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REGIO- AND STEREO-SELECTIVITY OF ALKENYL RADICAL RING CLOSURE: A THEORETICAL STUDY[1]

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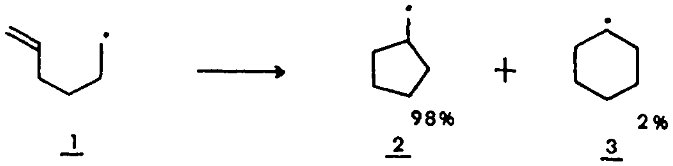
Abstract - A theoretical study has been undertaken of the relative rates and the regio- and stereo-chemistry of ring closure of a variety of alkenyl, alkenylaryl, alkenylvinyl and similar radicals. The method involves the application of MM2 force-field calculations to model transition structures for which the dimensions of the arrays of reactive centres have been obtained by MNDO-UHF techniques. The results, which generally accord with guidelines based on stereochemical considerations, show excellent qualitative and satisfactory quantitative agreement with experimental data. The method has been successfully applied to complex systems including ring closure of alkylperoxy radicals, and formation of the triquinane system by three consecutive cyclisations.

During the two decades since it was first reported,[2] ring closure of hex-5-en-1-yl radical (1) by intramolecular addition has been extensively investigated,[3-5] and has gained widespread acceptance as a mechanistic probe[3-6] and an accurate[7] radical "clock".[6] Nevertheless, some mechanistic features of this and of similar reactions of related radicals continue to attract interest. Perhaps the most important and the most fundamental of these relates to the regioselectivity of the reaction. Why does ring closure of hex-5-en-1-yl radical (1) afford mainly cyclopentylmethyl radical (2), the less thermodynamically stable of the two possible products, whereas analogous intermolecular processes invariably favour formation of the more stable possible product?



One explanation[8] for this behaviour suggests that $\Delta S^{\ddagger}_{1,5}$ the entropy change associated with formation of the transition structure for 1,5 ring closure will be less unfavourable than

$\Delta S^{\ddagger}_{1,6}$. Undoubtedly this is true, but the experimental data[9] indicate that the difference between $\Delta S^{\ddagger}_{1,5}$ and $\Delta S^{\ddagger}_{1,6}$ is too small to account for the observed regio-selectivity, and that it is the difference between $\Delta H^{\ddagger}_{1,5}$ and $\Delta H^{\ddagger}_{1,6}$ which dominates the reaction.

An alternative explanation[10,11] rests on the hypothesis that the 1,6-transition structure (4) is destabilised by an unfavourable non-bonded interaction between a pseudo-axial proton at C(2) and the *syn* proton at C(6). In accord with this hypothesis, substitution of the *syn* proton by methyl increases the regioselectivity, whereas substitution of the *anti* proton at C(6) by methyl does not.[10] On the other hand, methyl substitution at C(2) has little effect,[12] and alkenylaryl radicals (e.g. 29) undergo exclusive 1,5-ring closure[13] although they contain no pseudo-axial proton at C(2).

An hypothesis[14] which appears to account satisfactorily for all the experimental data relating to ring closure of 5-hexenyl radical and related species rests on the necessity for efficient overlap in the transition structure between the SOMO and π^*orbitals. Essentially, this theory contends that the strain engendered in accommodating the most favourable disposition of reactive centres is much greater for the 1,6 transition structure than it is for the 1,5; the difference in strain energy is sufficient to outweigh those steric and thermochemical factors favouring formation of the larger ring. A somewhat similar conclusion has been reached by Baldwin on the basis of approach vector analysis.[15]

Although the stereoelectronic approach to the mechanism of ring-closure of alkenyl radicals agrees well with experimental data,[5] and forms the basis of guidelines[16] of considerable predictive utility it has not yet received substantial theoretical support. Statistical mechanics calculations[17] have been of restricted scope, while semi-empirical molecular orbital methods have met with only limited success.[18,19] Thus Bischof's calculations[18] using the unrestricted Hartree-Fock (UHF) version of MINDO/3 give activation energies considerably larger than those obtained experimentally, and fail to account for the degree of regioselectivity manifested in ring closure of 5-hexenyl and 6-heptenyl radicals.[9]

Since the stereoelectronic hypothesis maintains essentially that the regiochemistry of ring closure of ω-alkenyl radicals reflects differences in the strain energies of relevant transition structures,[5] it would seem appropriate to use a theoretical method specifically designed to evaluate such energies. For this work we have chosen Allinger's MM2 version[20] of the force-field approach.[21,22] This program is parameterised for neutral molecules and should, therefore, be suitable for free-radical transition structures of low polarity.

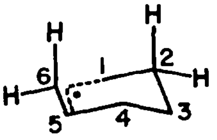
Although the MM2 program[20] and related force field methods[20-22] have been applied with considerable success to the calculation of the geometry and strain energy of a wide range of stable neutral molecules, there have been relatively few attempts to obtain transition structure energies by similar means. Recent examples have included calculations of the energies of model transition states or reactive intermediates in ester hydrolyses,[23] solvolyses of halides[24] and tosylates,[25] borohydride reduction of ketones,[26] chromic acid oxidation of alcohols,[27] and hydroboration of hindered cycloalkenes.[28] Perhaps the most sophisticated approach has been that of Houk and co-workers[29] who have combined geometries of small model systems obtained by *ab initio* methods with force-field calculations to predict the stereoselectivity of hydroboration of asymmetric olefins.

In this paper we use a somewhat similar approach to study the relative rates, regio- and stereo-chemistry of intramolecular addition in a wide range of ω-alkenyl radicals and related species. We show that there is excellent qualitative and satisfactory quantitative agreement between theory and experiment for simple systems, and that the method is of predictive utility for polycyclic and other complex systems.

REGIOCHEMISTRY

(a) Ring Closure of ω-alkenyl and related radicals

There is general agreement[30,31] that homolytic addition proceeds *via* a transition structure (5) in which the three reactive centres are situated at the vertices of a slightly obtuse triangle lying within a plane orthogonal to the nodal plane of the π system. For intramolecular addition in hexenyl radical this array must be accommodated within the gross transition structures (6,7) leading to the two possible cyclic products. However, the question then arises of what dimensions should be assigned to it. For the simple addition of methyl radical to ethylene, accurate dimensions are available from *ab initio* calculations.[32] It is unlikely, however, that precisely the same geometry will be appropriate for hexenyl transition structures since the arrangement of reactive centres will be affected by the overall molecular architecture of the system, and will reflect the interplay of steric and electronic interactions.



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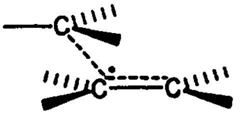

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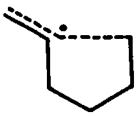

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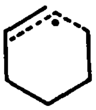

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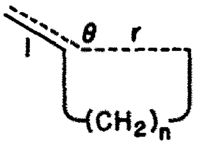
Some preliminary calculations confirmed this expectation. The MM2 program was applied to model *exo* and *endo* transition structures for ring closure of hexenyl radical in which C(1), C(5) and C(6) were fixed at relative positions similar to those of the reactive centres in the ethylene/methyl radical transition structure,[30-32] *viz* C(1)-C(5) = 2.40Å, C(5)-C(6) = 1.35Å, C(1),C(5),C(6) = 107°. The positions of the remaining atoms were then optimised by the MM2 program in the usual way to give the minimum total strain energy. In agreement with experiment the energy of the *exo* transition structure was less than that of the *endo*, but the difference between them (6.1 kcal mol^{-1}) was far greater than that observed experimentally[5,9] (1.7 kcal mol^{-1}).

We sought, therefore, methods for obtaining a more realistic estimate of the dimensions of the intimate array of reactive centres in each of the transition structures (6) and (7). *Ab initio* calculations are clearly not practicable on systems of such complexity. Accordingly we chose the MNDO-UHF method[33] which can handle reasonably large molecules within acceptable time limits, and gives geometries superior to those obtained by MINDO/3.

Unfortunately, there was lack of convergence when the MNDO transition state algorithm was applied to our systems. We chose, therefore, to determine the transition structure geometry by varying the reaction co-ordinate, *viz* the distance between the radical centre and one terminus of the olefinic bond, to obtain a path of minimum energy with respect to all other molecular co-ordinates. The transition state corresponds to the position of maximum energy along this path.

The dimensions for the intimate array of reactive centres obtained when the MNDO-UHF method was applied to each of the transition structures for *exo* and *endo* ring closure of 5-hexenyl, 6-heptenyl, and 7-octenyl radicals are given in Table 1. It is noteworthy that there is little variation in the values of r and l, the interatomic distances in the intimate array, but θ, the angle defined by the three reactive centres, is rather sensitive to ring size. The dimensions of the arrays of reactive centres were then incorporated into model transition structures, and the strain energies of their most stable conformers were calculated by the MM2 method. For this purpose the program was modified by inclusion of the parameters for a carbon radical centre developed by Beckhaus and Ruchardt.[34]



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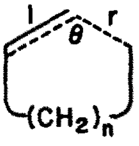

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Table 1. Dimensions[a] of the Intimate Array of Reactive Centres in Cyclic Transition Structures

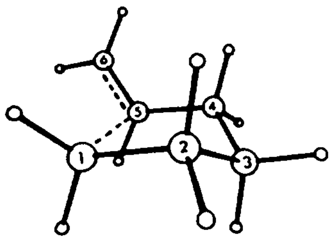
	<u>Exo</u> structure (8)			<u>Endo</u> structure (9)		
n	r	l	θ	r	l	θ
3	2.20	1.388	104.0	2.20	1.392	98.0
4	2.20	1.392	101.0	2.20	1.387	100.0
5	2.20	1.393	99.0	2.25	1.389	106.0

[a] r and l in Å; θ in degrees.

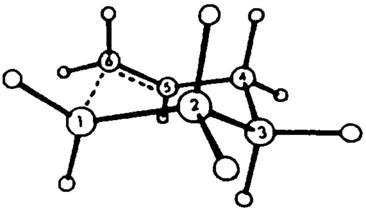
The recognition of the most stable conformer of each of the transition structures for ring closure of hexenyl radical presented no problems. Both the <u>exo</u> and <u>endo</u> structures (10 and 11 respectively) resemble a distorted chair form of cyclohexane (Fig. 1). The choice of the most stable conformer for the <u>exo</u> ring closure of heptenyl radical (12) was also clear cut: it also resembles a distorted chair form of cyclohexane with C(7) occupying a pseudo-equatorial position. However, the transition structure for <u>endo</u> ring closure of heptenyl radical can readily assume a number of low energy conformers. MM2 calculations on each of these showed the most stable conformer to be a modified chair (13) in contrast to the twist-chair conformation preferentially assumed by cycloheptane.[35] Similar calculations on a large number of possibilities showed that the transition structure for <u>exo</u> ring closure of 7-octenyl radical also assumes a cycloheptane-like chair conformation (14), but the <u>endo</u> structure (15) appears to be different from the twist-chair-chair or other low energy forms of cyclooctane.[36]

In order to obtain results which could be realistically compared with experimental kinetic data it was necessary to discount strain energy associated with movement of the three reactive centres along the reaction coordinate since this is compensated for by electronic interactions. Therefore, we substracted from the total strain energy of each hexenyl transition structure the strain energy arising from close approach of C(1) and C(5) and from stretching of the C(5)-C(6) bond. Also, we substracted from each the value of E_s(ground), the MM2 energy of hexenyl radical in its most stable open-chain conformation, and thus obtained values of ΔE_s, the MM2 calculated strain energy components of the activation energies. The values are given in Table 2, together with those similarly obtained for ring closure of heptenyl and octenyl radical.

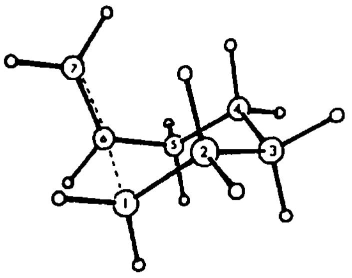
In accord with the stereoelectronic hypothesis[5,14] the calculated value of ΔE_s for <u>exo</u>-ring closure of hexenyl radical is less than that for <u>endo</u>. The difference in favour of <u>exo</u>-cyclisation (2.8 kcal.mol^{-1}) is somewhat larger than that obtained experimentally (1.7 kcal.mol^{-1}) but this is to be expected since the MM2 method makes no allowance for the more favourable electronic change associated with the incipient secondary radical in the <u>endo</u> structure. Similarly, the calculations successfully predict the regiochemistry of ring closure



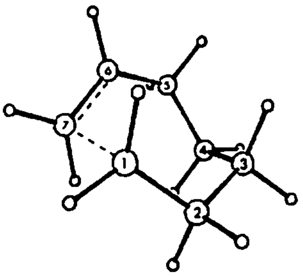
10 5-hexenyl, exo



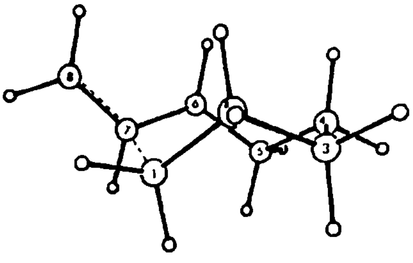
11 5-hexenyl, endo



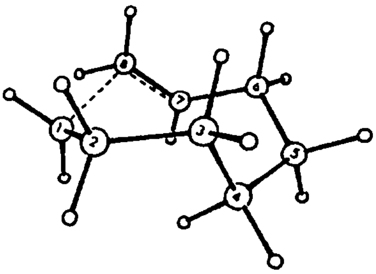
12 6-heptenyl, exo



13 6-heptenyl, endo



14 7-octenyl, exo



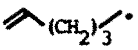
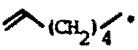
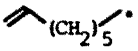
15 7-octenyl, endo

Figure 1. Model transition structures for ring closure of ω-alkenyl radicals

of 6-heptenyl radical (16), but overestimate the activation energy difference. However, it is significant that the calculations mirror experiment in that the difference in calculated values (ΔE_s) for heptenyl ring closure is less than it is for hexenyl.

The calculated energies for ring closure of 7-octenyl radical (17), however, do not agree with the behaviour of this radical as previously reported.[9] The MM2 values clearly predict that formation of the endo product will be strongly favoured, whereas the experimental results show only the seven membered cyclic product. In order to resolve this anomaly the system has been re-examined experimentally. Preliminary results[37] indicate that the previous results are erroneous, and that ring closure of 7-octenyl radicals proceeds exclusively in the endo mode to afford cyclooctyl radical. This outcome illustrates the predictive power of the MM2 method.

Table 2. Transition Structure Strain Energies, ΔE_s,[a] and Experimental Kinetic Data[a] for Ring Closure of ω-Alkenyl and Related Radicals.

Radical		E_s(ground)	ΔE_s(exo)	ΔE_s(endo)	k_{25}(exo)	k_{25}(endo)	E_{act}(exo)	E_{act}(endo)	Ref.
	1	2.9	7.5	10.3	2.3×10^5	4.1×10^3	6.8	8.5	7,9,41
	16	3.7	9.1	10.8	5.4×10^3	7.5×10^2	7.9	8.8	7,9
	17	4.0	15.0	13.0	$<7 \times 10^1$	1.2×10^2	nd.	9.6	9,37[b]
	18	3.4	9.7	9.5	5.3×10^3	9.0×103	8.5	8.0	38,39
	19	2.9	7.0	10.2	nd[c]	nd[c]	nd.	nd.	
	20	4.8	6.7	13.5	nd[c]	nd[c]	nd.	nd.	
	21	4.5	7.0	9.2	3.5×10^5	6.0×10^3	nd.	nd.	38
	22	6.6	6.0	9.7	3.6×10^6	$<1 \times 10^5$	5.4	nd.	41
	23	6.5	6.1	9.2	5.1×10^6	$<1 \times 10^5$	5.1	nd.	41
	24	7.0	6.8	8.3	3.2×10^6	$<1 \times 10^5$	5.5	nd.	41
	25	6.0	6.8	11.1	8.5×10^6	$<1 \times 10^5$	4.1	nd.	42
	26	-0.4	9.8	6.7	8.7×10^2	1.8×10^3	nd.	nd.	40
	27	-0.3	7.4	9.7	7.4×10^4	5.0×10^3	nd.	nd.	40
	28	2.3	7.5	14.7	2.8×10^4	$<6 \times 10^2$	8.3	nd.	42

[a] Energies in kcal.mol^{-1}; rate constants at 25° in s^{-1}; for definition of ΔE_s see text; nd: not determined.

[b] Recent experiments in these laboratories[37] indicate that the products from this reaction were wrongly identified in the earlier work[9]; the values have been transposed accordingly.

[c] Kinetic data are not available; the behaviour of closely related radicals is discussed in the text.

Having obtained such satisfactory concordance between theory and experiment for the alkenyl radicals (1,16,17) we decided to examine by the force-field method the regiochemistry of ring closure of a number of other ω-alkenyl systems. For each of the radicals (18-27) the energies of model transition structures incorporating the dimensions of the appropriate intimate array for 1,5- or 1,6-ring closure were calculated as described above. In the case of the hexynyl radical (28) we used the same angles, θ, and interatomic distances, r, as those for hexenyl transition structures (see Table 1), but the C(5)-C(6) distance (l) was set at 1.22 Å. MINDO/3 studies[30] suggest that θ should be larger for homolytic addition to alkynes than it is for addition to alkenes. If this were true, and θ for ring closure of hexynyl radical (28) were to be increased, the effect would be to raise slightly the value of ΔE_s for the *exo* structure, but to raise ΔE_s for the *endo* structure substantially.

Inspection of the results (Table 2) reveals that in every case the calculations correctly predict the regiochemistry of ring closure. This is especially significant for radicals **18** and **26**, two of a very small number of radicals which do not conform to the guideline in that they undergo preferential endo ring closure.[38-40]

Generally, ΔE_s, the calculated strain energy component of the activation energy is greater than the experimental activation energy, but there is satisfactory qualitative agreement between the two sets of data. Consequently, there also exists a reasonable correlation between the order of reactivity predicted from values of ΔE_s, and experimental rate constants. Thus, theory correctly predicts: (a) the relative order of rate constants for exo and endo ring closure of hexenyl, heptenyl and octenyl radicals, (b) the very high rate of exo ring closure of the oxygen containing radical (**25**) and the very high regioselectivity of its cyclisation, (c) the rate-enhancing effect of the gem dimethyl group in radicals (**22**-**24**), and the fact that this rate enhancement reflects an increase in the ground state strain energy of these radicals, and (d) that the unusual regioselectivity of ring closure of the 5-methyl substituted radical (**18**) reflects a decrease in the rate of 1,5-ring closure rather than an increase in the rate of 1,6-ring closure.

The calculations also allow us to dispose of one of the earlier explanations[10] for the preferential exo-cyclisation of 5-hexenyl radical, namely that the endo-mode is disfavoured by steric interaction between the pseudo axial proton at C(2) and the syn proton at C(6) in the transition structure (**4**). Inspection of the strain energy calculations reveal this interaction to be less than 0.1 kcal.mol^{-1}. When, however, there is a syn substituent at C(6) such interactions do occur. The large difference between the ΔE_s(endo) values for cis-hept-5-enyl radical (**19**) and its trans isomer (**20**) reflects the fact that the substituent occupies a pseudo-axial position in the chair-like transition for the former (**19**) and interacts strongly with the pseudo-axial protons at C(2) and C(4), whereas in the transition structure for the latter (**20**) the substituent is in the pseudo-equatorial position. Unfortunately, no experimental data are available for these systems. The 5-methyl substituted radicals have, however, been studied.[10] As expected on the basis of our calculations 5-methyl-trans-hept-5-enyl radical undergoes both exo and endo ring closure, whereas the corresponding cis radical undergoes solely exo ring closure.

The major components of the strain energies for each of the transition structures for some radicals of particular interest are listed in Table 3. The data reveal that Van der Waals (VDW) forces make important contributions to the total strain energies. 1,4 Interactions usually favour the endo transition structure while other VDW interactions tend to favour the exo structure; the net effect on regiochemistry is often relatively small. The significant interactions in determining regiochemistry are bending and torsion which, almost without exception, favour the transition structure of lowest total energy.

Further examination of these factors shows that the bending energy is largely associated with ring strain, and the torsion energy with deformation about the π bond. The very low strain energy for exo-ring closure of the 3-oxahexenyl radical (**25**) (and the very high energy of the endo-structure) reflect the favourable effect of the short (1.41Å) C-O bond and, small (106.8°) C-O-C bond angle [by comparison with C-C bonds (1.52Å, 109.5°)] on the bending and torsion strain of the exo-structure. Conversely, the relatively long (1.87Å) C-Si bonds in (**26**) lower the ring strain of the endo structure and increase that of the exo. This is as expected on stereo-electronic grounds.[5]

Table 3. Selected Components of the Transition Structure Strain Energies for Ring Closure of ω-Alkenyl and Related Radicals.

	Compression	Bending	VDW[a] 1,4	VDW[a] other	Torsion	Other	Total
1-*exo*	0.22	1.36	4.21	2.60	2.00	0.05	10.44
1-*endo*	0.42	2.00	2.98	4.77	2.99	0.08	13.24
endo-exo	+0.20	+0.74	-1.23	+2.17	+0.99	+0.03	+2.80
16-*exo*	0.31	2.52	3.58	3.57	2.71	0.15	12.84
16-*endo*	0.37	3.43	3.74	4.10	2.63	0.20	14.47
endo-exo	+0.06	+0.91	+0.16	+0.53	-0.35	+0.05	+1.63
17-*exo*	0.41	4.66	5.10	3.62	5.30	0.25	19.34
17-*endo*	0.47	3.18	5.12	3.95	4.33	0.21	17.27
endo-exo	+0.06	-1.48	+0.02	+0.33	-0.97	-0.04	-2.08
25-*exo*	0.26	1.36	5.46	2.55	0.77	0.79	11.19
25-*endo*	0.62	3.17	3.91	5.49	3.06	0.87	17.12
endo-exo	+0.36	+1.81	-1.55	+2.94	+2.29	+0.08	+5.93
26-*exo*	0.33	3.60	2.09	1.04	2.52	-0.22	9.36
26-*endo*	0.26	1.49	1.01	2.35	1.24	-0.12	6.23
endo-exo	-0.07	-2.11	-1.08	+1.31	-1.28	+0.10	-3.13
27-*exo*	0.28	1.73	3.07	0.64	1.51	-0.12	7.11
27-*endo*	0.36	2.33	1.05	2.44	3.33	-0.12	9.39
endo-exo	+0.08	+0.60	-2.02	+1.80	+1.82	0.0	+2.28
18-*exo*	0.40	2.12	4.82	1.92	3.77	0.03	13.06
18-*endo*	0.44	2.12	3.33	4.15	2.76	0.10	12.90
endo-exo	+0.04	0.0	-1.49	+2.23	-1.01	+0.07	-0.16

[a] Van der Waal's forces.

(b) Ring Closure of alkenylaryl and related radicals

As recent studies[43] have recently made available kinetic data for ring closure of alkenylaryl radicals, we have examined such systems by the MM2 method. As in the case of the ω-alkenyl radicals described above it was necessary first to estimate the dimensions of the intimate array of reactive centres. It was not practicable to conduct MNDO calculations on such a complex system as the ring closure of the *o*-(but-3-enyl)phenyl radical (29), and we assumed, therefore, that aryl and vinyl radicals would behave similarly and that ring closure of the hexa-1,5-dien-1-yl radical (34) would serve as a suitable model for alkenylaryl systems. The dimensions obtained by MNDO for the *exo* transition structure from 34 were: C(1)-C(5), 2.25Å; C(5)-C(6), 1.38Å; C(1)C(5)C(6), 98°; and for the *endo* structure: C(1)-C(6), 2.35Å; C(5)-C(6), 1.37Å; C(1)C(6)C(5), 92°. Typical transition structures are shown in Fig. 2.

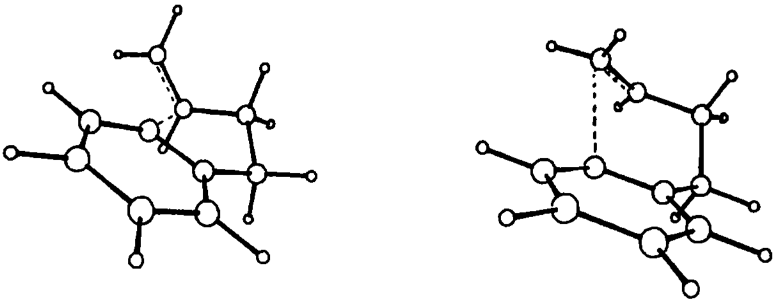
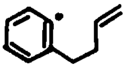
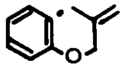
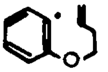


Figure 2. Model transition structures for (a) exo-, and (b) endo-ring closure of o-(3-butenyl)phenyl radical (29)

The MM2 method was then used to determine the strain energies of the most stable conformers of transition structures incorporating these dimensions. Since no parameters are available for a carbon σ radical centre those for an ordinary sp2 carbon were employed. As before, the results were corrected for steric interactions between the three reactive centres.

The data in Table 4 reveal excellent qualitative agreement between theory and experiment. Thus, the calculations correctly predict the observed preferential exo-mode of ring closure of each of the radicals (29-30) the relative order of reactivity for those cases where experimental data are available, and the fact that these radicals undergo more rapid ring closure than the corresponding alkenyl radicals. Detailed examination of the components of the transition structure strain energies reveals that exo ring closure of alkenylaryl radicals, like that of alkenyl radicals, is favoured over endo mainly because of smaller bonding and torsion energies.

Table 4. Transition Structure Strain Energies, ΔE_s,[a] and Experimental Kinetic Data[a] for Ring Closure of Alkenylaryl and Related Radicals.

Radical		E_s(ground)	ΔE_s(exo)	ΔE_s(endo)	k_{25}(exo)	k_{25}(endo)	E_{act}(exo)	E_{act}(endo)
	29	0.8	4.5	6.3	3.1×10^8	$<6 \times 10^6$	3.7	nd.
	30	4.3	1.8	6.1	5.3×10^9	$<5 \times 10^7$	3.1	nd.
	31	1.1	5.1	5.7	nd.	nd.	nd.	nd.
	32	3.7	2.3	5.6	1.7×10^9	3.6×10^7	3.1	5.9
	33	4.7	5.6[b]	7.6[b]	3.1×10^8	nd.	3.6	na.
	34	2.0	5.6	7.0	nd[c]	nd[c]	nd[c]	nd[c]

[a] Energies in kcal.mol^{-1}; rate constants[44] at 25° in s^{-1}; nd: not determined.

[b] Determined for transition structures with dimensions of the intimate array identical with those for ring closure of 6-heptenyl radical (see Table 1).

[c] Accurate kinetic data are not available, but preliminary results[45] indicate that ring closure is fast and exclusively exo.

Perhaps of more interest is a consideration of the factors responsible for the high rate of *exo* ring closure of alkenylaryl radicals. Comparison of the data presented in Tables 2 and 4 reveals that this is not just a reflection of the high intrinsic reactivity of radicals, although this is undoubtedly significant; the major factor is the low value of ΔE_s(*exo*) for alkenylaryl systems as compared with ΔE_s(*exo*) for their alkenyl counterparts. Table 5 shows the strain energy components for two typical radicals. The data reveal that ΔE_s(*exo*) for butenylphenyl radical (29) is less than that for hexenyl radical (1) because of favourable bending and VDW components. These in turn are associated particularly with the absence of the protons on C(1) and C(2) which give rise to non-bonded interactions in the hexenyl system.

Table 5. Transition Structure Strain Energy Components[a] for *Exo* Ring Closure of Hexenyl (1) and *o*-Butenylphenyl (29) Radicals.

	Hexenyl (1)			*o*-Butenylphenyl (29)		
	E_s(ground)	ΔE_s(TS)	ΔE_s (*exo*)[b]	E_s(ground)	ΔE_s(TS)	ΔE_s (*exo*)[b]
Compression	0.17	0.22	0.05	0.34	0.30	−0.04
bending	0.40	1.36	0.96	0.56	0.47	−0.09
VDW (1,4)	2.52	4.21	1.69	7.55	8.61	1.05
VDW (other)	−0.65	2.60	3.25	−0.97	−0.06	0.09
Torsion	0.43	2.00	1.57	−6.77	−4.12	1.35
Other	0.07	0.05	0.02	0.09	0.11	0.02
Total	2.94	10.44	7.50	0.80	5.31	3.19

[a] Energies in kcal.mol^{-1}

[b] ΔE_s (*exo*) = E_s(TS) − E_s(ground).

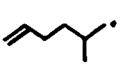
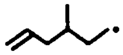
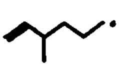
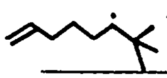
STEREOCHEMISTRY

(a) Substituted hexenyl radicals

A useful guideline[16] for ring closure of substituted hexenyl radicals states that 1- or 3-substituted radicals preferentially give *cis*-disubstituted products, while 2- or 4-substituted radicals give mainly *trans*. The explanation for the behaviour of species substituted at C(2), C(3) or C(4) rests on the hypothesis that the transition structure resembles the chair form of cyclohexane and that the most favourable conformer will contain the substituent in a pseudo-equatorial position. The conformer of an *exo* transition structure bearing a pseudo-equatorial substituent at C(3) leads to a *cis* disubstituted product. Conversely, conformers with pseudo-equatorial substituents at C(2) or C(4) give *trans* disubstituted products.

Our force-field calculations strongly support this view. The model transition structure (10) for *exo*-ring closure of hexenyl radical (Fig.1) does indeed closely resemble cyclohexane, and bears clearly distinguishable axial and equatorial protons at positions 2,3 and 4. Furthermore, as the data in Table 6 for radicals (38-40) clearly show, that conformer of the transition structure which contains the methyl substituent in the pseudo-equatorial position is of lower energy than the corresponding axially substituted species. Further analysis of the MM2 data reveals that axial substituents are disfavoured not only, as expected, by Van der Waals interactions, but also by bending and torsion strain.

Table 6. Transition Structure Strain energies, ΔE_s,[a] and Experimental Kinetic Data[a] for Ring Closure of Substituted ω-Alkenyl and Related Radicals.

Radical		E_s(ground)	ΔE_s(cis)	ΔE_s(trans)	k_{25}(cis)	k_{25}(trans)	E_{act}(cis)	E_{act}(trans)	Ref
	37	3.4	7.3	7.5	1.1×10^5	4.2×10^4	6.9	7.6	38
	38	4.7	7.3	6.3	2.4×10^5	4.5×10^5	6.5	6.1	41
	39	4.5	6.1	7.7	7.0×10^5	2.4×10^5	6.0	6.4	41
	40	5.0	7.9	6.2	7.5×10^4	3.6×10^5	7.7	6.6	41
	41	4.0	9.0	9.7	5.7×10^3	2.1×10^3	8.4	9.0	45
	42	6.4	8.5	8.2	nd.	nd.	nd.	nd.	

[a] Energies in kcal.mol^{-1}; rate constants at 25° in s^{-1}; for definition of ΔE_s see text; nd: not determined.

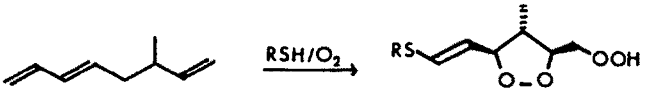
The effects controlling the stereochemistry of ring closure of 1-hexenyl systems are more subtle. The calculations correctly predict that 1-methylhexenyl radical will preferentially give the cis product, but the calculated difference in activation energies is very small and cannot account for the observed difference in reaction rates. Closer analysis of the data reveals that there is a delicate balance between effects favouring the two isomers. Torsional interactions favour formation of the cis-product whereas bending strain favours formation of the trans. When the methyl substituent is replaced by t-butyl both the torsion and bending interactions are increased considerably, but the dominant factor is now Van der Waals interaction which disfavours the cis-product. Experimental verification of preferential formation of the trans-product is not yet available.

Finally, it is noteworthy that the calculations also predict correctly the preferential formation of the cis-product from 1-methylhept-6-enyl radical (41). In this case the calculated difference between activation energies is more substantial and agrees nicely with experiment. Nevertheless, it is difficult to avoid the conclusion that there is not yet sufficient experimental data available to adequately test the calculations, and to resolve the question of whether the stereochemical preference exhibited in ring closure of 1-substituted alkenyl radicals is of steric origin, or, as has been suggested previously,[38] arises from electronic interactions.

(b) Ring-closure of substituted butenylperoxy radicals

The success of the force-field method when applied to the ring closure of substituted alkenyl radicals encouraged us to examine a more complex system. Thiol/oxygen co-oxidation of the triene (43) gives only one (44) of the four possible stereoisomeric cyclic peroxides.[46]

The explanation advanced[47] for this remarkable selectivity is that the reaction involves the intermediacy of two diastereoisomeric peroxy radicals (Fig.3), each of which is potentially capable of forming two cyclic products by _exo_ ring closure. However, evidence has been adduced[47] that the peroxy radicals are in rapid equilibrium through elimination/addition of molecular oxygen, and the outcome of the reaction is therefore determined by the relative heights of the barriers to ring closure. It was suggested that the barrier to formation of (44) was much less than those to other ring closures. This hypothesis can be tested by MM2 calculations.



43 44

The energies of the two diastereoisomeric peroxy radicals, and of the various transition structures were calculated on the assumption that the intimate arrays of centres would be similar to those for analogous carbon radicals. Although the experimental work[46,47] was conducted with arylthiols we chose to use, for the sake of convenince, model structures incorporating the methylthio moiety. The results are shown in Fig. 3. Interestingly, the peroxy radical which leads to the observed stereochemistry is of lower energy than its diastereoisomer but this is of no consequence to the eventual outcome because of their rapid interconversion. Since the calculated value of the strain energy for one transition structure is considerably less than that of each of the three alternatives all of the reaction is channelled through it to give eventually only the observed cyclic peroxide (44).

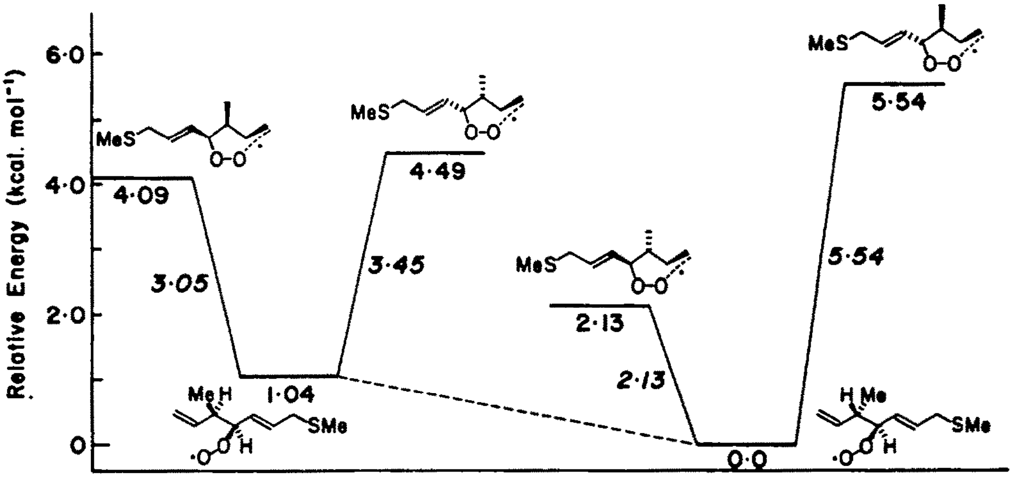


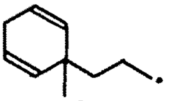
Figure 3. Calculated strain energies for diastereoisomeric peroxy radicals and for cyclic transition structures generated from them.

COMPLEX SYSTEMS

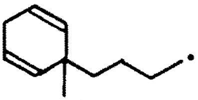
Much of the current interest in radical chemistry derives from the synthetic utility of radical ring closures for the construction of polycyclic systems.[48] Since it would be of considerable utility to be able to predict reliably the regio- and stereo-chemical outcome of the ring closure step before embarking upon an elaborate synthesis, we have commenced an examination of the applicability of our method to complex systems.

(a) Formation of Tetrahydroindanes and Related Systems

Ring closure of radicals (e.g. **45**–**47**) generated from precursors readily obtainable by Birch reductive alkylation of suitable aromatic esters provides a convenient route to a variety of tetrahydroindanes and related compounds.[49] In all of the reported work[49] the stereochemistry of the newly formed ring junction has been strictly cis. The data in Table 7 show why this is so. For exo ring closure of either the hexenyl or the heptenyl systems the calculated strain energies of the cis-transition structures are much less than those of the trans. There is a similarly large energetic advantage for formation of cis-products from ring closure of the aryl radical (**47**).



45



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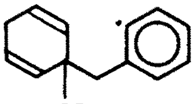

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Table 7. Transition Structure Strain Energies ΔE_s[a] for Ring Closure of Some Cyclohexadienylalkyl Radicals.

Radical	E_s(ground)	ΔE_s (cis)	ΔE_s (trans)
45	15.7	5.1	30.6
46	16.2	9.5	21.6

[a] Energies in kcal.mol^{-1}

(b) Formation of Triquinanes by Consecutive Ring Closures

It should, in principle, be possible to construct the triquinane ring system by a reaction involving three consecutive ring closures of a suitably constituted acyclic radical. Such a species, the trienyl radical (**48**), could be generated from readily obtainable precursors. However, the questions arise of whether the required consecutive ring closure will occur in practice, of whether such ring closures are likely to proceed, as desired, in the exo mode, and, if so, of whether there will be pronounced stereoselectivity. In connection with the last it is noteworthy that the expected product (e.g. **54**), is capable of existing in sixteen different diastereoisomers. We have now applied force-field calculations in an attempt to answer these questions.

Figure 4 presents possible intermediates in the reaction and calculated values of ΔE_s for the transition structures involved in their formation. As expected the first step is predicted to proceed solely in the exo mode; the value of ΔE_s for endo ring closure is much higher. The results also suggest that formation of **49**(cis) should be favoured over formation of **49**(trans). Since calculations revealed no low energy pathways for further ring closure of the latter we assume that it is not a feasible precursor for triquinanes.

The intermediate **49**(cis) can lead to four products by exo ring closure. The results suggest that formation of **50** and **53** should be favoured, but all the values of ΔE_s are so similar, that none of the intermediates (**50**–**53**) can be precluded from further consideration.

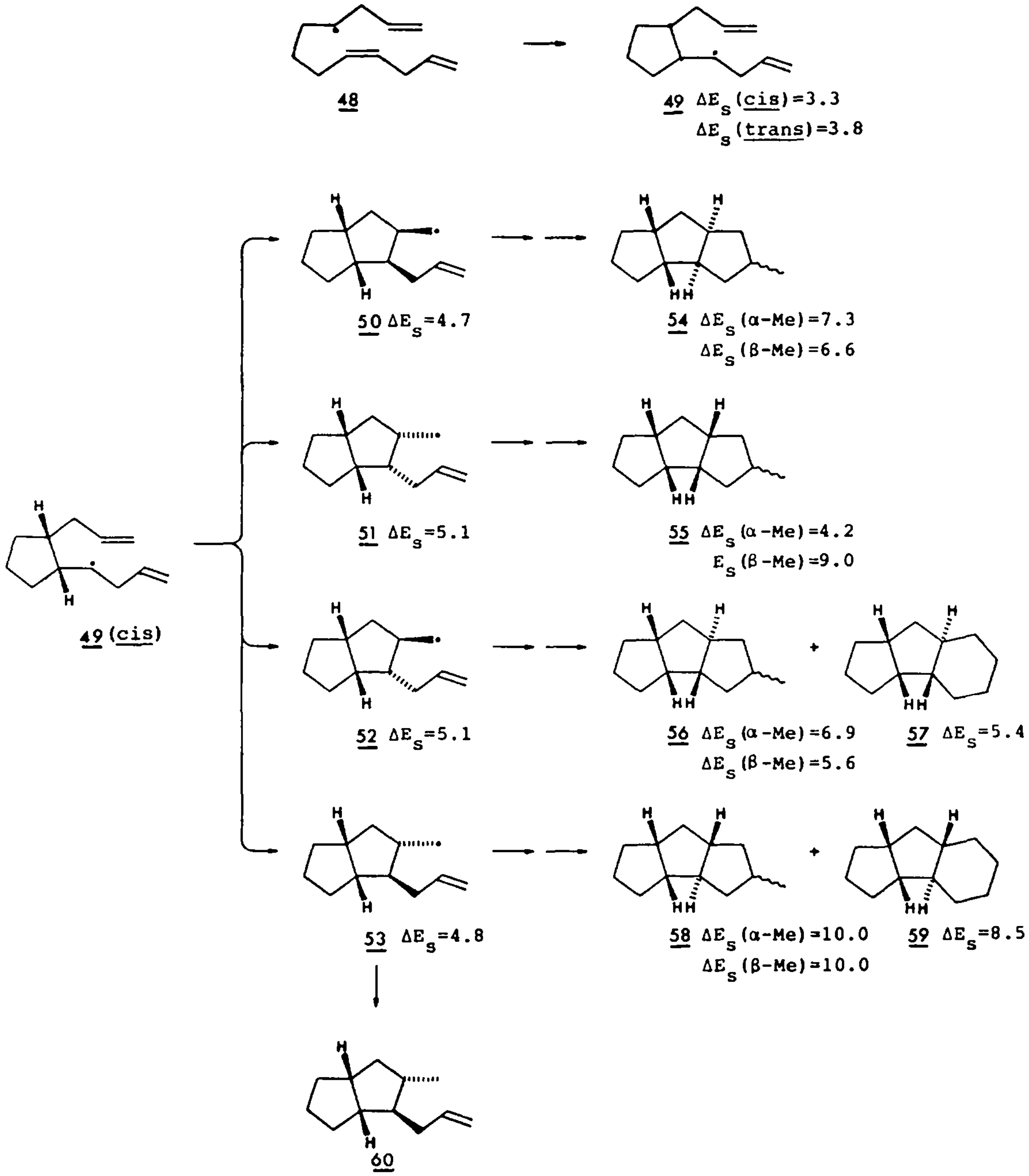

Figure 4. Possible products and transition structure energies (kcal.mol^{-1}) for consecutive ring closure of the trienyl radical (48)

Endo ring closure of 50 is a relatively high energy process (ΔE_s = 9.5 kcal.mol^{-1}) but the _exo_-processes giving rise (after hydrogen atom transfer) to the two isomers of 54 are feasible. Radical (51) has only one energetically attainable route open to it: formation of 55(α-Me). The alternative _exo_-ring closure and the _endo_ process (ΔE_s = 8.2 kcal.mol^{-1}) are both of much higher energy. On the other hand _endo_-ring closure of 52 to give 57 is relatively favourable as is the _exo_-process leading to 56(β-Me). Finally we note that all of the processes available to radical (53) are of relatively high energy, and we might expect this radical to afford a bicyclic product, and possibly some of the _endo_ cyclisation product (59).

In summary, it is difficult to arrive at a firm prediction for the outcome of this reaction because of the small differences between the values of ΔE_s for exo ring closure of **49**. Assuming that these differences are significant we would conclude that the reaction should definitely afford four triquinanes: the two isomers of **54**, **55**(α-Me), **56**(β-Me), and possibly a fifth, **56**(α-Me). Also it should afford two endo-cyclisation products, **57** and **59**, and probably a bicyclic product (**60**) arising from direct hydrogen atom transfer to **53**.

An experimental program designed to test these predictions has been initiated in these laboratories. Our preliminary experiments have shown[50] that the reaction of tributylgermane with the bromo precursor of **48** affords four triquinanes (yields: 18%,9%,12%,6%) of which the first two have been identified as the isomers of **54**, and the third is tentatively identified as **55**(α-Me), two endo-cyclisation products (10%,24%) tentatively identified as **57** and **59**, and one bicyclic product (14%) tentatively identified as **60**. Although much further work will be needed to confirm the identity of all the products, the fact that the method correctly predicts the structures of two products, and the type and number of four others (from a total number of more than thirty-two), provides powerful evidence of its utility.

CONCLUSION

We believe that the results presented above demonstrate that force-field calculations by the MM2 method can be successfully applied to model transition structures for radical ring closure. The best results are obtained when the transition structures incorporate dimensions for the intimate array of reactive centres obtained by ab initio or semi-empirical M.O. methods. Under these circumstances there is satisfactory qualitative agreement between the calculated strain energies of the transition structures and experimental activation energies for a large number of simple cyclisations. The method can be used to predict, the regio- and stereo-selectivity of ring closure of both simple and complex systems, and to provide insight into the probable course of a series of consecutive reactions. Its success provides powerful evidence of the validity of the stereo-electronic considerations on which it is predicated, and suggests that similar methods could be applied to other types of radical process.

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