TETRAHEDRON REPORT NUMBER 114

REGIO-SELECTIVITY AND STEREO-SELECTIVITY IN RADICAL REACTIONS
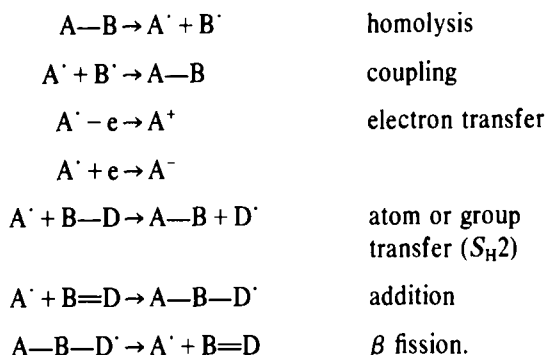
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INTRODUCTION

Most organic free-radical reactions involve one or more of the following elementary mechanistic steps in which A, B, and D represent atoms or groups, not necessarily carbon-centred.

$$A—B \rightarrow A^{\cdot} + B^{\cdot} \qquad \text{homolysis}$$

$$A^{\cdot} + B^{\cdot} \rightarrow A—B \qquad \text{coupling}$$

$$A^{\cdot} - e \rightarrow A^{+} \qquad \text{electron transfer}$$

$$A^{\cdot} + e \rightarrow A^{-}$$

$$A^{\cdot} + B—D \rightarrow A—B + D^{\cdot} \qquad \text{atom or group transfer } (S_H2)$$

$$A^{\cdot} + B{=}D \rightarrow A—B—D^{\cdot} \qquad \text{addition}$$

$$A—B—D^{\cdot} \rightarrow A^{\cdot} + B{=}D \qquad \beta \text{ fission.}$$

A radical A· generated in the presence of organic substrates may potentially be capable of undergoing a number of the above types of reactions; or, if only one reaction type is available, questions of regio- and stereo-selectivity may arise.

Given a number of possible reaction pathways, how may one predict which will be preferred? Emphasis has traditionally been placed on the use of thermochemical criteria. The fact that limited sets of data often fit the Evans–Polanyi equation,[1] and the undoubted success of recent quantitative approaches to the relationship between thermodynamic factors and kinetic parameters[2,3] have encouraged the qualitative view that radical reactions preferentially follow the most exothermic pathway as determined from bond dissociation energy data; they tend to afford the most stabilised possible product radical.

For many homolytic processes however, this view lacks experimental justification. The outcome of free radical additions, even in relatively simple systems, has been shown to depend on "the complex interplay of polar, steric, and bond strength terms".[4] Experiments with more elaborate systems, and especially those involving intramolecular reactions, reveal even more clearly that the idea that thermochemical factors are the primary arbiters of radical behaviour is a misconception.

The purpose of this review is to focus attention on the importance of steric and stereo-electronic effects in determining the regio- and stereo-selectivity of radical reactions. It makes no pretence to present an exhaustive survey of these and other significant factors; were it to do so it would cover, perforce, the whole gamut of organic free-radical chemistry. It is limited, therefore, to a personal view of a few selected topics which, while reflecting the Author's current research interests and his predilection for kinetic studies of unimolecular processes, hopefully will illustrate the factors affecting the regio- and stereo-chemical course of free-radical reactions. For a more complete coverage of these and related topics the reader is referred to excellent recent reviews by Tedder and Walton,[4,5] Rüchardt,[6,7] Wilt[8] and others.[9–12]

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ADDITION REACTIONS

(a) *Ring closure of hex-5-enyl and related radicals*

Hex-5-enyl radical (2) undergoes ring closure by intramolecular addition. This reaction provides a nice example of a homolytic process which proceeds contrary to predictions based on thermochemical criteria. The usual generalisation concerning the order of stability of alkyl radicals, *viz* tertiary > secondary > primary, suggests that one possible product [cyclohexyl radical (5)] is more stabilised than the other [cyclopentyl-carbinyl radical (4)], a conclusion supported by quantitative thermochemical calculations,[2,3,13] and appropriate experimental observations.[14,15] For example, the primary radical (4) rearranges to the secondary radical (5) in the gas phase at temperatures > 298°,[15] whilst similar rearrangements of substituted cyclopentylcarbinyl radicals, (e.g. 8) to cyclohexyl systems, (e.g. 10) *via* the acyclic system (9), proceed rapidly in solution at ordinary temperatures.[16]

Thus both theory and experiment unambiguously indicate cyclohexyl radical (5) to be more stabilised than cyclopentylcarbinyl (4). The behaviour predicted on thermochemical grounds for hex-5-enyl radical (2) is therefore clearcut: ring closure should proceed mainly by 1,6-bond formation to afford cyclohexyl radical (5). It is not surprising that early workers, aware of these considerations, and of the propensity of *intermolecular* addition to unsymmetrical olefins to afford the more substituted possible radical assigned 6-membered cyclic structures to the products of intramolecular addition in systems of the hex-5-enyl type.[17]
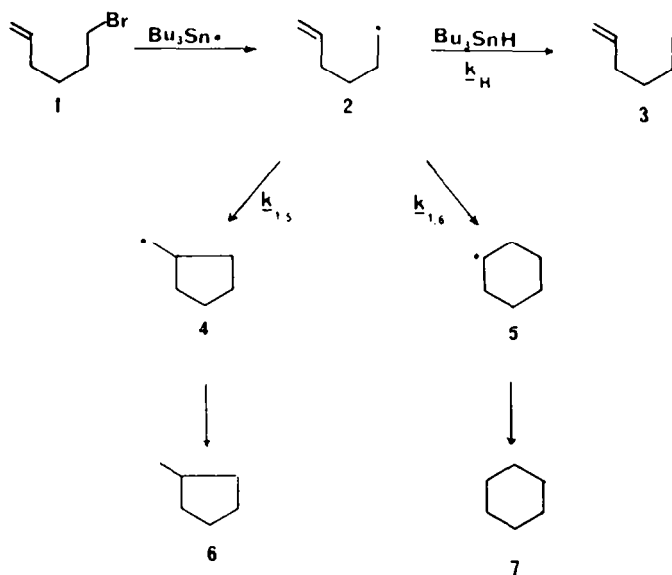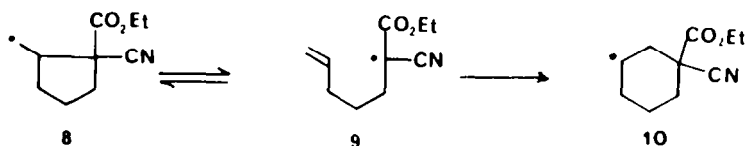

Fig. 1.

The failure of the thermochemical approach to rationalise the outcome of intramolecular additions was not revealed until later when careful analyses were made of the products formed from hex-5-enyl radical generated from a variety of precursors.[18] The outcome of the reaction of 1-bromohex-5-ene with tributylstannane (Table 1) is illustrative of the results obtained:[19-21] intramolecular addition proceeds in a highly regioselective fashion to afford mainly the product (6) of 1,5-ring closure.

As expected on the basis of the accepted mechanism[22] (Fig. 1) in which *unimolecular* ring closure of hex-5-enyl radical competes with *bimolecular* H-atom transfer from stannane the yields of cyclic products decrease with increasing stannane concentration. However, at any given temperature the ratio of yields of methylcyclopentane and cyclohexane is a constant which reflects the relative magnitudes of

Table 1. Relative yields[a] of products from the reaction of 1-halohex-5-ene with tributylstannane[b]

$T(°C)$	$[Bu_3SnH]_0$ (M)	$\underline{3}$(%)	$\underline{6}$(%)	$\underline{7}$(%)	$k_{1,5}/k_{1,6}$	$\Sigma k_c/k_H \times 10^2$ (mol l^{-1})
25	0.093	29.9	69.1	0.9	76	0.96
25	0.195	45.0	54.1	0.8	68	0.98
40	0.077	22.1	76.7	1.3	59	1.26
40	0.260	44.9	54.4	0.9	60	1.32
60	0.078	17.3	81.1	1.6	51	1.75
60	0.347	45.0	53.9	1.1	49	1.74
80	0.260	33.0	65.4	1.6	41	2.31
80	0.454	45.1	53.5	1.4	38	2.27
100	0.162	21.3	76.1	2.7	28	2.89
100	0.582	45.0	53.3	1.7	31	2.92

[a]   Total absolute yields of identified products were > 90%.

[b]   Data from Refs. 19–21.

the rate constants for 1,5- and 1,6-ring closure. The results indicate that $k_{1,5} \gg k_{1,6}$ ($k_{1,5}/k_{1,6} = 50$ at 60°).[19-21]

Further evidence in support of the mechanistic scheme (Fig. 1) and of the conclusions based thereon has come from the observations that each mode of ring closure is irreversible[13,23,24] under these conditions, that 2, 4 and 5 are discrete species,[25] and that a π complex is not involved.[13,24] Also, the hex-5-enyl radical can be directly observed in solution at low temperature by ESR spectroscopy,[25,26] but at higher temperatures it undergoes ring-closure to give cyclopentylcarbinyl radical (4) as the only detectable product. The ESR method has allowed direct measurement of the kinetic parameters for 1,5-ring closure;[26] the results ($k_c = 1 \times 10^5$ sec^{-1} at 25°) are in excellent agreement with those obtained indirectly from the results of reactions involving tributylstannane.[19-22]

It is abundantly clear, therefore, that ring-closure of hex-5-enyl radical proceeds in a highly regio-selective fashion to afford the less stable possible product. Why should this system contravene a widely accepted generalisation and behave so differently from related intermolecular reactions?

One explanation, first advanced by Capon and Rees,[27] invokes the more favourable entropy of activation associated with the formation of the smaller possible ring. Intramolecular reactions generally occur more readily than their bimolecular intermolecular counterparts because the latter involve substantial loss of translational entropy whereas the former involve only the loss of internal rotational degrees of freedom. Furthermore, the entropy change associated with loss of rotational freedom becomes increasingly unfavourable with increasing size of the ring being formed. It is reasonable, therefore, to expect that both ΔS and $\Delta S^\ddagger$ will be more unfavourable for 1,6-ring closure of hex-5-enyl radical than for 1,5-.

Capon and Rees considered that the magnitude of the difference of $\Delta S^\ddagger$ for the two processes would be sufficiently large to account for preferential formation of the smaller ring. This suggestion has been taken up by later workers.[28,29] Thus Bischof[29] used statistical thermodynamics and MINDO/3UHF to calculate the activation parameters for cyclization of lower ω-alkenyl radicals. He found that $\Delta S^\ddagger$ at 25° for 1,6-ring closure of hexenyl radical is 3.3 cal mol^{-1} °K more favourable than $\Delta S^\ddagger$ for 1,5-ring closure, and he concluded that it is this factor which controls the course of the reaction.

This hypothesis can be tested against experimental observation, for the accurate analysis of the relative yields of products from the reaction of 1-bromohex-5-ene with tributylstannane allows the difference between the activation parameters for the two modes of ring closure to be determined. Such experiments give $\Delta S^\ddagger_{1,5} - \Delta S^\ddagger_{1,6} = 2.8$ cal mol^{-1} °K^{-1} in reasonable agreement with Bischof's figure. However, the experimental results[20] also reveal that 1,5-ring closure has the more favourable enthalpy of activation [$\Delta H^\ddagger_{1,6} - \Delta H^\ddagger_{1,5} = 1.7$ kcal/mole]. These figures are probably subject to considerable experimental error because of the very large difference between $k_{1,5}$ and $k_{1,6}$. Nevertheless, simple calculations show that at ordinary temperatures the value of 3.4 cal mol^{-1} °K^{-1} for $\Delta \Delta S^\ddagger$ is far too small to account for

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the degree of regioselectivity exhibited by the ring-closure reaction. Although the more favourable value of $\Delta S^{\ddagger}$ contributes to the preference for 1,5-cyclization this is not the dominant factor.

An alternative explanation has been advanced by Julia[30,31] who developed LeBel's hypothesis[32] that an unfavourable non-bonded interaction between the pseudo-axial proton at C-2 and the *syn* proton at C-6 will destabilise the transition state (**11a**) for 1,6-ring closure by comparison with that (**12**) for 5-membered ring formation. In support of this proposal Julia[31] reported that the radical (**13**) containing a *syn* Me group, and thus putatively subject to a severe non-bonded interaction in the transition state (**11b**), affords only the 5-membered cyclic product, whereas its E isomer (**14**) undergoes both 1,5- and 1,6-ring closure. Although this evidence indicates the existence of a destabilising interaction between the *syn*-methyl group and the C-2 pseudo axial proton in (**11b**) the data do not allow its magnitude to be determined and it is not possible therefore to estimate whether a similar interaction involving the *syn* proton at C-6 in (**11a**) is likely to be significant.

11 a; $R^1 = R^2 = R^3 = H$
   b; $R^1 = R^3 = Me$, $R^2 = H$
   c; $R^1 = H$, $R^2 = R^3 = Me$

12

13   14
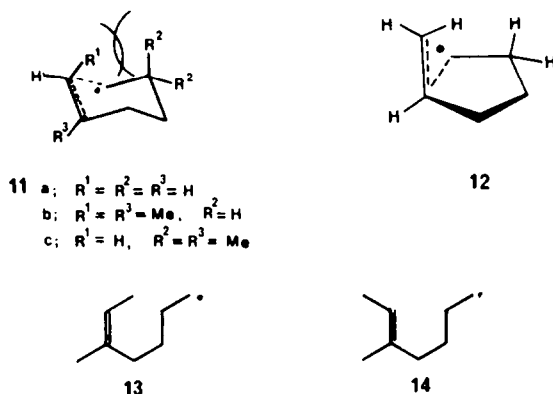
In an attempt to obtain more precise data concerning the magnitude of 2,6-non-bonded interactions in the transition state for 1,6-ring closure of hexenyl systems the behaviour of the Me-substituted radicals (**15, 16** and **17**) has been examined.[33] The results (Fig. 2) show that 1,6-ring closure of 2,2,5-trimethylhex-5-enyl radical (**17**) is disfavoured by comparison with the monosubstituted radical (**16**), and it is reasonable to attribute this effect to steric interaction between the pseudo-axial C-2 methyl substituent and the *syn* proton at C-6 in the transition state (**11c**). However, careful kinetic analysis[33] reveals that the contribution to transition state free energy arising from this unfavourable interaction is only about $0.8 \, \text{kcal mol}^{-1}$. The magnitude of the interaction in the transition state (**11a**) for the unsubstituted radical will be much less, and is clearly insufficient to account for the high preference for 1,5-ring closure. The conclusion that the Julia-LeBel hypothesis does not satisfactorily rationalise the behaviour of the hex-5-enyl radical is supported by the observation that alkenylaryl radicals (e.g. **18**), in which there is no pseudo-axial proton at C-2 in the transition state, undergo regiospecific formation of a 5-membered ring.[34,35]
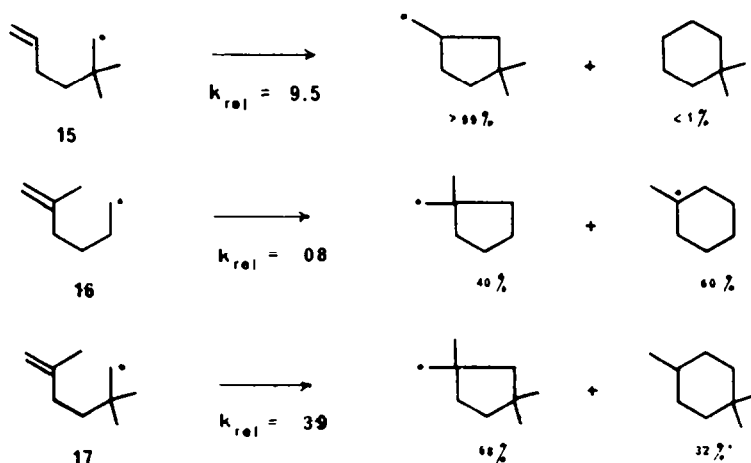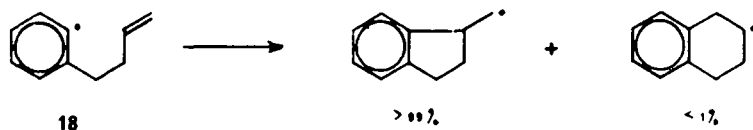

$k_{rel} = 9.5$

15   > 99 %   < 1 %

$k_{rel} = 08$

16   40 %   60 %

$k_{rel} = 39$

17   68 %   32 %

Fig. 2. Rate constants at 80° relative to k_c for hex-5-enyl radical.

18   > 99 %   < 1 %

An hypothesis[36,37] which appears to account satisfactorily for the behaviour of hex-5-enyl radical and a variety of related species potentially capable of undergoing ring closure is based on a consideration of stereo-electronic factors. Essentially, this theory contends that the strain engendered in accommodating the mandatory disposition of reactive centres within the transition complex for 1,6-ring closure outweighs those steric and thermochemical factors expected to favour the formation of the more stable possible product. When this hypothesis was first adumbrated[36] no direct evidence was available to show that the intimate structure (19) of the transition state for homolytic addition incorporates the three participating atoms at the vertices of an obtuse triangle orthogonal to the nodal plane of the π system. Indeed, this model of the transition complex was deduced from the outcome of hex-5-enyl cyclization reactions.[36,37] However, a number of theoretical treatments[38] now support the structure (19) and indicate that the dominant interaction for attack of an alkyl radical on an olefinic bond involves overlap of the semioccupied 2p orbital with one lobe of the vacant π^* orbital. Consequently, the transition complex is dipolar: the incoming radical behaves as a nucleophile and assumes a fractional positive charge whereas the olefinic moiety becomes fractionally negative. Inspection of models and statistical calculations[39] reveal that the required disposition of centres (19) can be much more readily accommodated in the transition complex (12) for 1,5-ring closure of hex-5-enyl radical than in that (11a) for 1,6-ring closure. A similar conclusion has been reached by Baldwin on the basis of approach vector analysis.[40]

If the view is correct that ring closure of hex-5-enyl radical is primarily under stereo-electronic control it should be possible to make a more general statement about the outcome of intramolecular

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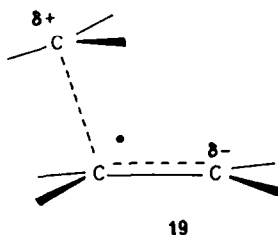
addition reactions of alkenyl radicals and similar species. This has been done:[41] "Intramolecular addition under kinetic control in lower alkenyl and alkynyl radicals and related species occurs preferentially in the exo-mode". That is to say that the exo-ring closure, (20)→(21) will be kinetically favoured over the endo process, (20→22), for those radicals where Y is a chain of up to 5 atoms (n ≤ 5), A=B is any double (or triple) bond, and X· represents a C, O or N centre.

20   21   22
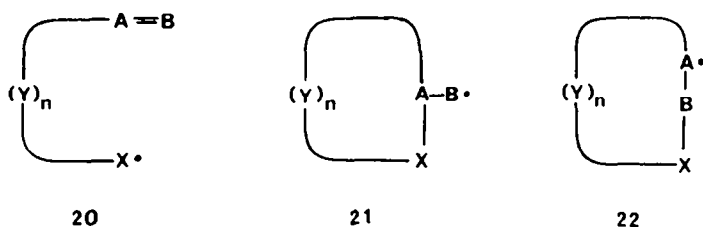
Examination of models of the two generalised transition complexes leading to 21 and 22 indicates that the degree of preference for exo-ring closure will depend, inter alia, on the length of the chain $(Y)_n$. When the chain is short (n = 1 or 2) the transition complex for the endo-process is very highly strained, but when the chain is long and flexible the difference in strain energy between the transition complexes leading to 21 and 22 will be small.

Accurate kinetic data pertinent to this guideline are available only for the lower alkenyl radicals (Table 2),[19–21,42] all of which undergo regiospecific or regioselective exo-ring closure. However, as expected, the degree of preference for the exo-mode decreases along the series butenyl, hexenyl, and heptenyl. The regiospecific exo-ring closure of the 7-octenyl radical probably reflects the existence of

Table 2. Rate constants at 65° and activation parameters for ring-closure of ω-alkenyl radicals[a]

Radical	% exo	k_{exo} (s^{-1})	$\Delta H^{\ddagger}_{exo}$ (kcal mol^{-1})	$\Delta S^{\ddagger}_{exo}$ (cal mol^{-1} K^{-1})	k_{endo} (s^{-1})	$\Delta H^{\ddagger}_{endo}$ (kcal mol^{-1})	$\Delta S^{\ddagger}_{endo}$
3-butenyl	100	1.8×10^4	10.5	-10			
4-pentenyl[b]	100	7×10^{-1}	16	-14			
5-hexenyl	98	3.6×10^5	6.1	-17	7×10^3	7.8	-20
6-heptenyl	85	1.1×10^4	7.5	-20	1.9×10^3	8.0	-22
7-octenyl	100	3.0×10^2	8.9	-23			

[a] Calculated from data presented in Refs. 19-21, 26.

[b] This reaction is too slow to be measured directly. The data presented here are estimated from data for the reverse reaction (Ref. 93).

unfavourable interannular non-bonded interactions in the cyclic transition complex leading to cyclo-octyl radical. Unfortunately, ring-closure of the 4-pentenyl radical proceeds too slowly at ordinary temperatures to be experimentally observable, but there can be little doubt that it will exclusively follow the *exo*-mode.

The kinetic data for cyclization of alkenyl radicals reflect the usual interplay of enthalpic and entropic factors. The value of $\Delta S^{\ddagger}$ decreases monotonically down the series butenyl to octenyl. This is to be expected because ring closure of any particular radical, as compared with that of its next lower homolog, involves the additional loss of rotational freedom of one CH_2 rotor. The value of $\Delta H^{\ddagger}$, however, appears, not unreasonably, to reflect approximately the heat of formation of the ring being generated. It is small for cyclopentyl and cyclohexyl rings, but much larger for 3- or 4-membered rings. The resultant rate constants for ring closure at ordinary temperature are in the order hexenyl > butenyl > heptenyl > octenyl > pentenyl.

Any structural feature which affects the ability of an unsaturated radical to accommodate the intimate transition complex for homolytic addition will necessarily affect also the rate and regioselectivity of ring closure. Intramolecular reactions of 3-oxahex-5-enyl radical (**23a**) and related species provide a case in point.[43-46] Since the length of the C–O bond is less than that of C–C and the bond angle C–O–C is less than that of C–C–C, the minimum C-1–C-5 distance in the unstrained radical (**23a**) is less than it is in hex-5-enyl, while the C-1–C-6 distance is greater. Consequently the 3-oxahex-5-enyl systems (**23a** and **23b**) undergo ring closure much more rapidly than their hexenyl analogs, and show a greater preference for the *exo*-mode.
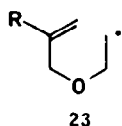

a, R = H
b, R = Me
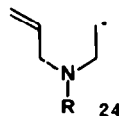
For similar reasons radicals containing a N atom in the chain (e.g. **24**) should show enhanced rates of *exo*-ring closure. Although accurate product and kinetic analyses have not been reported, support for this view comes from ESR measurements.[47] Also, it is significant that diallylamine and related compounds undergo facile cyclo-polymerisation.[48]

Alkenylaryl radicals are good examples of systems in which the lack of flexibility in the chain, due to the presence of the aromatic ring, greatly increases the difference in strain energy between the transition states for *exo-* and *endo*-ring closure. Consequently, the radicals (**25** and **26**), unlike related alkenyl systems undergo regiospecific ring closure.[34,35]

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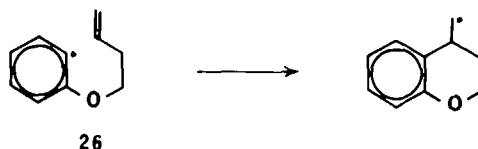
The collinear disposition of C-4, C-5 and C-6, affects similarly the flexibility of the 5-hexynyl radical which undergoes·1,5-ring closure, regiospecifically, but at a slower rate than does 5-hexenyl radical. Hept-6-ynyl and oct-7-ynyl also undergo regiospecific *exo*-cyclization. As expected, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ become increasingly unfavourable along the series hexynyl, heptynyl, octynyl (Table 3). Both the rates and regiospecifity of alkynyl radical cyclization are fully consistent with the concept of stereo-electronic control involving an early transition state.[49] The experimental observations do not, however, accord with predictions based on trajectory analysis.[40]

Table 3. Rate constants at 60° and activation parameters for *exo*-ring-closure of ω-alkynyl radicals[a]

Radical	k	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
	(s^{-1})	$(kcal\ mol^{-1})$	$(cal\ mol^{-1}\ K^{-1})$
5-hexynyl	4.6×10^{4}	7.5	-17
6-heptynyl	2.5×10^{3}	8.8	-19
7-octynyl	1.2×10^{2}	10.0	-21

a
    Calculated from data presented in Refs. 21 and 26.

Since the electronic interactions giving rise to the transition complexes (27, X = 0, NR, SiR$_2$, S, PR etc.) for addition of a hetero-atom-centred radical to a multiple bond might be considerably different from those for C centred systems (27, X = CR$_2$) it would be reasonable to expect that their general shapes·and dimensions would also differ. Intermolecular examples of such reactions might therefore vary considerably in their regioselectivity. Nevertheless, O and N centred radicals related to hex-5-enyl show a very high degree of preference for *exo*-ring closure in reactions which appear to be under stereo-electronic control.[50]
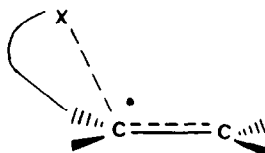

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As in the case of radicals containing N or O in the chain, the shorter bond length of C–O and C–N by comparison with C–C might be expected to enhance the regiospecificities and possibly the rates of reactions of 28a and 29 relative to those of hex-5-enyl (2). This appears to be so for O centred radicals. Thus, in contrast to its alkenyl analog (Fig. 2) which undergoes substantial 1,6-ring closure the radical 28b gives exclusively the product of 1,5-cyclization.[51] Furthermore, ESR[52] and product studies[51] suggest

that cyclization of **28a** is much faster $(k > 10^8\,\mathrm{sec}^{-1})$ than cyclization of 5-hexenyl radical. Neutral alkenyl–aminyl radicals, on the other hand, appear to cyclize rather slowly [k_c for **29**, R = Pr < $10^3\,\mathrm{sec}^{-1}$][53] but the related radical cations (**30**) undergo rapid ring closure.[54]
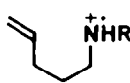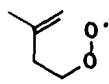

28

a, R = H
b, R = Me

29   30

31

CH₂SAr
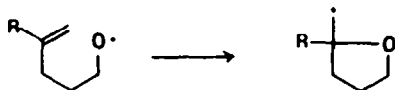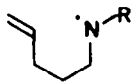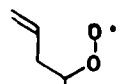
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Alkenylperoxy radicals such as **31**[55] and **32**[56,57] undergo regiospecific *exo*-ring closure. However, the rate constants for such processes appear to be considerably less than those for analogous C-centred radicals.[58]

Since the C=X bond in systems such as **33**, (X = SiR₂, PR or S) is longer than the C–CH₂· bond in hex-5-enyl the difference in strain energy between the transition complexes for *exo*- and *endo*-ring closure should be less. Nevertheless **34** and **35** appear to undergo regioselective 1,5-cyclization.[59,60] The data for S centred radicals are less clearcut. Thus **33** (X = S) gives both 5- and 6-membered cyclic products in relative yields which depend on the experimental conditions.[61] This is typical of reversible reactions when the final outcome reflects the interplay of the relative rates of ring-closing, ring-opening, and chain-transfer processes. By and large, the experimental results seem to accord with the view that $k_{1,5} > k_{1,6}$ as expected on stereo-electronic grounds.
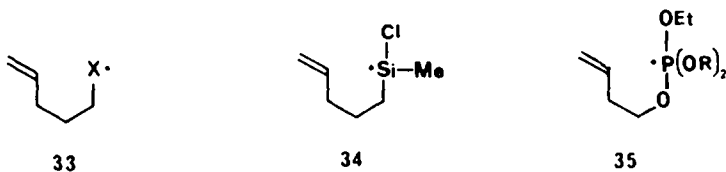

33   34   35

R = CH₂CH₂CH=CH₂

Although only a limited amount of data is available it appears that radicals of the general type (**20**) containing a hetero-atom in the unsaturated moiety often show a preference for *exo*-ring closure. Examples include cyclization of the cyano radical (**36**) $(k_c = 4.0 \times 10^3\,\mathrm{sec}^{-1}$ at $25°)$[62] and the CO containing radical (**37**).[63] The latter reaction is especially significant for the alternative *endo*-process would afford the highly stabilised benzylic radical (**38**).

Finally, it is noteworthy that ring closure of 4-arylbutyl radicals (e.g. **39**) under *kinetic control* gives preferentially the *exo*-product (e.g. **40**) in a fast, but reversible process.[64]

I now turn to a discussion of the effects of substituents on homolytic intramolecular addition reactions. Substituents at the reactive centres in an alkenyl radical will affect the energy of the transition complex through their interactions with the free spin, through polar effects, and through steric effects developed by the mutual approach and change in configurations of the radical centre and olefinic moiety.

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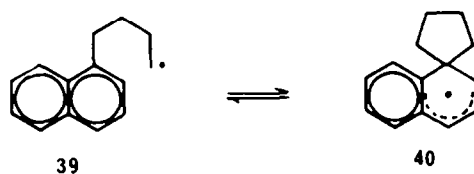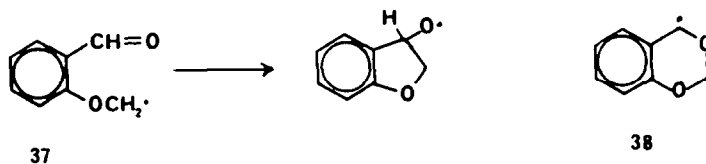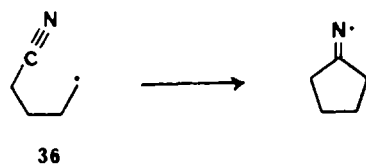
Substituents elsewhere in the chain will influence the outcome of intramolecular addition through their effects, arising from non-bonded interactions, on the energies of the various possible conformers of cyclic transition complexes.

The effects of alkyl substituents at C-1 or C-6 in the hex-5-enyl radical, predicted on the basis of the thermochemical hypothesis that the rates of closely related reactions reflect the relative stabilities of reactants and products, are clearcut: the rate of 1,5-ring closure should be diminished by substitution at C-1 and enhanced by substitution at C-6. However, the experimental data (Table 4)[65] do not reveal such

Table 4. Relative rate constants for *exo*- and *endo*-ring-closure of substituted hex-5-enyl radicals[a]
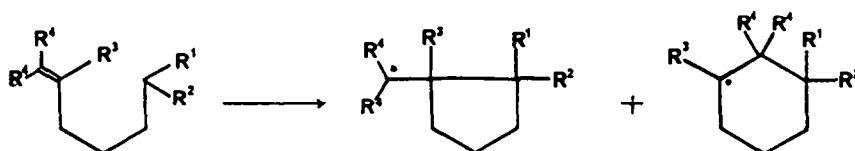

| R^1	R^2	R^3	R^4	k_{exo}	k_{endo}	k_{exo}/k_{endo}
H	H	H	H	1.0	0.02	48
Me	H	H	H	1.4	0.02	78
Pr	H	H	H	1.6	0.008	206
Me	Me	H	H	1.4	0.02	68
H	H	H	Me	2.4	<0.01	>200
H	H	Me	H	0.022	0.04	0.62
H	H	Pr^i	H	0.022	0.07	0.31
Me	Me	Me	H	<.0002	0.02	<.01

[a] Data from Ref. 65.

effects. There are at least two possible plausible explanations. First, it appears that homolytic addition proceeds through a very early transition state in which there is little change of configuration at C-1 or C-6 and little transfer of spin density.[38] Secondly, it seems possible that changes in energy arising from the interactions of substituents with fractional charges at C-1 and C-6 in the polar transition state (19) will be in the opposite direction to those changes expected to result from interactions with the free spin. Consequently, the two effects tend to counterbalance each other.

Accurate kinetic data are not available for ring closure of radicals such as 9 containing substituents at C-1 expected to exert a strong conjugative effect on the adjacent radical centre. However, it is known[12] that these types of radical often afford mainly products of *endo*-ring closure. Nevertheless, such results are not incompatible with the concept of stereo-electronic control, for careful experimental scrutiny of their behaviour suggests that *exo*-ring closure is the kinetically controlled process, but being freely reversible,[16] is often superseded by slow but essentially irreversible *endo*-ring closure.[66] Also, the transition complexes for these weakly exothermic reactions may lie towards the product end of the ring-closure reaction co-ordinate. Consequently, stereo-electronic effects will be of lesser importance.

Substitution at C-5 in hex-5-enyl and related radicals has a profound affect on the regioselectivity of ring closure. For example, reactions involving the intermediacy of 5-methylhex-5-enyl radical (41) favour the formation of *endo*-products.[65] The thermochemical explanation for this phenomenon, *viz.* that the difference in hyperconjugative stabilization between the *tertiary* radical (43) and the *primary exo*-product (42) is sufficient to outweigh those factors favouring *exo*-ring closure, is plausible, but incorrect. The kinetic data (Table 4) clearly show that the observed preference for *endo*-ring closure reflects not an enhanced rate of formation of 42 but a greatly retarded rate of 1,5-cyclization.

41   42   43

$$k_{42}/k_{43} = 0.63$$
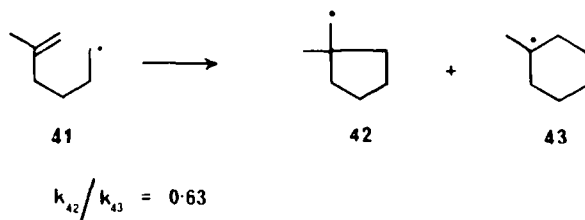
It might be argued that we see here the outcome of some previously unrecognised steric effects peculiarly associated with the hexenyl system. This is not so. Careful kinetic analysis[67] of the reactions of 44a and 44b has shown that the methyl substituent in 44b markedly diminishes the rate of attack at the more substituted terminus of the double bond. Furthermore, scrutiny of intermolecular addition processes, both in the gas phase[4,5] and in solution[68] leads to similar conclusions.[4-6] It follows that Markownikoff addition of a radical to an unsymmetrical olefin is not, as is often supposed, a reflection of the relative stabilities of the two possible products. Rather, it is a consequence of the fact that "substituents on an olefinic bond disfavour addition at the substituted position".[41]


44   a, R = H
        b, R = Me
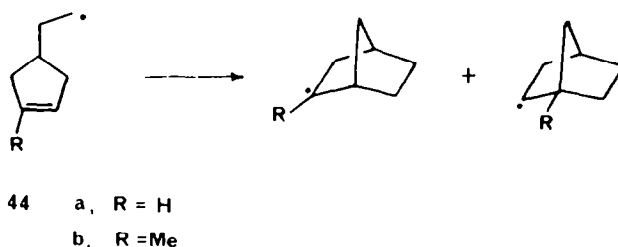
This phenomenon is probably of steric origin. The extremely low relative rate constant for 1,5 ring closure of the radical (45) (Table 4) fully substituted at C-1 and C-5 indicates that non-bonded interactions between the two reaction centres must be important. However, substituents at C-1 alone do not retard ring closure. This suggests that the formation of the transition complex involves considerable configurational change at C-5, and that it is this change toward sp^3 hybridization which is effected by substituents, presumably through B strain.[65]

In some cases (e.g. 46a) alkyl substitution at C-5 does not reverse the normal preference for *exo*-ring closure.[44] However, the kinetic data indicate that such radicals still undergo 1,5-cyclization more slowly than their unsubstituted counterparts.[69] When the substituent at C-5 is capable of interacting strongly with an adjacent radical centre it may increase the rate of *endo*-cyclization. Nevertheless, it will still

retard the rate of 1,5-ring closure. Thus the phenyl substituted radical (46b) undergoes *endo*-ring closure more rapidly than the parent, but *exo*-ring closure occurs more slowly.[69]
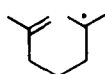

45
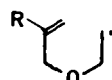
46

a, R= Me

b, R= Ph

c, R= H

Substituents at C-2, C-3 or C-4 of the hex-5-enyl system enhance the rate of 1,5-ring closure. The 2,2-dimethylhex-5-enyl radical (15), for example, has a rate constant for cyclization about ten times larger than that for cyclization of the parent (2).[33,70,71] Mono-substituted radicals show somewhat smaller rate enhancements.[70] Such acceleration of ring formation is attributable to the Thorpe–Ingold or gem-dialkyl effect.[72] In terms of a widely accepted explanation[73] the presence of the two Me substituents in 15 causes extra *gauche* interactions in the ground state which are partly relieved when the cyclic transition state is attained. The net result is that the free energy of the reactant ground state is raised relative to that of the cyclic transition state and the rate of ring closure is enhanced accordingly. In accord with this hypothesis the effect of substitution is mainly to lower the value of $\Delta H^{\ddagger}$ for ring closure.[33]

I turn now to the consideration of the stereo-chemical course of intramolecular addition in substituted alkenyl radicals. *Exo*-ring closure of hexenyl radicals and related systems monosubstituted at C-1, C-2, C-3 or C-4 gives rise to mixtures of *cis*- and *trans*-disubstituted cyclic products. The limited experimental data suggest that most such reactions conform to the rule[41] that 1,5-ring closures of 1- or 3-substituted systems afford mainly *cis*-disubstituted products, whereas 2- or 4-substituted systems give mainly *trans*-products.

The preferential formation of *cis*-products from 1-substituted radicals (e.g. 47)[46,74] has been ascribed to the effects of orbital symmetry: the favourable interaction in the transition complex (49) for *cis*-cyclization between the hyperconjugatively delocalised semi-occupied orbital and the vacant π^* orbital of matching symmetry outweighs the non-bonded repulsion between C-6 and the 1-Me substituent.[46] If, however, the C-1 substituent is bulky simple steric factors take precedence, and the *trans*-product predominates.[75]
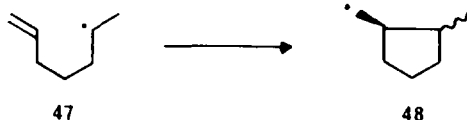

47

48

cis/trans = 2

A reasonable alternative explanation is that the preferred *cis*-cyclization of 47 reflects a favourable electrostatic interaction in a dipolar transition state (50). In accord with this view, the radical ion (51) affords specifically the radical (52)[76] whereas the related protonated system (53) gives a mixture of both possible products (54 and 55).[77]


49

50

51   52

53   54 (59%)   55 (41%)
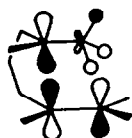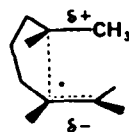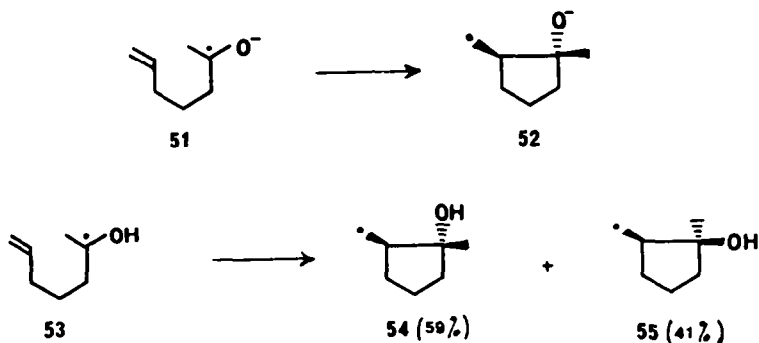
The fact that 1,5-ring closure of 2-methylhex-5-enyl radical (56) affords a mixture of 58 and 59 in which the *trans*-stereoisomer predominates whereas the 3-substituted radical (57) gives a similar mixture containing mainly *cis*-product[70] indicates that the outcome of these and similar reactions does not reflect the relative thermodynamic stabilities of the products. Conformational effects in the cyclic transition states must, therefore, be critical.

56

57   58   59
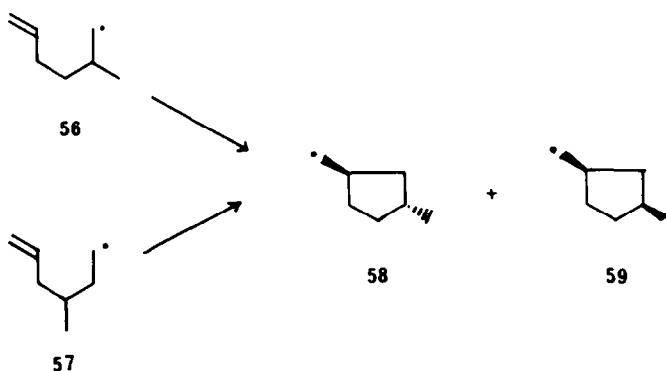
Theoretical calculations[38] indicate that the distance between C-1 and C-5 (2.3 Å) in the transition state for *exo*-ring closure of hex-5-enyl radical is not much less than the distance between C-1 and C-3 (2.5 Å) in cyclohexane. If this is correct, the usual representation (12) of the transition state is inaccurate. It will, in fact, resemble the chair-form of cyclohexane (e.g. 60). Consequently, for any monosubstituted system there will be two possible conformations of the transition state (e.g. 60 and 61), of which that containing the substituent in the pseudo-equatorial position will be of lower energy. Thus the most stable conformation of the transition state for a 3-substituted radical will be that 60 which leads to the *cis*-product. Conversely the preferred transition states for 2- or 4-substituted radicals, since they bear the substituents in pseudo-equatorial positions, lie on the pathways to *trans*-products.[70]

60   61
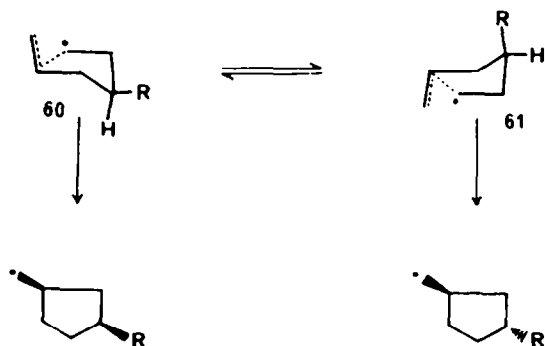
Since the difference in energy between the two conformers of a cyclic transition state will reflect the conformational preference of the substituent the stereo-selectivity of ring closure should be most pronounced when the substituent is bulky. Although this hypothesis has not yet been rigorously tested it is noteworthy that the 3-substituted peroxy radical (62) affords *exclusively* the *cis*-product (63).[57]

62   63

(b) *Formation of some bicyclic systems*

The preceding section presents examples of ring closure of hex-5-enyl radical and related acyclic systems which, by and large, support the view that such reactions conform to simple guidelines based primarily on steric and stereo-electronic considerations. It is of some interest to examine to what extent these guidelines apply to reactions of more complex systems.

One of the earliest reported examples of the formation of bicyclic systems was the ring closure of 4-cyclohexenylbutyl radical (64).[36] Contrary to the expectation, based on thermochemical criteria, that this reaction should afford preferentially the more stable tertiary radical (65) the products were found to be derived from both possible intermediates (65 and 66) with the latter predominating. Kinetic analysis indicated that the rate constant for 1,5-ring closure of 66 is considerably less than that for *exo*-cyclization of hex-5-enyl radical. Since the radical (64) may be formally regarded as a 5-substituted hexenyl system this outcome conforms to the guideline[41] that substituents on an olefinic bond disfavour homolytic addition at the substituted position. A consequence of this guideline is that 6-membered rings may be efficiently formed by homolytic cyclization, only if the ring closure is freely reversible, or if both C-1 and C-5 in a hex-enyl system are fully substituted. Radicals derived from substrates containing a terpenoid moiety fulfil the latter requirement (e.g. 67 → 68).[78]

64   65   +   66

67   68
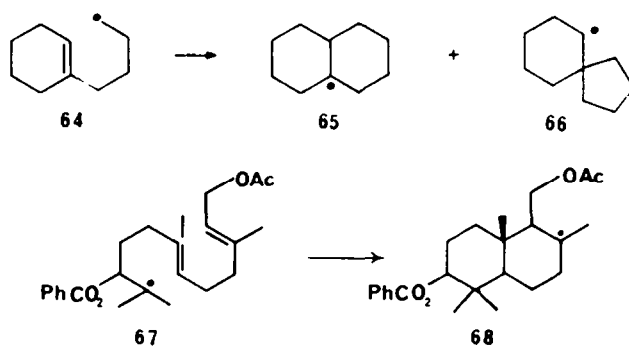
Since the major cyclised product from a 1-substituted hex-5-enyl system is the *cis*-isomer, any subsequent ring closure affords a *cis*-fused bicyclic system. The formation of 69 by reaction of cyanopropyl radicals with diallylamines provides a good example.[79] Similarly the major product (71) from the ring closure of the dienyl radical (70) contains reactive centres suitably disposed for a second ring closure to afford *exo*- and *endo*- 72.[80] 1,5-Ring closure of the *trans*-radical (73) is very slow because of the high strain energy of the *trans*-fused bicyclic product (74).

Me₂ĊCN

69

70   71   72

73   74
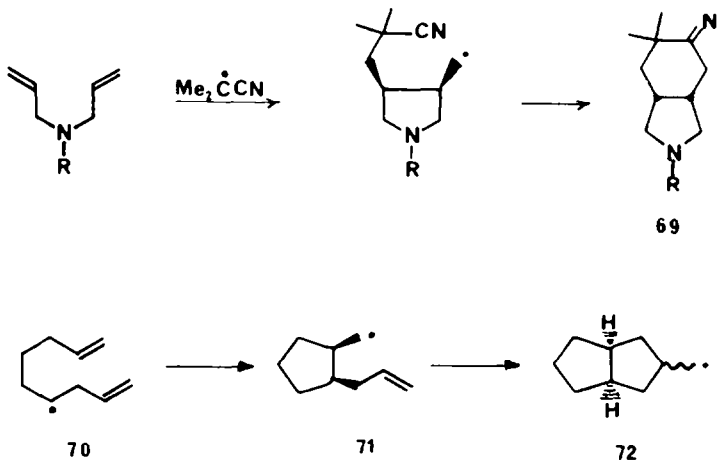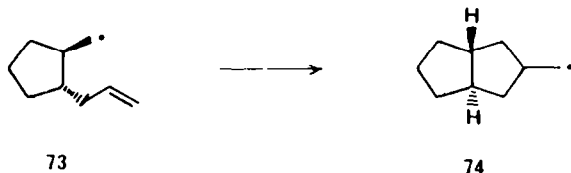
The *cis*-intermediate (71) is formally a 3,4-disubstituted hex-5-enyl system in which the relative configurations at C-3 and C-4 are defined by the ring. The guideline[41] is therefore ambiguous. In one possible product the new radical centre is *trans* to the formal 4-substituent, in the other it is *cis* to the 3-substituent. In fact, both bicyclic radicals are formed with the former predominating.[80]

Ring closures of the butenyl cycloalkyl radicals (75a, 75b) are even more complex. Since they may be regarded as 1,2-substituted hexenyl systems the expected major products are those (76a, 76b) which contain the carbinyl radical *cis* to the formal 1-substituent and *trans* to the formal 2-substituent. However, accurate product analysis shows that actual major products (77a, 77b) are the all *cis*-compounds.[80,81] Although this outcome conflicts with the guideline it is compatible with the concept of stereo-electronic control. Inspection of models shows that overlap between the semi-occupied orbital and the π^* orbital is attained most efficiently when 75b reacts through the conformer containing the substituent in a pseudo-axial position.

75   76   77

a, n = 1
b, n = 2
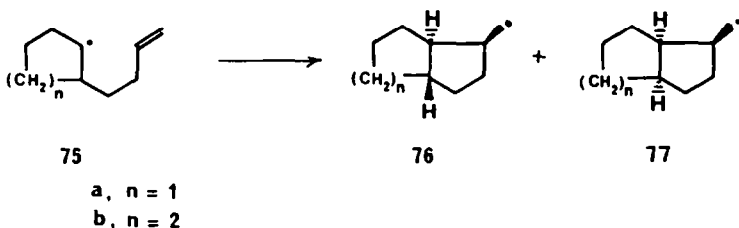
Finally, it is noteworthy that the stereo-selectivity of ring closure of 2- or 3-substituted hexenyl radicals has important implications for the practicability of forming bicyclic systems by two successive ring closures. For example, ring closure of the radicals (78 or 81) containing an allyl or a vinyl substituent at the 3-position, respectively, gives mainly *cis*-disubstituted products (79 or 82) in which the new reactive centres are conveniently disposed for a second cyclization step.[70,82] Consequently, bicyclic systems can be obtained in reasonable yield by this route.[70,82] However, the 2-vinylhex-5-enyl radical under similar conditions gives but a poor yield of bicyclic products: the major product is *trans*-3-methyl(vinyl)cyclopentane.[82]

Since the radical (82) is formally a 2,4-disubstituted hex-5-enyl system it is expected according to the guideline[41] to afford the product (*exo*-83) in which the carbinyl centre is *trans*- to each formal substituent. However, in this case the guideline cannot apply for the constraints associated with the

78   79   80

81   82   83

84
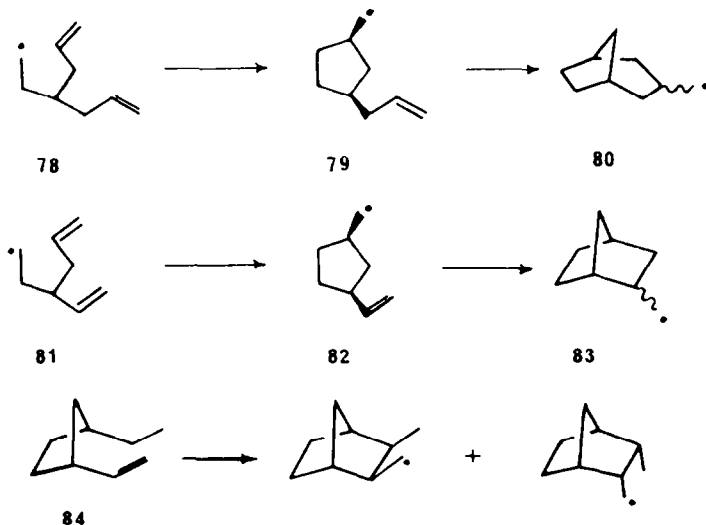
cyclopentane ring require that each formal substituent occupy a pseudo-axial orientation in the transition state for the second ring-closure. Consequently, both the *endo*- and *exo*-isomers of **83** are generated with some preference for the latter.[82] However, it is noteworthy that the radical (**84**) containing a Me group at C-1 of the hexenyl system gives mainly products containing the two Me substituents in the *cis*-relationship.[83]

In summary, existing experimental data indicate that the guideline[41] concerning the stereoselectivity of ring closure of hexenyl radicals cannot be fully applied to systems which afford bicyclic products. However, in each case the outcome of such reactions is fully consistent with the steric and stereo-electronic considerations on which the guideline is based.

(c) Intermolecular additions

A detailed discussion of steric and stereo-electronic effects in intermolecular addition reactions is beyond the scope of this review. However, the importance of these effects in such processes should not be underestimated. For example, the fact that addition of alkyl radicals occurs preferentially at the unsubstituted terminus of the double bond in methylmaleic anhydride ($k_{85}/k_{86} \sim 50$)[68] must be ascribed, at least in part, to steric effects. For similar reasons attack of thiyl radicals on **87** or **88** occurs selectively or specifically at the least substituted terminus of the two double bonds.[56,84] Other evidence for the significance of steric effects on intermolecular processes, particularly in the gas phase, has been presented by Tedder and Walton.[4,5]

Intermolecular processes are generally much less sensitive than their intramolecular analogs to stereo-electronic effects because they are not usually subject to those constraints placed on the trajectories of mutual approach of the reactive centres when they are situated within the one structure. Nevertheless, the outcome of homolytic additions to rigid or conformationally biased cyclic olefins is often consistent with the concept of stereo-electronic control. For example, the spatial requirements of

R·→

85 + **86**

RS·

87

ArS·

88
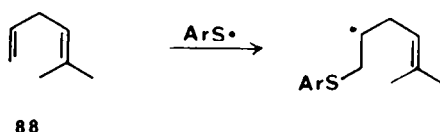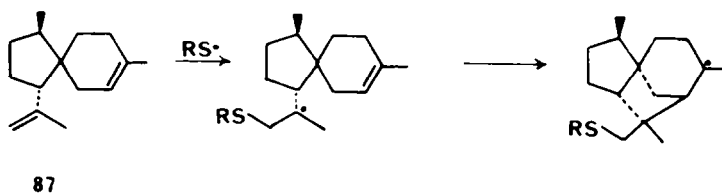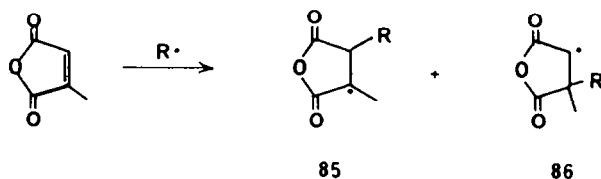
the transition complex for homolytic addition (**19**) can be attained if methanethiyl radical approaches the double bond of 4-t-butylcyclohexene in the plane of the π orbital, and either above or below one terminus. Attack on C-1 from below affords directly the axially substituted radical in its chair form (**90**). Conversely, attack from above affords directly a twist-boat intermediate (**91**) which then gives the equatorially substituted radical (**92**). Since the free-energy of **91** is greater than that of **90** the former pathway is preferred and axially substituted compounds are the major products of free-radical addition of thiols to **89**.[85,86]
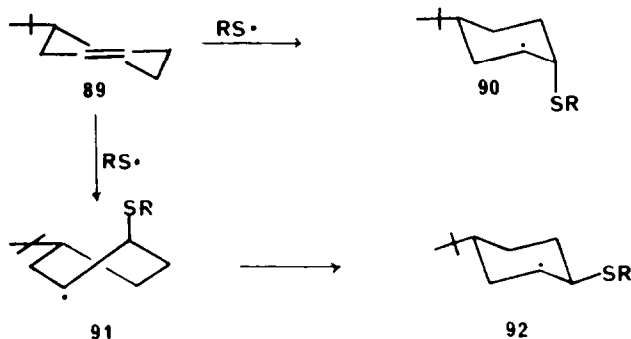
The preferred formation of axially substituted products by homolytic addition of hydrogen bromide to conformationally biased cyclohexanes can be similarly rationalised on stereo-electronic grounds.[86,87]

β-FISSION

Homolytic addition of a simple C-centred radical to an olefin is usually exothermic. The formal

equilibrium for such reactions in solution at ordinary temperatures, $R\cdot + \underset{\diagdown}{\overset{\diagup}{C}}=\underset{\diagup}{\overset{\diagdown}{C}} \rightleftharpoons R-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}\cdot$, lies heavily,

therefore, in favour of the addition process, and the reverse reaction, β-fission, is too slow to be experimentally accessible. However, when, as in the ring opening of cyclopropylcarbinyl or cyclobutyl-carbinyl radicals, β-fission is accompanied by the relief of ring strain, the equilibrium is displaced to the left. Consequently many such ring-opening reactions are sufficiently rapid to compete effectively with intermolecular processes, and can be studied by kinetic ESR spectroscopy[9,10,88] and other suitable experimental techniques.

There is abundant experimental evidence from both kinetic and product studies to show that ring-opening of cyclopropylcarbinyl and cyclobutylcarbinyl systems is highly sensitive to stereo-electronic effects. A good example is provided by a comparison of the behaviour of the two isomeric steroid radicals (93 and 95) each of which undergoes regiospecific ring opening with a rate constant of about $3 \times 10^7 \text{ s}^{-1}$ at 25°.[89,90] Since 93 gives exclusively the more stabilised product (94), and 95 the less, it is clear that these reactions are relatively insensitive to thermochemical factors. Inspection of models suggests that they are under stereo-electronic control; in each case cleavage involves preferentially that β,γ-bond which is most nearly in the eclipsed conformation with respect to the semi-occupied orbital.[41] Numerous other examples[91] of reactions, e.g. 96 → 97,[92] and 98 → 99,[93,94] which follow the less exothermic possible pathway lead to the same conclusion.
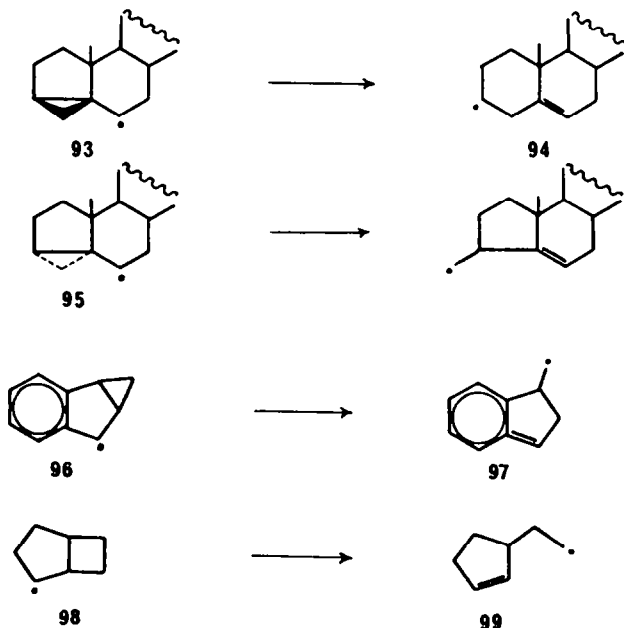
One explanation[37,89] for these observations is that the transition complex (101) for a β-fission process, like that (19) for the reverse reaction, involves a triangular disposition of reactive centres, and is generated by interaction (100) of the semi-occupied orbital with the σ^* orbital of the bond undergoing cleavage. One consequence of this notion is that the mandatory orbital overlap will be readily attained in cycloalkylcarbinyl systems containing a freely rotating exocyclic radical centre, but will not be attained when the radical centre is situated within the ring. The experimental data accord with this prediction; the conversion of cyclopropyl radical into allyl radical, although highly exothermic,[2,95] has a large activation energy,[96] and proceeds very much more slowly than does the mildly exothermic β-fission of cyclopropylcarbinyl radical ($k \sim 1.3 \times 10^8 \, s^{-1}$). Similarly, ring-opening of cyclobutyl radical is a very slow process.[96] Larger cycloalkyl radicals, being more conformationally mobile, should be able to attain more readily the stereo-electronic requirements for β-fission. In such systems, however, ring opening is endothermic and, therefore, is not observed unless there is some additional factor such as in 102, which unlike the similar but more rigid system 96, undergoes ring expansion.[97]

100

101

102
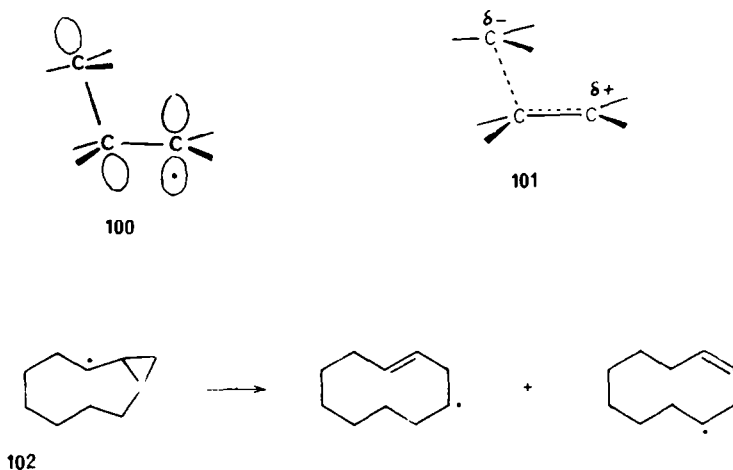
Another consequence of stereo-electronic control of ring opening of cyclopropylcarbinyl and cyclobutylcarbinyl radicals is that the configurations of the products reflect the conformational preferences of the transition complexes.[93,98] Thus, the preferential formation of the trans-hex-2-enyl radical (106) from 1-cyclobutylethyl radical reflects the greater stability of the transoid conformation (105) as compared with the cisoid conformation (103) in which non-bonded interactions are more severe.

103

104

105

106
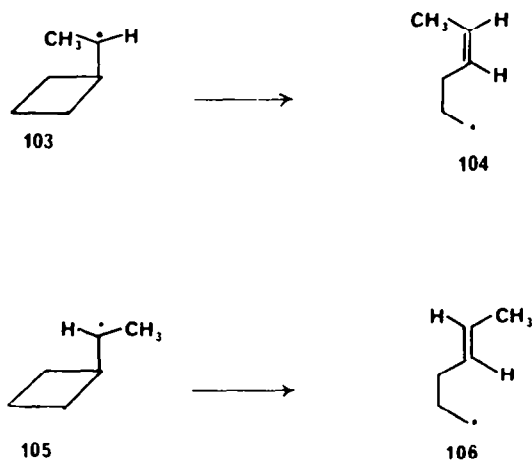
The stereo-electronic hypothesis also provides the basis of an explanation for the curious behaviour of some cyclopropylcarbinyl radicals (e.g. 107)[98-100] which preferentially afford the less stabilised possible product (e.g. 108) even though there is no obvious steric reason why the less exothermic mode of fission should be favoured over the more exothermic. However, if the dominant interaction leading to such processes is between the semi-occupied orbital and an adjacent β,γ-σ^* orbital then a fractional

positive charge will be generated at the original radical centre, and the transition complex (101) will be dipolar. Consequently, an alkyl substituent at the γ-position will disfavour formation of the transition state through its polar effect on the developing fractional negative charge. Ring opening will therefore proceed in that direction which affords the *less* substituted product radical. Consideration of the effect of substitution on the energy of the σ* orbital leads to exactly the same conclusions.[99] In accord with this hypothesis radicals (e.g. 109, 110) containing an α-substituent capable of stabilising an adjacent fractional positive charge should be particularly prone to undergo ring opening to give the *less* substituted radical product. The experimental evidence supports this view.[98,101]

107 → 108

109   110

R = OH, OSnBu₃
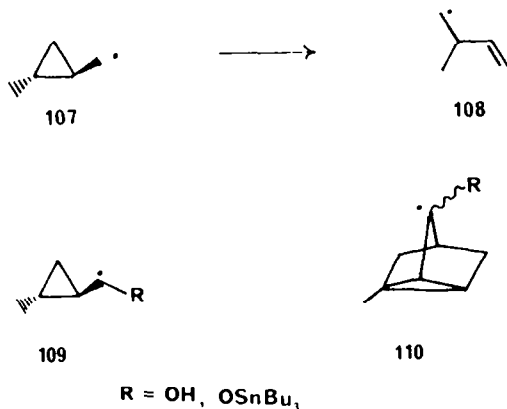
Such experiments also bring into question the mechanism of the reduction of cyclopropyl ketones by dissolving metals. The fact that the major product (112) of reduction of 111 arises by fission of the *less* substituted β,γ-bond has been adduced as evidence for the intermediacy of the dianion (113).[102] We now see, however, that this outcome is not necessarily characteristic of anionic ring cleavage, for the radical anion (114) is expected to undergo homolytic β-fission to give 115.

111   Li→   112

113   114   115
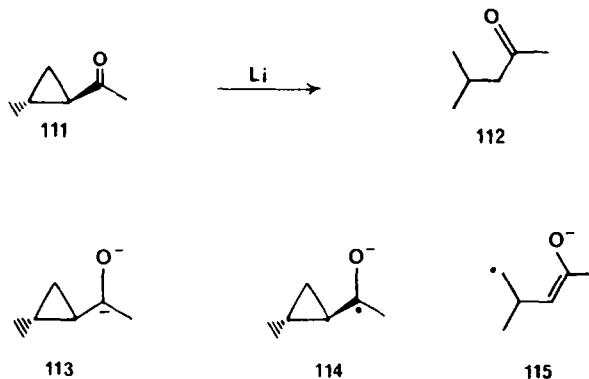
Because the rate constant for ring-opening of cyclopropylcarbinyl radical is so large it is difficult to carry out accurate kinetic studies on substituted species. The limited data available[98] suggest that the α-substituted system (116) undergoes β-fission a good deal more slowly than the parent, but it is not apparent whether this reflects conformational effects or stabilization of the radical by the substituent. Comparison of the kinetics of ring fission of 117a and 117b indicates that the substituent in the latter significantly increases the rate of cleavage of the adjacent bond, but the basis of this effect is not clear.[98]

116   117

a,   R = H
b,   R = Me
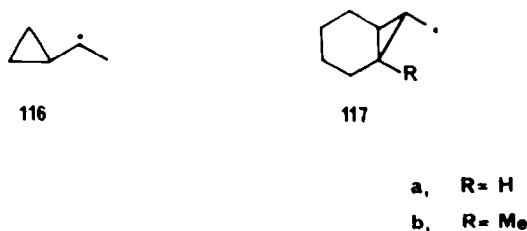
The kinetic behaviour of cyclobutylcarbinyl radicals is more amenable to examination. An extensive table of data[93] indicates (a) that Me substitution at the α-, β- or δ-positions has little effect, (b) that the cis-γ-substituted radical (118) opens more rapidly than its trans-isomer ($k_{118}/k_{119} = 6$); and (c), that γ-substitution strongly enhances the rate of β-fission ($k_{121}/k_{120} = 300$). These observations can be rationalised in terms of the steric effects of substituents on the compressional energy of the substrate as the reaction proceeds. In ring-opening of the cyclobutylcarbinyl system there is little change in hybridisation or configuration at C-α but C-γ is transformed from sp^3 to sp^2 hybridisation and the resulting change in configuration relieves both B strain and eclipsed interactions with vicinal substituents.

118   R = cis Me

119   R = trans Me

120   R = H

121   R = Me
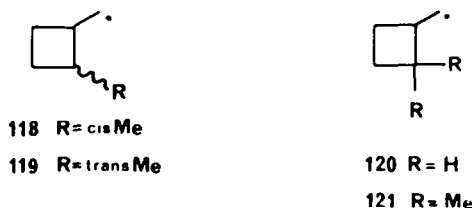
Ring fission of radicals containing hetero-atoms should also be susceptable to stereo-electronic effects, and there is some evidence that this is so. For example, 122 undergoes β-fission more rapidly than its less conformationally mobile lower homolog (123) but less rapidly than analogous acyclic radicals such as $(Me_3CO)_2CH\cdot$ in which the preferred coplanar arrangement of the semi-occupied orbital and a β,γ C–O bond can be readily attained.[103] For similar reasons the radicals (124)[104] and (126)[105] undergo preferential fission of the exocyclic C–O bond even though the endocyclic processes (e.g. 126 → 125) are the more thermochemically favoured.

122   123

124

125   126   127
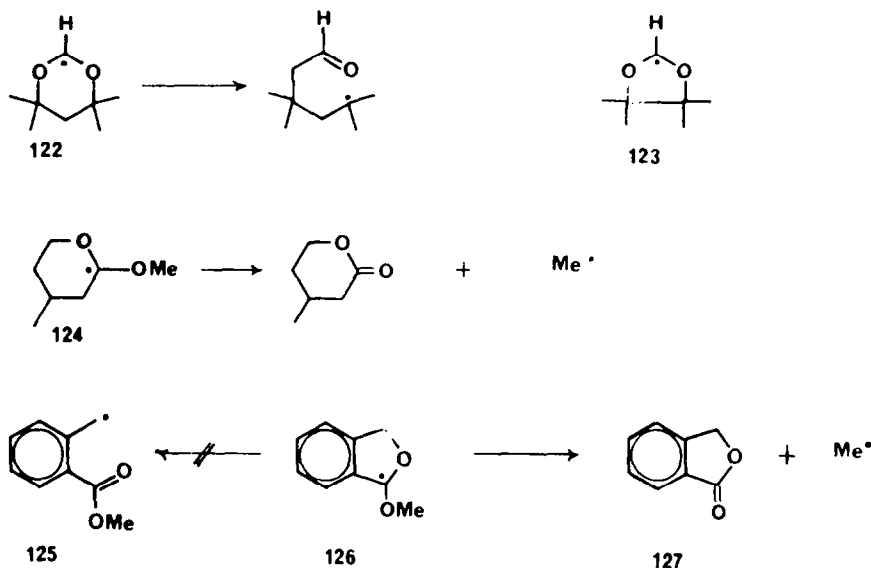
Although the stereo-electronic demands of the transition complex for β-fission can most readily be perceived by their effect on reactions of cyclic systems, some acyclic systems also display sensitivity to stereo-electronic factors. The elimination of sulphur centred radicals from β-thioalkyl radicals and similar species provides a case in point.

Treatment of either diastereoisomer of the bromosulphide (128a) with tributylstannane affords the same mixture of cis and trans-2-butene in which the latter predominates.[106] The diastereoisomeric sulphones (128c) behave similarly.[107] These results can be rationalised on the assumption that β-fission proceeds rapidly only in those two conformers in which the semi-occupied orbital eclipses the C$_\beta$–S bond. If bond rotation proceeds more rapidly than elimination, equilibrium is attained between 129 and 130. The preferred formation of trans-butene then reflects the higher concentration of the transoid conformer (130) in the equilibrium mixture.

However, reactions of the analogous β-bromo-sulphoxides (128b) with tributylstannane are stereo-selective.[108] β-Fission of β-phenylsulfinyl radicals occurs more rapidly than bond rotation. Con-

sequently, the equilibrium **129b → 130b** is not attained and the isomer ratio of butenes produced reflects the conformational preference of the starting material.

A recent examination[109] of the reaction of 3-deuterio-2-(trimethylstannyl)butane with trichloromethyl radical suggests that conformational equilibrium is attained between **129d** and **130d** more rapidly than β-fission.
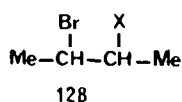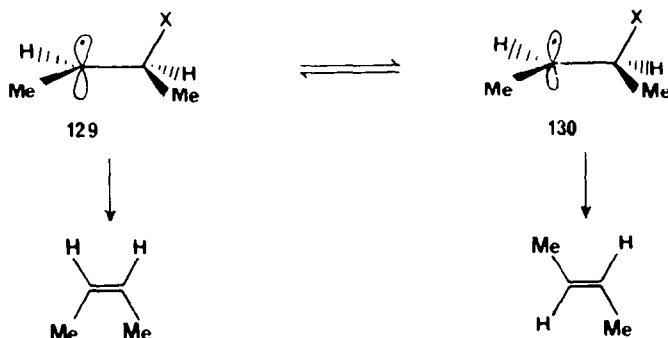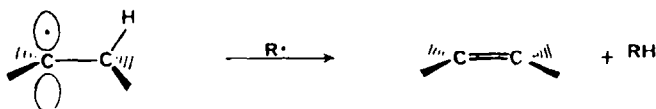

DISPROPORTIONATION

Since disproportionation, although formally an atom-transfer process, involves cleavage of a C_β–H bond in the donor radical to form an olefin it is mechanistically related to the β-fission reactions discussed in the previous section. The two transition states should be similar, and the donor radical in disproportionation should show the same sensitivity to stereo-electronic effects as is exhibited by radicals undergoing β-fragmentation; namely, H-atom transfer will be favoured when the C_β–H bond eclipses the semi-occupied orbital.[41]

The first two reports of experimental investigations of the stereo-chemical course of disproportionation gave contradictory conclusions. Agosta and Wolff,[110] using deuterium labelled substrates, were able to show that conversion of the bi-radical (**131**) into the olefin (**132**) involves preferential transfer of the pseudo-axial H-atom. Since there is no other obvious explanation for this stereo-selectivity, they concluded that it reflects the fact that interaction of the axial C–H bond with the adjacent semi-occupied orbital is more favourable than that of the equatorial C–H bond.
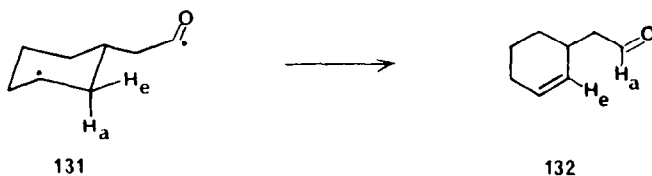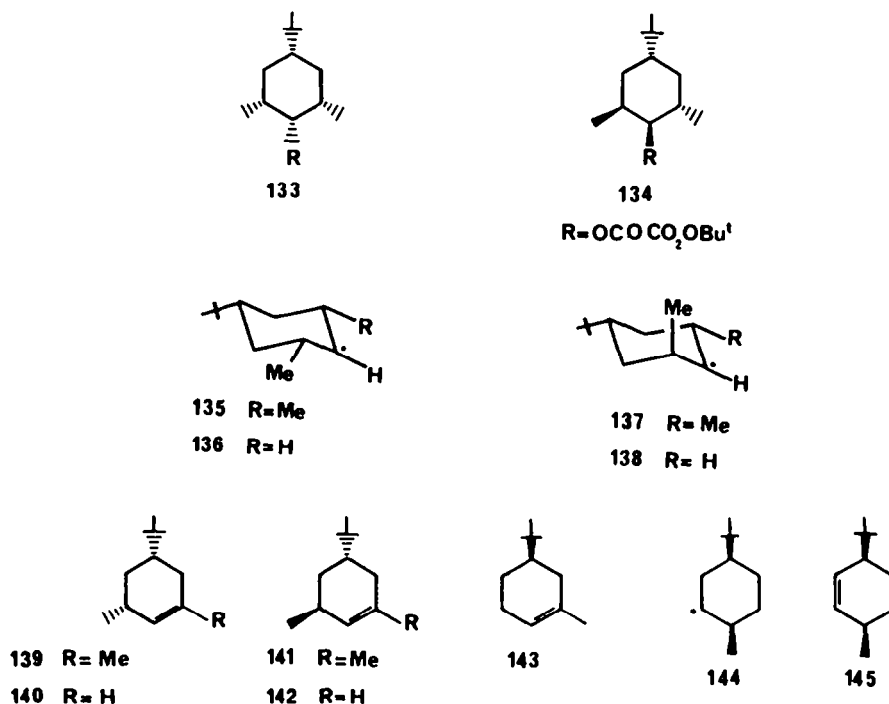

Livant and Lawler,[111] on the other hand, came to the opposite conclusion after studying the CIDNP spectrum of the cyclohexene formed when bromocyclohexane was treated with magnesium in tetrahydrofuran. Their results were consistent with the preferential cleavage of equatorial C_β–H bonds in cyclohexyl radical.

More recent experiments[112,113] have confirmed the preferential transfer of axial H-atoms from suitably substituted cyclohexyl radicals. Thermolysis of the peroxy-ester (**133**) in dilute cyclohexane

solution gave only **139** whereas similar treatment of the isomeric peroxide (**134**) gave both **139** and **141** with the latter predominating (**141/139%** = 8.2).

These results can be rationalised on the assumption that homolysis of **133** and **134** affords conformationally biased substituted cyclohexyl radicals which react through the chair-like conformations (**135** and **137**), respectively, in which the t-Bu substituent is pseudo-equatorial. The radical (**135**) has two equivalent β-hydrogens and so affords only the olefin (**139**). However, **137** has one equatorial and one axial β-H-atom, of which the latter is preferentially lost to afford **141** as the major component of the mixture of product olefins. Simple thermochemical criteria indicate that fission of the pseudo-equatorial C–H bond to give **139** should be preferred since this would relieve 1,3-non-bonded interactions of the axial Me group in **137**. The fact that the thermochemically favoured route is the less important indicates that the reaction is under stereo-electronic control.

Examination of the behaviour of the disubstituted radicals (**136** and **138**) generated from appropriate esters of monoperoxy-oxalic acid or diacyl peroxides led to a similar conclusion.[113] The radical (**136**) which contains two axial β-hydrogens in its more stable conformer gives approximately equal amounts of the

133   134

R=OCOCO₂OBuᵗ

135 R=Me   137 R= Me
136 R=H   138 R= H

139 R= Me   141 R=Me   143   144   145
140 R= H   142 R=H

olefins (**140** and **143**), but its isomer (**138**) in which the Me group is axial gives mainly (80% relative) the product (**142**) of cleavage of the sole axial C_β–H bond. Finally, it is noteworthy that the radical **144** undergoes selective loss of the axial β-H-atom to give mainly **145**.

It appears, therefore, that disproportionation of conformationally biased cyclohexyl radicals is under stereo-electronic control and conforms to the same guideline as that which applies to β-fission, *viz*, bond homolysis is favoured when the bond undergoing cleavage can assume co-planarity with the semi-occupied orbital.[41]

S_H REACTIONS

Atom-transfer and related S_H processes should be susceptible to two distinct types of stereo-electronic effect. The first reflects the ability of the system to attain a favourable disposition of the three reaction centres at the transition state. The second arises from the interaction of the bond undergoing fission with an adjacent occupied or semi-occupied orbital.

Intramolecular H-atom transfer (e.g. **146→148**) provides a good example of the first type of stereo-electronic effect. The well-known preference for such reactions to proceed through a 6-membered cyclic array (**147**) is a consequence of the inability of smaller rings to accommodate the required approximately colinear relationship of the three atoms intimately involved. Although the same colinear arrangement can be accommodated within larger rings such transfers are less favourable because they

involve a greater entropic penalty and more severe non-bonded interactions. The scope and mechanism of this type of reaction have been extensively reviewed.[114]
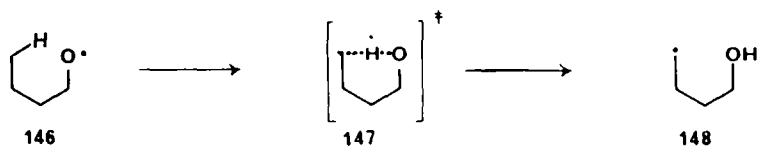

Intramolecular homolytic substitution at sulphur illustrates another aspect of this type of stereo-electronic effect.[115] For example, **149** undergoes exclusive formation of **151** even in that case where the alternative process (**149**→**150**; R=Me) is clearly more exothermic. Similarly **150** gives solely **151**. These results suggest that the reaction involves a colinear arrangement of the C...S...C array (e.g. **152**) which cannot be accommodated on the endocyclic substitution pathway (**149**→**150**). Alternatively, an intermediate sulphuranyl radical (e.g. **153**) may be involved. However, if this is the case there must be a preference for both the entering and leaving groups to occupy apical positions.[116]
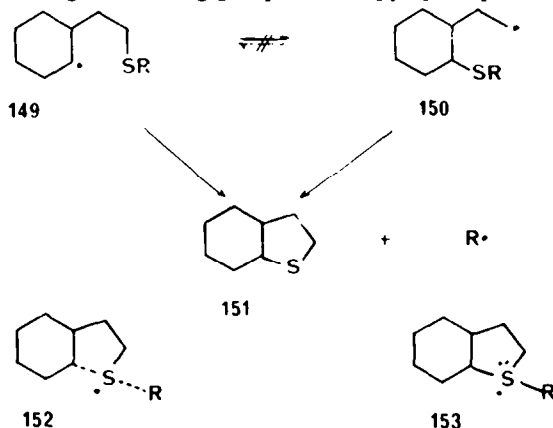
Stereo-electronic factors also influence dramatically the rate of homolytic substitution on peroxidic oxygen. Treatment of β-bromo cyclic peroxides (e.g. **154**) with tributylstannane gives mixtures of peroxides and hydroxy-epoxides, the relative yields of which reflect the relative rates of intramolecular S_H attack at oxygen and direct H-atom transfer to the intermediate radical (e.g. **155**).[117] The results suggest that the rate of the S_H process depends on the stereo-chemical relationship of the semi-occupied orbital to the O–O bond. In the radical (**156**) containing a 6-membered ring the four atoms involved in the S_H transition complex, viz. ·C–C–O–O are able to assume co-planarity. Consequently, efficient overlap can be attained between the semi-occupied orbital and the σ^* orbital of the O–O bond. This is not so for the 5-membered peroxide (**155**) in which the maximum dihedral angle about the C–O bond between the radical centre and the leaving O atom is about 165°. Since the radical centre in the 7-membered cyclic radical (**157**) is located within the ring it is impossible for the required orbital overlap to be attained, and the S_H reaction occurs too slowly to compete with atom transfer under these experimental conditions.
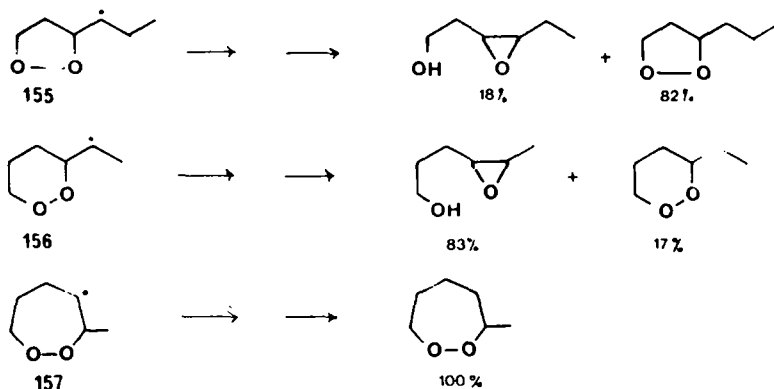

Relative Yields of Products from Reduction of Cyclic Bromo Peroxides.
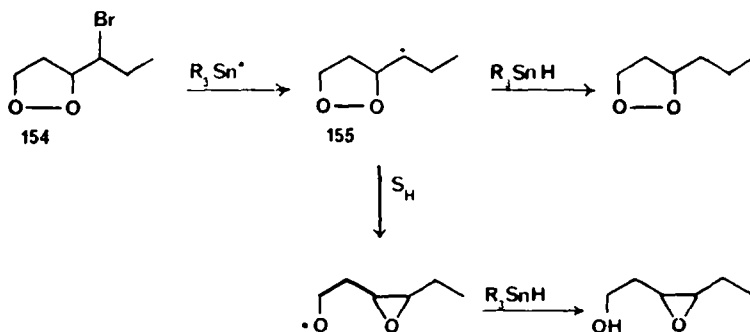
The second type of stereo-electronic effect of importance in S_H reactions is related to the presence within the substrate of atoms or groups bearing filled p or π orbitals. It is well known that bonds adjacent to O, N or double bonds show a high propensity to undergo homolytic fission. This behaviour is consistent with thermochemical considerations; the product radicals are stabilised by conjugative interaction of the free-electron with the adjacent p or π system. However, the question then arises of whether bonds in any particular substrate which are in equivalent positions but are not stereo-chemically identical will show the same reactivity.

Some information relevant to this question was provided by Cross and Whitham[118] who, having observed that the copper catalysed reaction of t-butyl perbenzoate with the conformationally biased olefin (158) affords mainly the trans-benzoate (159), suggested that preferential loss of an axial H-atom in the first step, and axial approach of the cupric carboxylate in the second, reflects the more favourable interaction of axial bonds with the adjacent π orbitals by comparison with equatorial bonds. Similar stereo-electronic arguments were advanced later to account for the stereo-specific formation of 161 from 160 in the same type of reaction.[119] In fact, these arguments cannot be sustained with respect to the H-atom abstraction step because the intermediate radicals being either planar or configurationally mobile can be formed by loss of either axial or equatorial hydrogen. The nature of the final products does not, therefore, reflect the stereochemistry of H-atom transfer.


158   159

160 R = H

161 R = OCOPh
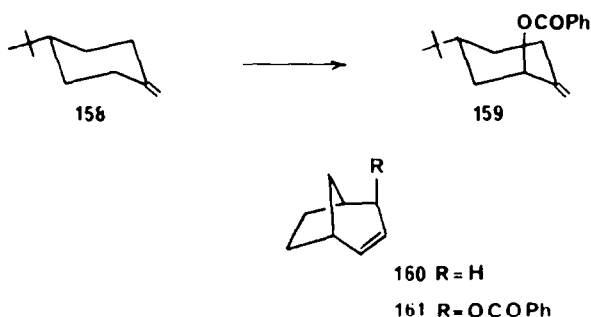
Firmer evidence for stereo-selectivity in homolytic fission of allylic C–H bonds was provided by an examination of copper-catalysed benzoyloxylation of the isomeric p-methenes.[120] The trans-isomer which contains two pseudo-axial allylic hydrogens in its more stable conformer (162) shows a preference for transfer of the hydrogen adjacent to the Me group, whereas the cis-isomer (163) reacts preferentially at the position adjacent to the isopropyl substituent. A comparison of the relative rates of reaction of the two isomers indicated that an allylic pseudo-axial hydrogen undergoes transfer to t-butoxy radicals at least 1.7 times more rapidly than a pseudo-equatorial hydrogen. This order of reactivity is the reverse of that expected on simple thermochemical grounds.


162   163

cis-p-Methene is not a particularly suitable probe for stereo-electronic effects because the difference in free energy between the more stable conformer (163) and the alternative half-chair form is relatively small. Recent experiments[41,113] with conformationally biased compounds related to 4-t-butyl-

methylenecyclohexane (158) have afforded more clear-cut evidence. For example, determination of their relative rates of reaction with t-butoxy radicals has shown that the olefins (164 and 166) possessing two allylic axial C–H bonds are about twice as reactive as compounds (165 and 167) which contain only one such bond. This is contrary to expectation based on thermochemical criteria, for in each pair of isomers (164 and 165) and (166 and 167) those that contain axial Me substituents are of the higher free energy. Experiments based on the isolation of products have been less successful.[113] The olefin (164) containing two axial allylic C–H bonds reacts smoothly with t-butyl perbenzoate to give mainly 168, but its isomer (165) affords mainly tars. Possibly the axial Me group in the expected intermediate 169 hinders its reaction with cupric carboxylate.
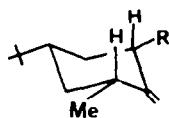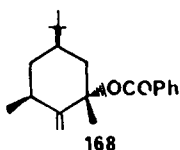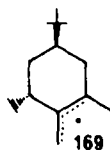

164, R = Me
166, R = H
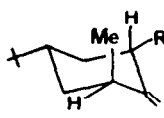
165, R = Me
167, R = H

168

169

Further work in this area is clearly required. Nevertheless, the existing evidence supports the idea that homolytic fission of a C–H bond is favoured when it can assume co-planarity with an adjacent π orbital.[41]

Evidence concerning stereo-electronic effects on the formation or fission of allylic carbon-heteroatom bonds is even more fragmentary. However the observations[77] that 4-t-butylcyclohexene on treatment with N-bromosuccinimide or t-butyl hypochlorite gives mainly pseudo-axial halides (170, X = Br or Cl) and that these react much more rapidly with tributylstannane than their equatorial isomers (171, X = Br or Cl) suggests that both bond formation and bond fission are under stereo-electronic control.


170

171
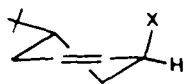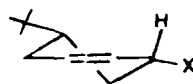
Since α-alkoxyalkyl[121] and α-aminoalkyl[122] radicals are stabilised by interaction of the semi-occupied orbital with the adjacent lone pair we might reasonably expect that the ease of formation of such radicals should be sensitive to stereo-electronic effects. It is, of course, well known that the stereo-electronic effects of lone pairs on heteroatoms profoundly influence reactivity in heterolytic reactions.[123] The evidence for similar effects in homolytic processes is less extensive. Nevertheless, recent work[124-126] with ethers and amines strongly suggests that the homolytic reactivity of C_α–H bonds is determined by their orientation with respect to the adjacent N or O lone pairs.

The reactions of conformationally biased dioxanes with t-butoxy radicals provide good examples. ESR and other kinetic techniques[104,124,125] have shown that abstraction of axial hydrogen from 172 or 174 occurs some nine times more rapidly than abstraction of equatorial hydrogen from their isomers (173 or 175). This stereo-selectivity cannot reflect thermochemical factors because the more reactive isomer (172) of the pair (172, 173) has the *lower* free energy. Of the pair (174, 175) the more reactive isomer (175) has the *higher* free energy.
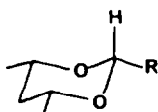

172 R = Me
174 R = OMe
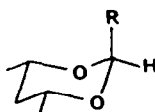
173 R = Me
175 R = OMe

If, as is usually assumed,[104,127] ethereal oxygen is sp^2 hybridized with two lone pairs of equal energy, it follows (see 176) that one lone pair on each oxygen of 1,3-dioxane is disposed in an antiperiplanar relationship to the axial C–H bond at C-2. There is no such relationship with equatorial C–H bonds. If, in accord with an alternative view,[128] one lone pair of oxygen occupies a p-type orbital, then the axial C–H bond at C-2 lies close to the axis ($\theta = 30°$) of the adjacent p-lone pair, whereas the equatorial C–H is orthogonal to it. Thus, either model for the electronic configuration of oxygen leads to the same conclusion: the C–H bonds to undergo preferential homolytic fission in a variety of ethers[104,113,124,125,129] are those which can most nearly assume coplanarity with adjacent lone pairs.


176 177 178
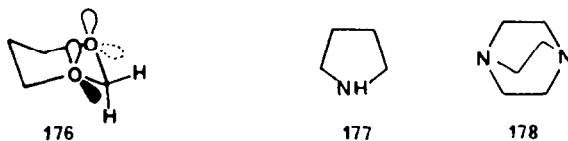
Kinetic studies[126] of the reactions of amines with t-butoxy or t-butylperoxy radicals, or with benzophenone triplet have revealed similar stereo-electronic effects. Pyrrolidine (177), for example, in which there is relatively good overlap ($\theta = 30°$) between C_α–H and the nitrogen lone pair, is some two orders of magnitude more reactive towards attack by t-butylperoxy radicals than is DABCO (178) in which the overlap is poor ($\theta = 60°$).

179 180

182 181
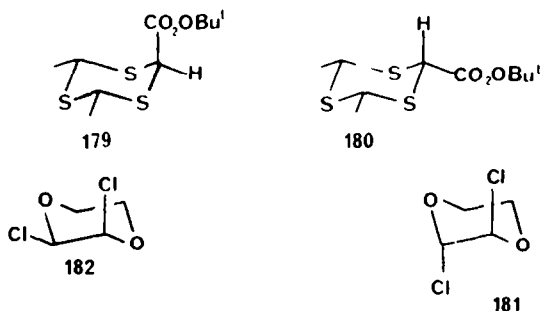
There are few experimental results available concerning stereo-electronic effects on homolysis of bonds other than C–H and involving heteroatoms other than N or O. However, the observations that the perester (179) undergoes thermolysis more rapidly than its isomer (180),[131] and that the diaxial di-chlorodioxan (181) reacts with tributylstannane almost twice as fast as the isomer (182)[41,113] accord with the view that homolytic fission of a bond is favoured when it can assume co-planarity with an adjacent filled orbital.

CONCLUSION

The foregoing survey of radical reactions exhibiting regio- and/or stereo-selectivity which cannot be rationalised on purely thermochemical grounds is by no means complete. Radical coupling reactions, for example, have not been discussed, although existing data on recombination rates and the relative proportions of meso and racemic products,[131] and the recent observation of the stereo-specific formation of 184 from 183[57] indicate that steric and stereo-electronic effects play an important role in this type of reaction. Nor have I discussed the remarkable stereo-selectivity exhibited by some atom transfer reactions in the presence of metallic salts (e.g. 185 → 186).[132]

183 184

185

186
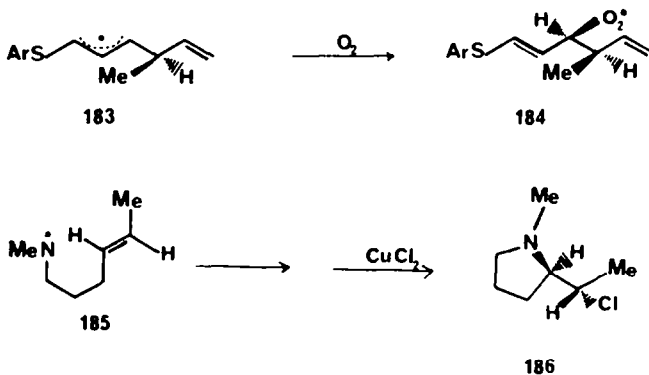
Nevertheless, the examples presented here are sufficient to show that a wide variety of radical reactions proceed in stereo- and/or regio-selective fashion, and that this behaviour can often be rationalised on the basis of simple notions concerning the way in which steric and stereo-electronic factors affect the relative stabilities of possible transition complexes. Hopefully, the recognition that radical processes may exhibit such selectivity, sometimes in high degree, and that, in many cases, their outcome may be predicted by the application of simple rules, will lead to the development of new efficient and specific synthetic methods.

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