

Origins of the Regioselectivity of Cyclopropylcarbinyl Ring Opening Reactions in Bicyclo [n.1.0] Systems

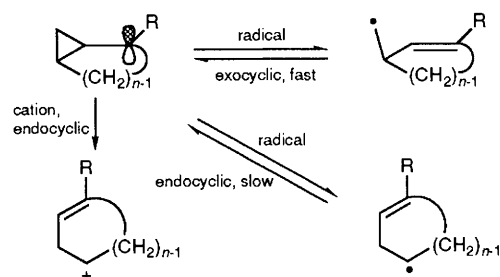
Robert A. Batey, Peter Grice, John D. Harling, William B. Motherwell* and Henry S. Rzepa*†

Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY, UK

Addition of $\cdot\text{CCl}_3$ radicals to sabinene **1** ($\text{R}^1 = \text{Pr}^1$) and a related bicyclo [4.1.0] derivative in BrCCl_3 results in kinetic trapping of the *exo* ring opened intermediate but in CCl_4 as solvent the major products are derived from the thermodynamically more stable *endo* radical; the radical and cationic regioselectivities are related to the features of a PM3 SCF-MO orbital correlation diagram.

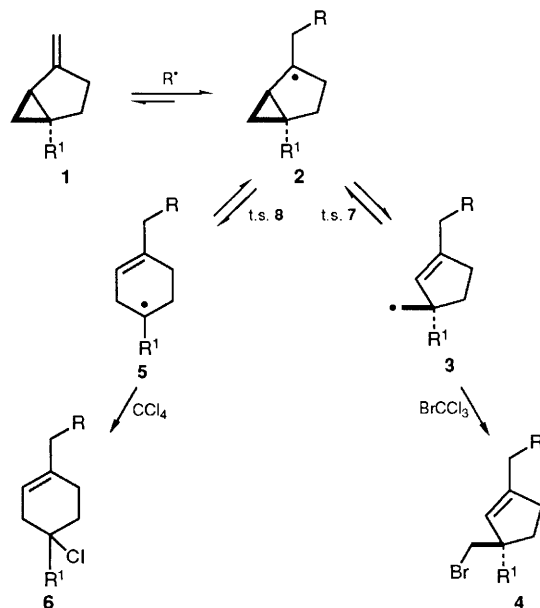
Although cyclopropylcarbinyl ring opening reactions are well understood in simple monocyclic systems, the incorporation of this nucleus into a fused bicyclo [n.1.0] framework introduces additional factors of increased conformational rigidity, ring strain, and differing rate of reversible ring opening and reclosure. The literature on both radical¹ and cationic² ring opening reactions reveals a preference for exocyclic radical ring opening on both kinetic (for $n = 3-6$) and on thermodynamic grounds of ring strain³ (for $n = 4-6$), which contrasts sharply with a fundamental preference of the cation for the endocyclic mode (Scheme 1). Simple inspection of molecular models would of course suggest that for either reactive intermediate, orbital overlap is considerably poorer in the endocyclic bond fission.

Our interest in developing preparatively useful radical reactions based on this framework⁴ leads us to report here the following experimental observations on a series of reactions using haloform solvents and dibenzoyl peroxide as initiator, together with a detailed theoretical analysis of the observed regioselectivities.



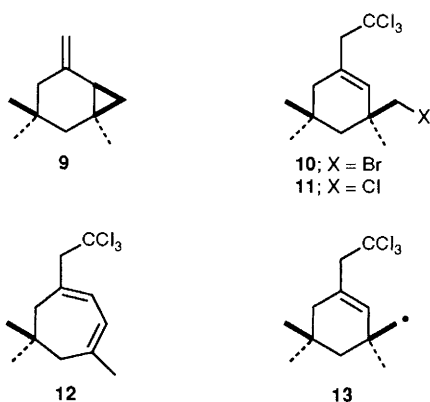
Scheme 1

Reaction of sabinene **1**, ($\text{R}^1 = \text{Pr}^1$) in BrCCl_3 (Scheme 2) proceeds *via* radical **2** ($\text{R} = \text{CCl}_3$) which undergoes kinetically favoured *exo* ring opening to the primary radical **3**. Rapid bromine atom abstraction from solvent to give the observed product **4** in good yield (74%) renders the formation of **3** essentially irreversible. By way of contrast, we have confirmed the original observation of Davies⁵ that reaction in CCl_4 affords exclusively the six membered ring product **6** ($\text{R} = \text{CCl}_3$, 88%), owing we believe to slower abstraction of the more tightly bound chlorine atom from solvent permitting reversible reclosure of **3**, and allowing alternative endocyclic ring opening to give the thermodynamically favoured radical **5**.



Scheme 2 t.s. = transition state

† E-mail: rzepa@ch.ic.ac.uk.



The bicyclo [4.1.0] congener **9** in BrCCl_3 gave the cyclohexenyl adduct **10** ($\text{X} = \text{Br}$, 87%) whereas reaction in CCl_4 afforded both the chloro analogue **11** ($\text{X} = \text{Cl}$, 20%) and the cycloheptadiene derivative **12** (40%) produced from the expected tertiary chloride, the presence of which could be inferred from the NMR spectrum prior to chromatography. Clearly the rate of reclosure of radical **13** must also be slower than for **3**. This result is also consistent with isomerisation studies in both cyclohex-3-enylmethyl⁶ and cyclopent-3-enylmethyl⁷ radicals during dehalogenation with tri-*n*-butylstannane under dilute conditions, and suggests that thermodynamic ring strain imposed during the reclosure step does not dominate over *e.g.* the early nature of the transition state proposed for radical addition to double bonds.

Earlier theoretical work³ on radical ring opening using unrestricted Hartree-Fock MINDO/3 and MNDO SCF-MO methods had suggested little difference in energy between the *exo*- and *endo*-cyclic ring opening transition states in [3.1.0] and [4.1.0] systems, whilst supporting the greater thermodynamic stability of the *endo*-cyclic ring opened product. We have now investigated the origins of the kinetic *exo* specificity of the radical ring opening reaction, and in particular the reversal of this selectivity for the cation, using PM3 molecular orbital calculations.⁸ The *endo* radical transition state **8** ($\text{R}^1 = \text{Me}$, $\text{R} = \text{H}$) was calculated[‡] to be 3.1 kcal mol⁻¹ (1 cal = 4.184 J) lower than the *exo* isomer **7**, but significantly the difference increased to 7.6 and 8.9 kcal mol⁻¹ for the cation at solvent permittivity of $\epsilon = 80$ and 5, respectively.⁹ Whilst the calculated relative energies of radical transition states **7** and **8** do not correspond with the known *exo* radical preference, the greater *endo* discrimination for the cation is consistent with experiment.

The origins of this effect are revealed when the nature of the critical molecular orbitals and their energies are inspected *via* a valence orbital correlation diagram constructed along the two alternative reaction pathways (Fig. 1). For the radical, the highest doubly occupied, singly occupied and lowest unoccupied MOs comprise bonding (ψ_{22}), non-bonding (ψ_{23}) and antibonding (ψ_{24}) combinations of the nascent π system atomic orbitals and the product radical *p* orbital. Orbitals ψ_{23}

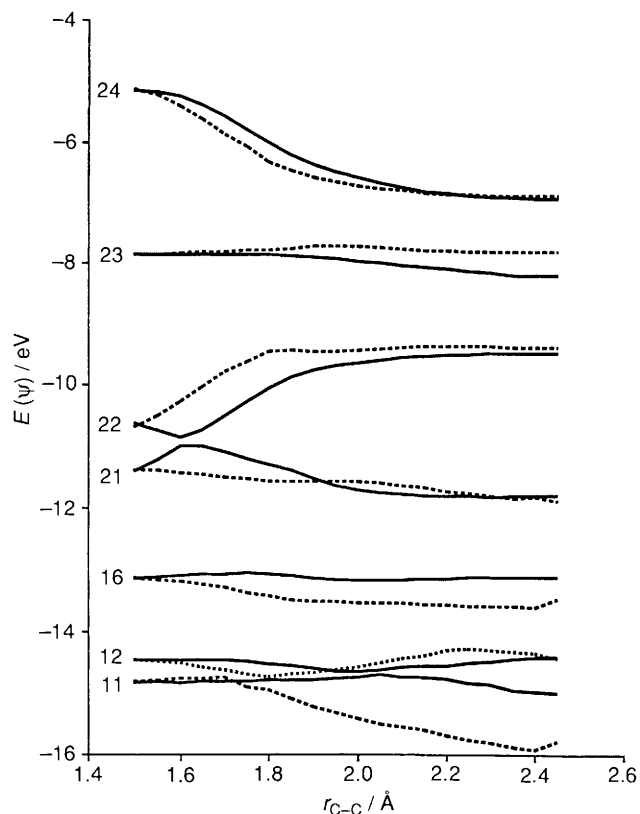


Fig. 1 Valence orbital energies $E(\psi)$ 11, 12, 16, 21, 22, 23 (offset by -4 eV) and 24 (offset by -8 eV) as a function of the breaking C-C distance for orbitals for exocyclic (solid line) and endocyclic (dashed line) radical ring opening

and ψ_{24} are involved in a weakly avoided crossing, arising from the partially orthogonal relationship of the orbitals involved in the reactant and product radical centres, hence imparting some antibonding character to the SOMO orbital ψ_{23} at the transition state. As noted above, the greater geometrical mismatch results in destabilisation of radical **8** because of this slightly higher energy for ψ_{23} . Nevertheless the effect is small and if the alternative exocyclic radical product is not efficiently trapped, thermodynamic control results in *endo*-cyclic opening. However, cationic **8** is no longer energetically disfavoured with respect to **7** because ψ_{23} is now unoccupied.

Unfavourable orbital alignment in the *endo*-cyclic mode also destabilises ψ_{22} , doubly occupied for both radical and cation. The origins of the overall calculated 7–9 kcal mol⁻¹ cationic preference for this mode must therefore originate in the lower energy valence orbital manifold (Fig. 1). A particularly prominent feature in these energy levels for the exocyclic reaction path is a strongly avoided crossing between ψ_{22} and ψ_{21} at $r_{\text{C-C}}$ ca. 1.6 Å which imparts a significant slope to ψ_{21} , a feature absent for the *endo*-cyclic pathway. This slope may render the *endoxo* selectivity particularly sensitive to the transition state geometry; indeed the cationic transition state **7** ($r_{\text{C-C}}$ 2.05 Å) is later than **8** ($r_{\text{C-C}}$ 1.85 Å) for this reason. The regioselectivity for the cation can also be identified in part with orbitals ψ_{16} and ψ_{11} (Fig. 1). Whilst the other *endo/exo* pairs of orbitals in this region are approximately matched in energy, these two orbitals significantly favour *endo*-cyclic opening, due in part to the incorporation of the cleaving *endo*-cyclic C-C bond into a 'W' relationship with adjacent σ -bonds (Fig. 2). We conclude that whilst the radical *exo* preference is owing to a less favourable SOMO orbital overlap for the *endo* transition state, the cationic preference of the latter originates in part from a more favourable alignment of

‡ Calculations were performed with full geometry optimisation using either AMPAC 2.1 or MOPAC 5.0, employing the 'half-electron' formalism for doublets to eliminate significant problems of spin contamination found with the unrestricted Hartree-Fock method, and the self-consistent reaction-field (SCRF) solvation formalism for cations.⁹ Calculated radical energies in kcal mol⁻¹ (C-C bond length, Å): **7**, 41.6 (1.92), **8**, 38.5 (1.87), **3**, 18.5 (2.45), **5**, 3.8 (2.45). Calculated cation energies for $\epsilon = 5$ (C-C bond length, Å): **7**, 162.0 (1.98), **8**, 153.1 (1.85), **5**, 129.2 (2.45). Calculated cation energies for $\epsilon = 80$ (C-C bond length, Å): **7**, 149.9 (2.05), **8**, 142.3 (1.85), **3**, 142.0 (2.45), **5**, 113.4 (2.45).

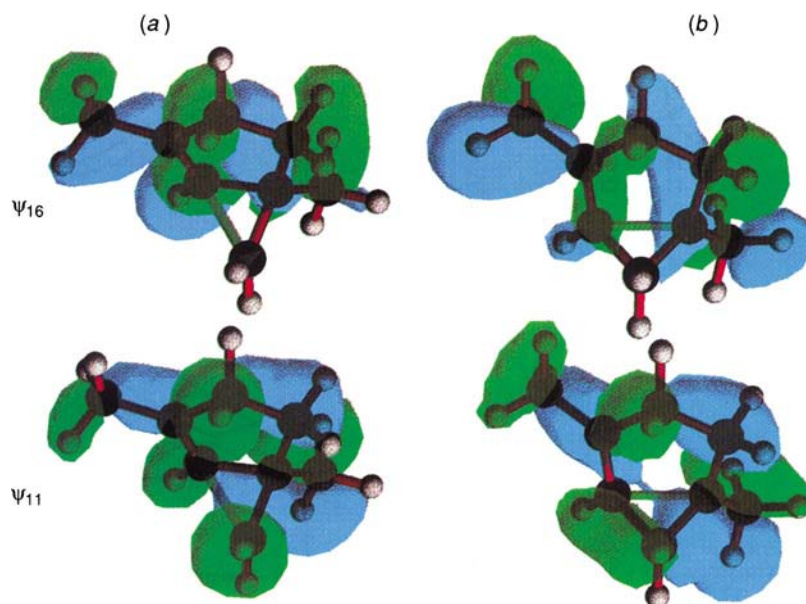


Fig. 2 Calculated PM3 molecular orbitals ψ_{16} and ψ_{11} (contoured at 0.03 au) for (a) **7** and (b) **8** radical transition states

the σ -framework. Our experimental and theoretical results also emphasise the caveat that, from the mechanistic standpoint, endocyclic ring cleavage of a norcarane derivative is not, *per se*, sufficient evidence for a carbocation intermediate.¹⁰

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