2NO_2	4.2×10^{-9}	2.6
$\text{CMe(SO}_2\text{Et)}_2$	7.8×10^{-11}	-2.9

* $\log k_{obs} - \log k_1 + 11$

All of the substrates in Table 3 react by the $(\text{ElcB})_R$ mechanism in which expulsion of the leaving group is rate-determining. The range of reactivity is very wide, spanning roughly 18 powers of 10, and the rank data spans about 12 powers of 10. The relationship between observed rate constant and rank is shown in the table. Raw kinetic data has to be processed to allow for the effect of the leaving group Z on the pre-equilibrium formation of the carbanion. It should be particularly noted in the context of this article, that methoxy is a moderately ranked nucleofuge and that carbon nucleofuges are particularly poor. Incidentally, it maybe seen that there is no relationship between pk_a of the conjugate acid of the leaving group and its nucleofugality in this system. The sulphonium group, with a strongly polarised C-S bond is highly ranked.

The availability of this data allows a quantitative examination of the effect of straining the bond connecting the leaving group in terms both of reactivity of the substrate and the change in rank or nucleofugality (Scheme 4)

effect on reactivity?
on rank?
$\xrightarrow{\hspace{2cm}}$

Z = O or C;   G = carbanion stabilising
                              group
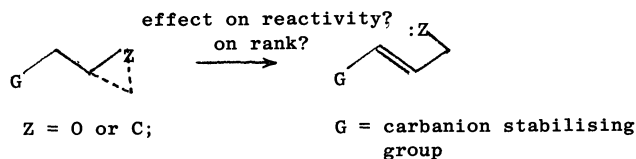
SCHEME 4.   Strained leaving groups

Initial experiments were carried out with the oxacycle series (13) (Table 4).

The alkoxy group was known to be only a moderate nucleofuge and as the results of Table 4 clearly show, when the leaving group is contained in a three-membered ring, the observed rate of elimination is accelerated some 2 million-fold over the unstrained (acyclic) system. Unfortunately, these results do not give any information on the extent to which the known strain energy of the oxiran promotes cleavage of the C-O bond in the process of elimination. As mentioned above, measurement of nucleofugality can be achieved only when cleavage of the bond to the leaving group is the sole rate-determining process. For

TABLE 4.   Eliminative Ring Fission of Oxacycles

(2)   (3)
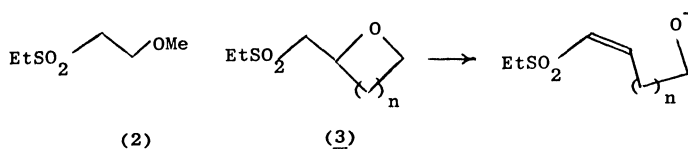
a, n = 0; b, n = 2; c, n = 3

Substrate	k_{obs}≠	Mechanism	k_{H-D}^{β} exch	Rank*	Strain Energy
(2)	7.5×10^{-5}	$(E1cB)_R$	**	6.1	–
(3a)	185	(E_2)	2.5	–	27.3
(3b)	1.39×10^{-3}	$(E1cB)_R$	0.95	7.4	5.6
(3c)	2.0×10^{-3}	$(E1cB)_R$	**	7.5	1.2

≠ $M^{-1}s^{-1}$; Reactions in NaOEt-EtOH at 25°; * log k_{obs}–log$_{deprotonation}$ + 11

calc. for Et=Ph; see original paper. ** $k_{elimination} \ll k_{H-D\ exchange}$

the oxiran (Table 4) the observed rate of elimination shows a primary kinetic deuterium isotope effect showing that deprotonation is either the rate-determining process or is concerted with loss of the leaving group in the process of ring fission.   For the five-membered ring system (Table 4), the primary kinetic deuterium isotope effect is close to unity, ring fission is rate-determining and acceleration over the acyclic system is modest.   This is not in any event surprising because of the small extent of strain in the five-membered ring.   The effects are too small to interpret with any degree of certainty.   Even were the acceleration entirely due to strain, the strain energy of the five-membered ring is insensitively expressed in acceleration of bond cleavage.

It was clear from these results that a large degree of ring strain produced a large increase in reactivity, and in the case of the oxiran, sufficient to change the mechanism of the reaction from a stepwise process to a concerted one, at the same time conferring nucleofugality upon the leaving group probably comparable to that of, for example, bromide ion which, in such sulphonyl activated systems, is involved in a concerted mechanism (14).

It was known from the work on nucleofugality in acyclic systems that carbon leaving groups were the poorest of all.   The next stage was therefore to examine carbon leaving groups in the context of eliminative ring fission.

The general system employed is shown in Scheme 5.

k_{obs}	$4.8 \times 10^{-3}\ M^{-1}s^{-1}$
$k_{detritiation}^{\beta}$	$1.2 \times 10^{-1} M^{-1}s^{-1}$
$k_{H/D}^{\beta}$	1.03
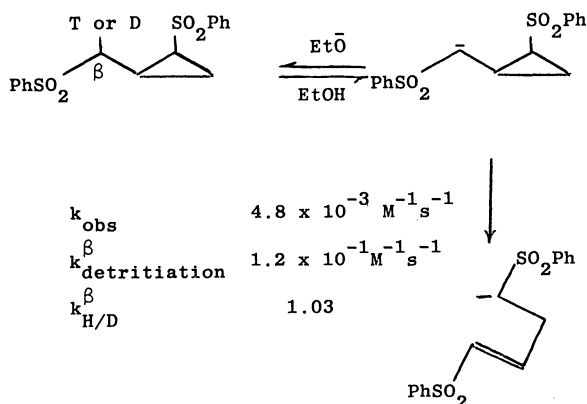
SCHEME 5.   Eliminative ring fission in cyclopropanes

It was important to find out whether or not deprotonation was involved in the rate
determining stage as only if it were not could the system be employed in the examination
of the effect of strain.   In the event, values in Scheme 5 show that the rate of
β-detritiation was substantially larger than the observed rate constant for formation of
the initial ring opened product (reactions were followed by formation of
phenylsulphonylbuta-1,3-diene which arises as a result of a rapid prototopic shift and
subsequent elimination of sulphinate ion).   The primary deuterium isotope effect was
close to unity and there was no question, therefore, that in this system pre-equilibrium
formation of the cyclopropylmethyl carbanion was rapid and the subsequent ring fission of
this species was slow.   Knowledge, as before, of the deprotonation behaviour of the
sulphone allows the rank of the strained leaving group to be evaluated and its value is in
Table 5.   From the standpoint of evaluation of the effect of strain on nucleofugality,
comparison with an acyclic analogue was required and this requirement shows up some of the
difficulties inherent in this type of investigation.   A simple sulphonyl-stabilised
carbanion is not expelled in a simple sulphonyl activated 1,2-alkene forming elimination
and recourse was had to the tetra-sulphone in Table 5.   It had been shown earlier that
nucleofugality was insensitive to the activating group (16), but the required use of a
bis-stabilised leaving group, of course, gives the rank a maximum value as a
mono-stabilised leaving group will be less readily expelled.

TABLE 5.   Rank change due to ring strain

$$(MeSO_2)_2CHCH_2\overset{\overset{Me}{|}}{C}(SO_2Et)_2 \xrightarrow{Et\bar{O}} (MeSO_2)_2C=CH_2 + {}^-C(SO_2Et)_2 \qquad Rank\quad -2.9^*$$

$$+8.8$$

$$+8.8$$
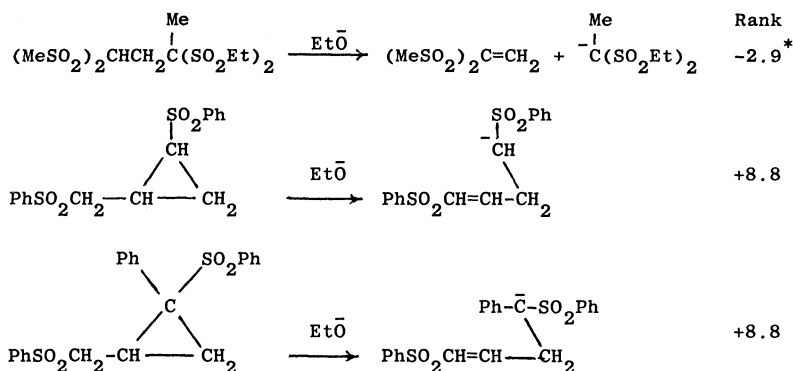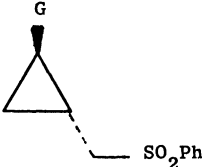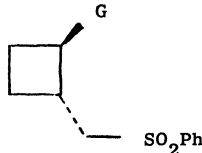
* N.B.   For bis-stabilised leaving group.

The Table shows a difference in rank of 11.7 units between the acyclic system with its bis-
stabilised leaving group and the cyclopropane.   If the further assumption is made that the
strain energy of the cyclopropane is unaffected by the substituents attached to it in this
case, the rank difference corresponds to approximately 18 kcal mol^{-1}. Thus about 60% of a
strain energy of cyclopropane is expressed in acceleration of ring fission by reduction of
the free energy of activation.   We were able to calibrate the extent of ring fission in
the rate determining step by placing of an additional phenyl group on the leaving group.
It can be seen from Table 5 that this has a small effect on rate but no net effect on
rank; all of the effect of the phenyl group is on the pre-equilibrium deprotonation.
This implies that there is very little localisation of charge on the leaving group in the
transition state because Bordwell and his collaborators have shown that attachment of a
phenyl group to a secondary sulphonyl-stabilised carbanion reduces pK$_a$ by 5.7 units.   The
further implication of these results is, of course, that the strain energy of a
cyclopropane decreases very rapidly as one of its bonds is extended, and this point will
be made again later.

An obvious extension of this work was to examine cyclobutanes with a similar substitution
pattern (17).   The substrates were obtained by essentially conventional procedures and
the *prima facie* expectation was that because of the very similar ring strain energies of
cyclopropanes and cyclobutanes the results would be rather similar.   These are in Table 6.
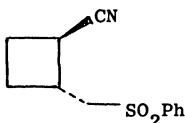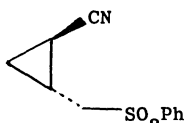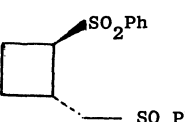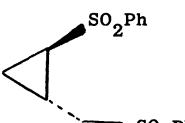
TABLE 6.   Correlation of ring opening with ring strain energies

G	Strain (kcal mol^{-1})	Ring Fission k_{rel}^{*}(G=CN) k_{rel}^{*}(G=SO$_2$Ph)		Rate of Detritiation k_{rel}
(cyclopropane with SO$_2$Ph)	27.4	4840	57600	1.7
(cyclobutane with SO$_2$Ph)	26.0	1	1	1
Open chain G = (MeSO$_2$)$_2$		$\sim 10^{-9}$	$\sim 10^{-9}$	

*Reactions in EtONa-EtOH at 25°C

The first striking point is that, notwithstanding the similar ring strain energies, three-membered rings react very much faster than four-membered rings, irrespective of whether the stabilising group attached to the leaving group is cyano or phenylsulphonyl. The phenomenon is not associated with the deprotonation behaviour because the rates of detritiation of the two systems are extremely similar.   Acceleration by ring strain is, of course, very evident – the cyclobutanes are about 10^9 times more reactive than the acyclic analogue system.   The rate ratio between three- and four-membered ring systems, however, is very much larger than would be expected from the ring strain energy differences which, if expressed to the same extent as for the three-membered ring systems, would give values of relative rates of about 6 instead of 10$^{3.5}$ and 10$^{4.5}$ respectively for the cyano and phenylsulphonyl-stabilised leaving group systems.   Proper examination of such an anomaly requires more detailed examination of the activation parameters. These are in Table 7.

TABLE 7.   Activation parameters

	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal K^{-1} mol^{-1})	Rank
(cyclobutane, CN / SO$_2$Ph)	31.3	+17	4.9
(cyclopropane, CN / SO$_2$Ph)	24.9	+12	8.4
(cyclobutane, SO$_2$Ph / SO$_2$Ph)	29.9	+9	4.3
(cyclopropane, SO$_2$Ph / SO$_2$Ph)	17.7	-10	8.8

It can be seen that enthalpies of activation for cleavage of the four-membered rings are very much more positive than for those for the three-membered rings, the effect being partially offset by the more positive entropy parameters for the four-membered rather than for the three-membered systems. It is clear that ring strain is benefiting the three-membered rings much more than the four-membered rings, but that in the latter, fission of the larger ring introduces a greater degree of randomness into the transition state for cleavage. The nucleofugality data of Table 7 directly reflect the differences in ease of ring fission between the two systems.

Given that the very similar ring strain energies of the two systems are being manifested in very different ways, it is appropriate to summarise for the two systems those components of strain energy which are relevant to the problem. Table 8 shows that while for the three-membered ring, torsional and valence deformation energies account for the total ring strain energy in the four-membered ring, the most substantial component is composed of the repulsive 1,3- and 2,4-interactions. Those components in common with the three-membered ring are much less important.

TABLE 8.   Components of ring strain

	Valence deformation	Torsion	1,3 Repulsive interaction
Cyclopropane	75%	25%	-
Cyclobutane (planar)	20%	30%	50%
Cyclobutane (puckered)	20%	20%	60%

Simple consideration of the process of ring fission (Scheme 6) shows that for cyclopropane, extension of one bond so as to make the remaining angle tetrahedral, causes extension of the other bonds as ring opening occurs.
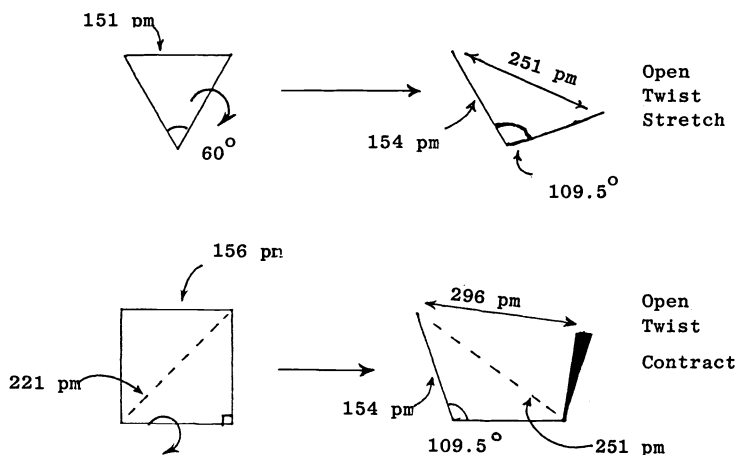
SCHEME 6.   Ring opening to tetrahedral angle

By contrast, for cyclobutane, opening to the tetrahedral angles actually results in contraction of the other bonds. A simple MM calculation of excess enthalpy as a function of bond cleavage for the two ring systems is shown in Figure 2 (17). It can be seen that for any but very small bond extension, the excess enthalpy of the ring decreases more rapidly as a function of bond extension for the three-ring rather than for the four-ring. If it is broadly assumed that the extent of ring fission at the transition state is the same for both systems, and that the degree of bond extension is that which is appropriate to the loss of 60% of the excess enthalpy of the cyclopropane (above), then from Figure 2 the difference in reactivity between the cyclopropane and the cyclobutane systems can roughly be accounted for.
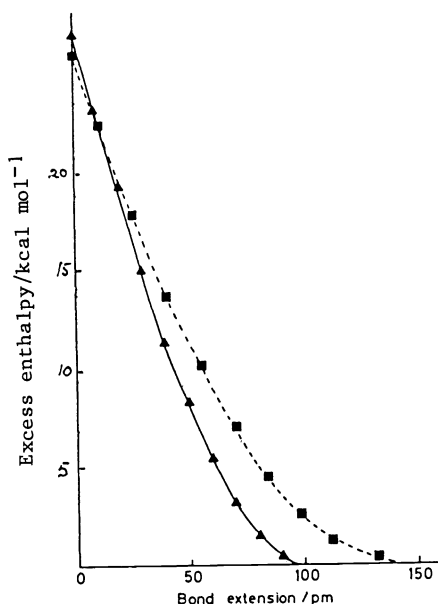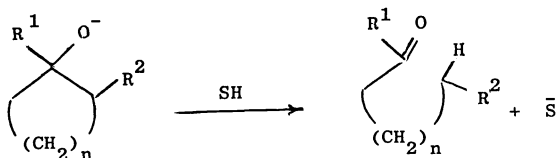
Fig. 2. Excess enthalpy as a function of bond extension for:
■, cyclobutane; ▲, cyclopropane

Ring Fission in Cycloalkanols

It has been known for many years that cyclopropanols readily undergo ring fission in the presence of bases with the formation of open chain aldehydes or ketones (Scheme 7) (18).

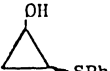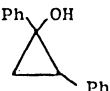SCHEME 7.   Eliminative fission of cycloalkanols

The regiospecificity of the reaction is entirely in accord with the carbonyl forming elimination of a carbanion, but this carbanion is so unstable that enforced general acid catalysis is required for the reaction to proceed (19).   Because of the remarkable differences between the rates of fission in cyclopropylmethyl and cyclobutylmethyl carbanions, we considered it of interest to examine other cycloalkanols with the results in Table 9 which include those of the earlier work (19, 19a).

The results show that ring cleavage of cyclopropanols is sensitive to the leaving group; attachment of a phenyl group to the leaving 'carbanion' produces a 10^5-fold increase in rate. Accurate data is not available for cyclopropanol (19a), but β-phenylthiocyclopropanol is clearly much more reactive. Comparison of cyclopropanols with cyclobutanols shows very large rate ratios and it is again found that a β-phenylthio group considerably raises reactivity. It is concluded that there is considerable transfer of charge to C_β in both cyclopropanols and cyclobutanols.

It is quite impossible to account for the differences in behaviour between the two systems on the basis of strain energy differential. The assumptions made in the construction of Figure 2 cannot yield energy differences between the two systems in the process of bond fission which can account for the reactivity differences.

Two very tentative explanations to account for the difference in behaviour of the cycloalkanols occur to us.

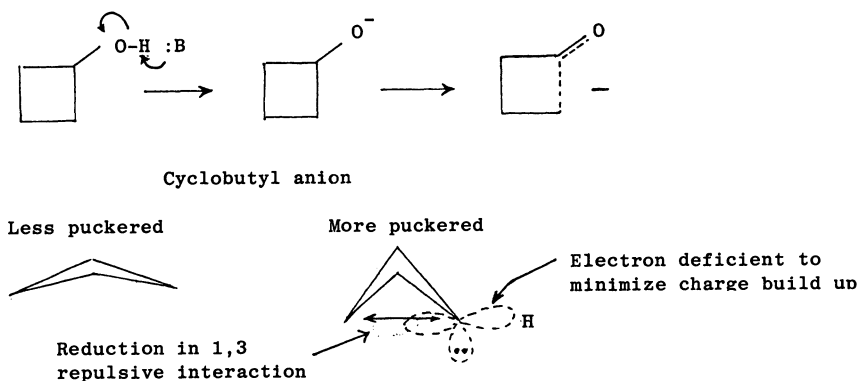TABLE 9.   Eliminative ring fission of cycloalkanols

$$k_{rel}^{a}$$

Structure	k_{rel}^{a}
cyclopropanol (OH)	1.7×10^{-3} [b†]
1-phenylcyclopropanol (Ph, OH)	1 [ce]
2-(phenylthio)cyclopropanol (OH, SPh)	393 [d]
1-phenyl-2-phenylcyclopropanol (Ph, OH, Ph)	10^{5} [c]
cyclobutanol (OH)	2.6×10^{-10} [e †*]
1-phenylcyclobutanol (Ph, OH)	1.3×10^{-9} [e †*]
2-(phenylthio)cyclobutanol (OH, SPh)	2.3×10^{-4} [d †*]

[a] reactions in aqueous sodium hydroxide with small amounts of co-solvent in some cases; [b] ref. 19a; [c] ref. 19; [d] ref. 22;

[e] H.A. Earl, unpublished work.   [†] approximate value [*] estimated from reactions at higher temperatures.

First, it is possible (Scheme 8), to the extent that the oxy-anion resembles a cyclobutyl carbanion in possessing a considerable degree of negative charge on the α-carbon atom, that the 1,3-repulsive interaction is reduced by the reduction of electron density in the orbital directed towards C3 because of the high charge density in the orbital orthogonal to this one.   Calculations on cyclobutyl carbanion (20) suggest such a conclusion.   The overall result is essentially to stabilise the closed ring.   No quantification of this sort of suggestion is at the moment possible.   A simple alternative possibility (21) has been used to interpret successfully somewhat similar differences in behaviour between cyclopropylmethyl and cyclobutylmethyl radicals.   While C–H bonds in cyclopropane are known to have substantially greater bond dissociation energies than in cyclobutane, the carbon-carbon bonds of cyclopropane should have correspondingly lower bond dissociation energies than those in cyclobutane.   There are, of course, many difficulties with such an argument.   In the first place, the systems which we are trying to understand are undergoing *heterolytic* fission, and it is clear that bond dissociation energy is only a rather small factor determining the ease of heterolytic bond cleavage.   Furthermore, it is not at all clear that such an averaging procedure will in any case give a true reflection of the differential ease of cleavage of cyclopropyl *versus* cyclobutyl ring bonds.

Cyclobutyl anion

Less puckered   More puckered

Electron deficient to
minimize charge build up

Reduction in 1,3
repulsive interaction

SCHEME 8.   Ring opening of cyclobutanol
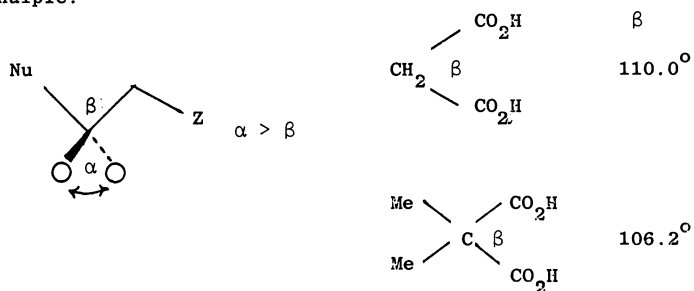
The Thorpe-Ingold Effect

The Thorpe—Ingold effect (23) is a familiar effect on reactivity in which *gem*–dimethyl substitution assists the closure of rings.   Most results on this effect are qualitative: some quantitative ones on oxy—anion cyclisation are in Table 10.
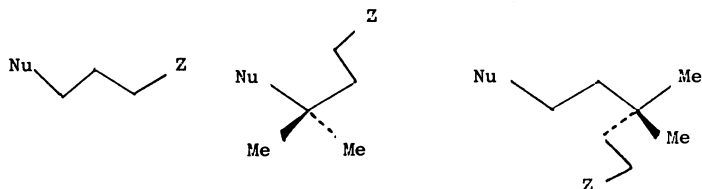
TABLE 10.   The Thorpe-Ingold effect

| k_{rel} | 1 | 4×10^4 | 400 | 2.8×10^6 |

| k_{rel} | 1 | 3.8×10^2 | 2.2 |

There has been controversy over the origin of the Thorpe—Ingold effect;   on the one hand an enthalpic explanation is advanced in which non-bonded interaction between a pair of methyl groups reduces the angle between the other two groups attached to the quaternary carbon and hence favours ring closure particularly when the ring is small.   This explanation is supported not only kinetically in terms of the greater effectiveness of the Thorpe—Ingold effect in the cyclisation of small rings, but also in the measured angles of *gem*–dimethyl compounds (Scheme 9).   The alternative view is an entropic one in which the existence of a quaternary carbon atom in the chain statistically increases the proportion of conformations available to the system from which ring closure can proceed.   It seems probable that the truth is, as so often, a combination of both viewpoints.

Enthalpic:

$\alpha > \beta$

110.0°

106.2°

Entropic:

SCHEME 9. Interpretations of the Thorpe-Ingold Effect

It was of interest to examine the incidence of the Thorpe-Ingold effect in ring fission reactions and, with the systems which we had available, were initially surprised to find no apparent effect (Table 11). The almost coincident values pointed to no effect, but examination of the activation parameters (Table 12) showed that, notwithstanding the small rate differences between the *gem*–dimethyl and the *nor*–systems, considerable energetic differences were revealed by the activation parameters for both the *cis* and the *trans* *gem*–dimethyl compounds. The enthalpies of activation were substantially larger than for the unsubstituted compounds and the coincidence of rates was due to compensation by the entropy term. These results are consistent with an enthalpic origin for the Thorpe–Ingold effect.

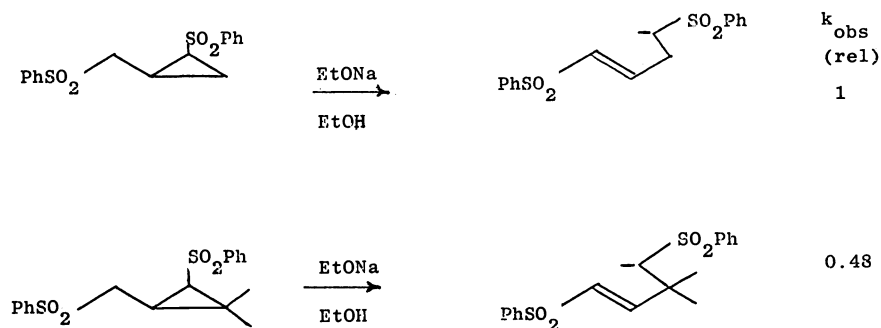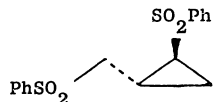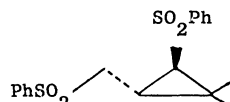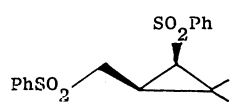TABLE 11. The anti Thorpe-Ingold effect (24)

k_{obs} (rel)

1

0.48

TABLE 12.   Activation parameters for ring fission (24)

	25° k $(s)^{-1}$	$\Delta H^{\ddagger}$ kcal mol^{-1}	$\Delta S^{\ddagger}$ cal $K^{-1}mol^{-1}$
(structure: SO₂Ph / PhSO₂)	4.8×10^{-3}	17.7	-10
(structure: SO₂Ph / PhSO₂)	2.7×10^{-3}	22.8	+ 7
(structure: SO₂Ph / PhSO₂)	2.4×10^{-3}	25.5	+15

Strain in intramolecular nucleophilic substitution

We have studied systems involving intramolecular nucleophilic substitution (Scheme 10).

$$Nu: \quad E \longrightarrow LG \quad \longrightarrow \quad Nu \longrightarrow E \quad + \quad :LG$$
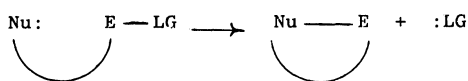
SCHEME 10.   Strain in ring formation?

Such reactions have a very long history; the syntheses by W H Perkin (25) of cycloalkane bis-carboxylates from α,ω-dihalides and sodio-diethyl malonate undoubtedly involve cyclisation of an ω-halogeno alkyl malonate ion.   Notwithstanding the fact that Perkin showed clearly that both 3- and 4-membered ring systems could readily be formed in this reaction, it was widely assumed that these reactions were slow.   This prejudice was reinforced by the accurate work of Freundlich (26) on the cyclisation of ω-halogeno alkylamines showing clearly that 3- and 4-membered rings were formed very slowly by comparison with 5-membered rings.   A general rationalisation of ring closure reactions was advanced by Ruzicka (27) who analysed such reactions in terms of the enthalpy terms (very unfavourable for 3-membered rings) and entropy terms (very favourable for 3-membered rings) giving an overall picture for ease of ring closure from small to large rings.
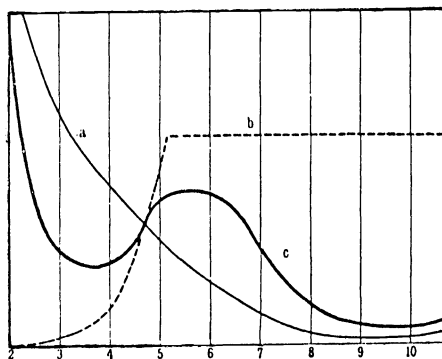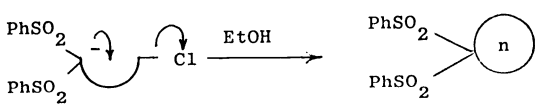

Fig. 3. The Ruzicka hypothesis (27) relating ease of ring closure (curve c) to distance between bonding atoms ($\equiv$ entropy) (curve a) and effect of ring size strain factor ($\equiv$ enthalpy) (curve b).

We had shown some time ago that the generalisations about the difficulty of closing small rings by intramolecular nucleophilic substitution are simply not supported by the experimental facts (28).   While it was recognised that when the nucleophile was a nitrogen or oxygen nucleophile, ring closure of 3-rings was very much slower than that of 5-rings, when the nucleophile was a sulphur, or more particularly, a carbon nucleophile, then ring closure of 3-membered rings was very much more favourable than for any other size, with 3:5 ratios of up to 23000 being observed.   No activation parameters, however,

were available for such systems, because the very rapid closure of 3-membered rings made the obtaining of accurate rate data difficult.   Recently, Mandolini and his collaborators (29) have investigated cyclisation of ω-bromo-alkylmalonate ions in DMSO in which 4- to 22-membered ring systems are formed.   They find an excellent correlation between the strain energy of the cycloalkane formed and the difference between the enthalpy of activation for the intra-and inter-molecular reactions.   Our own work (30) on the cyclisation of bis-sulphonyl stabilised carbanions shows that the tempting Ruzicka generalisation cannot be adopted.   Rates and ring strain energies for 3- to 5-membered rings systems are shown in Table 13.   The really striking feature of this set of results, of course, is the fact that a 3-membered ring closes nearly 1 million times as rapidly as the less strained 4-membered ring.   Similar results had been obtained a considerable time ago by Knipe (31) in the malonate system.   In contrast to the bromo-alkyl malonates, this system was susceptible to examination of kinetics by stop-flow methods and activation parameters are also in Table 13.   The remarkable lack of correlation of enthalpies of activation with ring strain is at once apparent, and the *lower* enthalpy of activation for the 3-ring than for the 4-ring is striking.   While the enthalpy of activation for the 5-membered ring is substantially less than that for the 3-membered ring, this difference is a very insensitive function of the strain energy difference between the two model cycloalkanes.   We conclude that the transition state for this system is a very open one and this is confirmed by the substantial element effect and the insensitivity to solvent effects.

TABLE 13.   Strain in intramolecular nucleophilic displacement?

Ring Size n	k_{rel}	Ring strain kcal mol^{-1}	$\Delta H^{\ddagger}$ kcal mol^{-1}	$\Delta S^{\ddagger}$ kcal mol^{-1}
3	1	27.4	20.5	10
4	6.7×10^{-6}	26.0	21.8	-9
5	1.6×10^{-2}	6.1	16.3	-12

Conclusions

Strain and steric effects are often used, as patriotism by a scoundrel, as the last refuge for those who have difficulty in understanding rate effects.   The work reported here draws attention to the fact that generalisations in this field are to be avoided.   It is quite clear that the influence of strain is extremely dependent on the transition state of the reactions involved and this unsurprising conclusion is frequently ignored.   It is also evident that strain is far too much of a blanket expression to have very much general value and that its incidence in determining the energies of transition states always bears close examination so that there may be a chance of extracting valuable rationalisations.

REFERENCES

1. J. Herriot, *All Creatures Great and Small*, Bantam Press, New York (1972)
2. For a review see C.J.M. Stirling, *Tetrahedron* 00, 000-000 (1984).
3. For many references, see Ref. 2.
4. D.H. Wertz and N.L. Allinger, *Tetrahedron* 35, 3 (1979).
5. D.F. De Tar, D.F. McMullen and N.P. Luthra, *J. Am. Chem. Soc.* 100, 2484 (1978).
6. P. Müller and J.-C. Perlberger, *J. Am. Chem. Soc.* 98, 8407 (1976), and references cited.
7. W. Barse, H.-D. Beckhaus and C. Rüchardt, *Chem. Ber.* 116, 1042 (1983), and references cited.
8. J.S. Lomas and J.E. Dubois, *J. Org. Chem.* 47, 4505 (1982).
9. J.L. Fry, E.M. Engler and P.v.R. Schleyer, *J. Am. Chem. Soc.* 94, 4628 (1972).

10. A.S. Pell and G. Pilcher, *Trans. Faraday Soc.* <u>61</u>, 71 (1965).

11. J.I. Lynas-Gray and C.J.M. Stirling, unpublished work.

12. C.J.M. Stirling, *Acc. Chem. Res.* <u>12</u>, 198 (1979), and references cited.

13. R.J. Palmer and C.J.M. Stirling, *J. Am. Chem. Soc.* <u>102</u>, 7888 (1980).

14. D.R. Marshall, P.J. Thomas and C.J.M. Stirling, *J. Chem. Soc. Perkin II*, 1914 (1977).

15. G. Griffiths, S. Hughes and C.J.M. Stirling, *J. Chem. Soc. Chem. Commun.* 236 (1982).

16. P.J. Thomas and C.J.M. Stirling, *J. Chem. Soc. Perkin II*, 1130 (1978).

17. H.A. Earl, D.R. Marshall and C.J.M. Stirling, *J. Chem. Soc. Chem. Commun.* 779 (1983).

18. C.J.M. Stirling, *Chem. Rev.* <u>78</u>, 517 (1978).

19. A. Thibblin and W.P. Jencks, *J. Am. Chem. Soc.* <u>101</u>, 4963 (1979).

19a.C.H. DePuy and L.R. Mahoney, *J. Am. Chem. Soc.* <u>86</u>, 2653 (1964).

20. N.L. Bauld, J. Cessac and R.L. Holloway, *J. Am. Chem. Soc.* <u>99</u>, 8140 (1977).

21. K.U. Ingold, B. Maiillard and J.C. Walton, *J. Chem. Soc. Perkin II* 970 (1981).

22. A. Bury and C.J.M. Stirling, to be published.

23. A.J. Kirby, *Adv. Phys. Org. Chem.* <u>17</u>, 208 (1980).

24. P.P. Piras and C.J.M. Stirling, *J. Chem. Soc. Chem. Commun.* 660 (1982).

25. W.H. Perkin, *J. Chem. Soc.* <u>47</u>, 801 (1885).

26. H. Freundlich and H. Kroepelin, *Z. Phys. Chem.* <u>122</u>, 39 (1926).

27. L. Ruzicka, W. Brugger, M. Pfeiffer, H. Schinz and M. Stoll, *Helv. Chim. Acta* <u>9</u>, 499 (1926).

28. C.J.M. Stirling, *J. Chem. Ed.* <u>50</u>, 84 (1973).

29. M.A. Casadei, C. Galli and L. Mandolini, *J. Am. Chem. Soc.* 1051 (1984).

30. F. Benedetti and C.J.M. Stirling, *J. Chem. Soc. Chem. Commun.* 1374 (1983).

31. A.C. Knipe and C.J.M. Stirling, *J. Chem. Soc. B*, 67 (1968).