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Substituent Effects on the Rearrangements of Cyclohexyl to Cyclopentyl Radicals Involving Avermectin-related Radicals

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Abstract

The rearrangement of a substituted cyclohexyl radical to a cyclopentylmethyl radical on the skeleton of Avermectin B_1 has been investigated using density functional (UB3LYP/6-31G(d)) and G3MP2B3 computational methods. The rearrangement is preferred when highly radical stabilizing groups are present at the 2- and 3-positions of the cyclohexyl radical. A substituent on the 3-position of the cyclohexyl radical enables ring-cleavage of the cyclohexyl radical, while a radical stabilizing substituent on the 2-position of the cyclohexyl radical stabilizes the final cyclopentylmethyl radical, enabling the overall rearrangement and reversing the normal thermodynamic preference for the hexenyl radical ring-closure.

Introduction

Many different radical reactions have proven useful in organic synthesis.[1] In particular, intramolecular radical additions to carbon-carbon double and triple bonds have been thoroughly studied[2] and are especially valuable for the formation of five- and six-membered rings.[3].

We recently reported on our studies dedicated towards understanding structure-activity relationships of Avermectin B_1, **1**, the extraordinary, highly potent macrolide discovered more than two decades ago at Merck.[4,5] During the synthesis of an Avermectin analogue, an apparent radical ring-cleavage followed by a ring-closure produced a ring-contracted product, Scheme 1.[5] This rearrangement from a cyclohexyl radical to a cyclopentylmethyl radical was unforeseen, since previous reports demonstrated that tin hydride typically traps the cyclohexyl radical.[1o,6].

A similar radical-induced ring contraction was found in literature, Scheme 2. Surzur and co-workers showed that the thiyl radical undergoes a ring-closure, ring-cleavage, ring-closure progression.[7] The last two steps are related to the rearrangement investigated in this paper. Energetics for the rearrangement reported by Surzur were investigated by this group, Scheme 2. Free energies of activation for each step are very reasonable (4 – 8 kcal/mol) and each radical intermediate is either the same energy as the previous intermediate or more stable than the previous intermediate.

The ring-closure reactions of 5-hexenyl radicals have been thoroughly studied.[8,9] The 5-exo product is generally the kinetically favored major product (Baldwin's Rules).[10] The energies

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of activation for the 6-endo and 5-exo ring-closures of 5-hexenyl radical have been established theoretically and experimentally (8 – 9 kcal/mol and 6 – 7 kcal/mol, respectively).[8b,8e,9].

The energetics of conversions of cyclohexyl radical, **a**, to cyclopentylmethyl radical, **c**, are investigated here for a variety of substituted model systems. Our goal was to determine how cyclohexyl substituents induce the conversion of **1** to **4**.

Computational Methodology

Quantum mechanical investigations were carried out with Gaussian 98 and Gaussian 03.[11] Geometry optimizations followed by frequency calculation without zero-point vibrational corrections were performed using UB3LYP/6–31G(d).[12] Energetics of the simplest cases were verified with G3MP2B3. G3MP2B3 is a variation of Gaussian-3 theory (G3).[13] In G3MP2B3, geometries and zero-point energies are obtained from unrestricted B3LYP density functional theory calculations. B3LYP geometry optimization is followed by a series of high-level single point calculations. This method has been shown to be highly accurate in evaluating free energies of formation and thermochemical and kinetic properties of radicals,[14] with a mean absolute deviation of *c*. 1 kcal/mol from experimental values.[14k]

Results and Discussion

The rearrangement of cyclohexyl to cyclopentylmethyl radicals could occur by sequential ring-opening, ring-closure or by a concerted 1,2-shift, Scheme 3. Typically, the radical produced after initial attack of the silylmethyl radical, such as substituted cyclohexyl radical **5**, is trapped by tributyltin hydride or is involved in further radical cyclization,[1o,6] but in the macrocycle, the rearrangement occurs prior to trapping.

The ring expansions of cyclopentanones have been proposed to proceed via a 1,2-shift, Scheme 4.[15] The 1,2-shift is favored over ring-cleavage, ring-closure by almost 5 kcal/mol at UB3LYP/6-31G(d) in the system shown in Scheme 4. Both possibilities were investigated for the cyclohexyl radical and two derivatives, Table 1. Reaction free energies relative to the cyclohexyl radical, **a**, are given in Table 1.

Without the acyl group in the ring, the 1,2-shift is disfavored. Activation free energies for the concerted 1,2-shifts are 16 – 25 kcal/mol higher than the barrier for ring cleavage, Table 1. In cyclopentanones, the 1,2-shift is favored because the radical center can partially reside on the oxygen of the acyl group. In model systems of the Avermectin derivative, the beta carbon is always sp^3 hybridized and delocalization cannot occur. Additional substitution at the beta carbon in these model systems will further favor sequential ring-opening, ring-closure due to increased steric interactions in the transition state for the 1,2-shift (a pseudo-trigonal bipyramidal geometry). The sequential ring-opening, ringclosure process was investigated for subsequent model systems.

In the unsubstituted case, the cyclohexyl radical, **9-a**, is most stable. Ester or formyl substituents at the 2-position, **10** or **11**, cause **10-c** and **11-c** to be the most stable radical. Activation energies for system **9** are similar to published energetics for the 6-endo and 5-exo closures.[8]

Previous investigations have shown that UB3LYP geometries and energies are quantitatively accurate for evaluation of the energies of radical reactions.[9,16,17] Implementing UB3LYP is particularly useful in evaluating larger systems, when the use of higher-level calculations becomes impractical. The quantitative accuracy of UB3LYP is confirmed in Table 1, where G3MP2B3 free energies of reaction and activation free energies are shown to be within 2 kcal/mol of the UB3LYP/6-31G(d) energetics. Since the UB3LYP/6-31G(d) energetics are in good agreement with the G3MP2B3 energetics, and G3MP2B3 is computationally prohibitive on

larger systems, only UB3LYP/6-31G(d) energetics were obtained for the more heavily-substituted cases.

A model system to mimic the avermectin system, containing a siloxycycle fused to the cyclohexyl radical, was investigated. Table 2 and Table 3 contain the results. With additional substituents on the cyclohexyl radical, two possible cyclohexane chair conformations were investigated for their relative stabilities. The position of the siloxycycle oxygen is used to differentiate the two possible cyclohexane chairs; this oxygen may be equatorial (e.g. **12-a-eq**) or axial (e.g. **12-a-ax**), Figure 1. Table 2 and Table 3 contain energetics for the more stable chair conformer of the cyclohexyl radical. In the case of **17**, these cyclohexyl chair conformers are equi-energetic, and energies for both are listed.

The overall rearrangement is endergonic without the presence of a highly radical stabilizing substituent, **12**. The ring-opening remains highly endergonic (14 – 25 kcal/mol) until addition of vinyl or butadienyl substituents at the 3-position of the cyclohexyl radical **a**, **19** – **22**, Table 3. These substituents stabilize the hexenyl radical, **b**. The vinyl (**19**) and vinyl, hydroxyl (**20**) groups lower the free energy of ring-opening to −2 kcal/mol and −8 kcal/mol, respectively. These systems have significantly lower energies of activation for ring-opening than **9** (17 and 15 kcal/mol versus 31 kcal/mol). A butadienyl substituent is better able to stabilize a radical, and, therefore, **21c** is even more stable and affords a more exergonic ring-opening. A highly stabilizing group at the 3-position of radical **a** enables ring-cleavage. The experimentally observed rearrangement can be replicated computationally with a butadienyl group at the 3-position of the cyclohexyl radical, and a formyl substituent at the 2-position, Figure 2

Introduction of a fused oxolane further mimics the macrocycle of interest. The energies for this model system are shown in Table 4. The saturated oxolane model system has a high **TS1** and a large energy of ring-opening, 24 and 9 kcal/mol (**23-TS1** and **23-b**, respectively). A vinyl substituent on the oxolane ring (**24**) stabilizes radical **b** so that the free energy of ring-opening is exergonic, Figure 3. The activation energy of ring-opening is lowered by 8 kcal/mol from **23** to **24**. Geometries for **24** are shown in Figure 4. Similar to the results shown in Table 3, butadienyl substitution (**27**) further stabilizes **b** and lowers **TS-1**.

A model system that contains the seventeen-membered macrocycle, **28**, was investigated. Alkyl and ether substituents on the macrocycle were modeled using methyl groups and methyl ethers, respectively. Conformational searches were performed on each radical intermediate using using MACROMODEL/MAESTRO[18] with the Amber* force field[19] to locate relative minima. Each local minimum was then optimized in Gaussian 03[11] with UHF/3-21G(d), followed by UB3LYP single point calculations. Energetics and geometries for this model system are given in Figure 5.

With the macrocycle in place, the activation energy for ring-cleavage remains reasonable. The hexenyl radical, **28b**, is much less stable within the macrocycle, at −7 kcal/mol as opposed to −13 in **27**, but the activation energy for ring-closure is smaller (11 kcal/mol versus 14 kcal/mol). Radical **28c** is less stable than **28b**, but the barrier of ring-closure is small enough that the two radicals would be in equilibrium. The barrier for quenching **28b** is most likely relatively high due to steric interactions, Figure 5, and the product from quenching the cyclopentylmethyl radical predominates. In spite of our favorable comparisons of UB3LYP with higher accuracy methods for simple systems, UB3LYP may be overestimating the stability of the macrocyclic hexenyl radical in this highly substituted system.

Computed energetics discussed herein indicate that the rearrangement of the cyclohexyl radical to form the cyclopentylmethyl radical should be viable, even without the macrocycle, if appropriate substituents are present. For example, model system **19** has favorable energetics for the rearrangement with a formyl substituent at the 2-position and hydroxyl and vinyl

substituents at the 3-position. In this system, the cyclopentylmethyl radical is favored both kinetically and thermodynamically.

Conclusions

The unexpected product observed when an Avermectin B_1 derivative undergoes radical cyclization has been explained. A cyclohexyl radical can rearrange to a cyclopentylmethyl radical via ring-opening followed by 5-exo ring-closure when highly radical stabilizing substituents are present at the 2- and 3- positions of the cyclohexyl radical. In the avermectin-derived macrocyclic radical, butadienyl and hydroxyl groups stabilize the hexenyl radical permitting the ring opening of the parent cyclohexyl radical. Without at least one highly radical stabilizing group at the 3-position, ring-cleavage would not be energetically favored. The ester group at the 2-position reverses the thermodynamic preference for ring-closure, causing the cyclopentylmethyl radical to be favored over the cyclohexyl radical both kinetically and thermodynamically.

Further investigation into substituent control of this rearrangement will be reported in future publications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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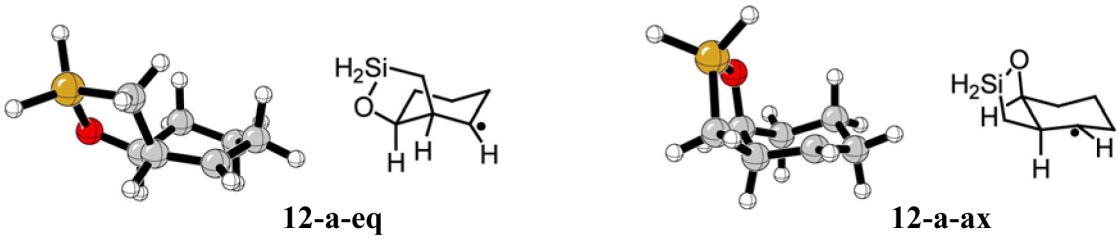


Figure 1.
The two chair conformations of fused siloxycycle-cyclohexyl radical, **12a**.

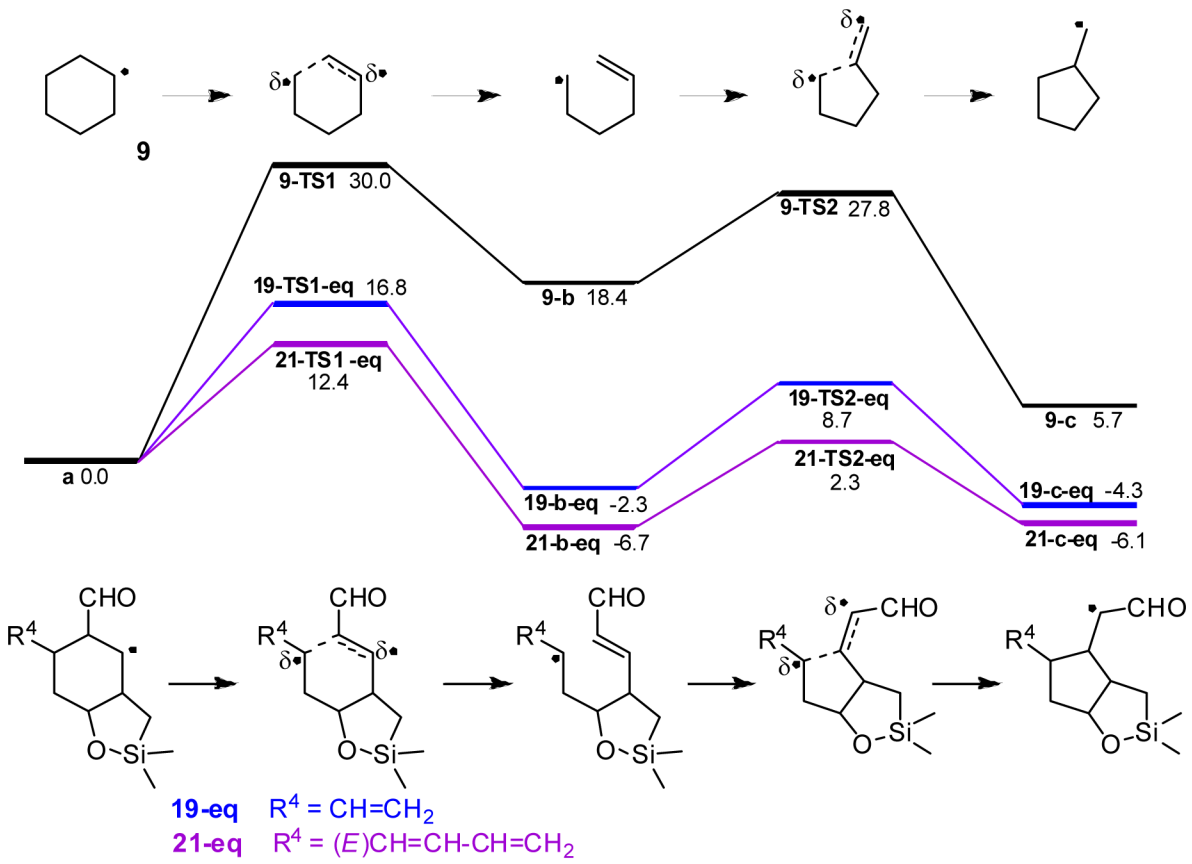


Figure 2.
Potential energy surface of rearrangement from cyclohexyl radical to cyclopentylmethyl radical for **9**, **19**, and **21** (relative free energies at UB3LYP/6-31G(d) in kcal/mol).

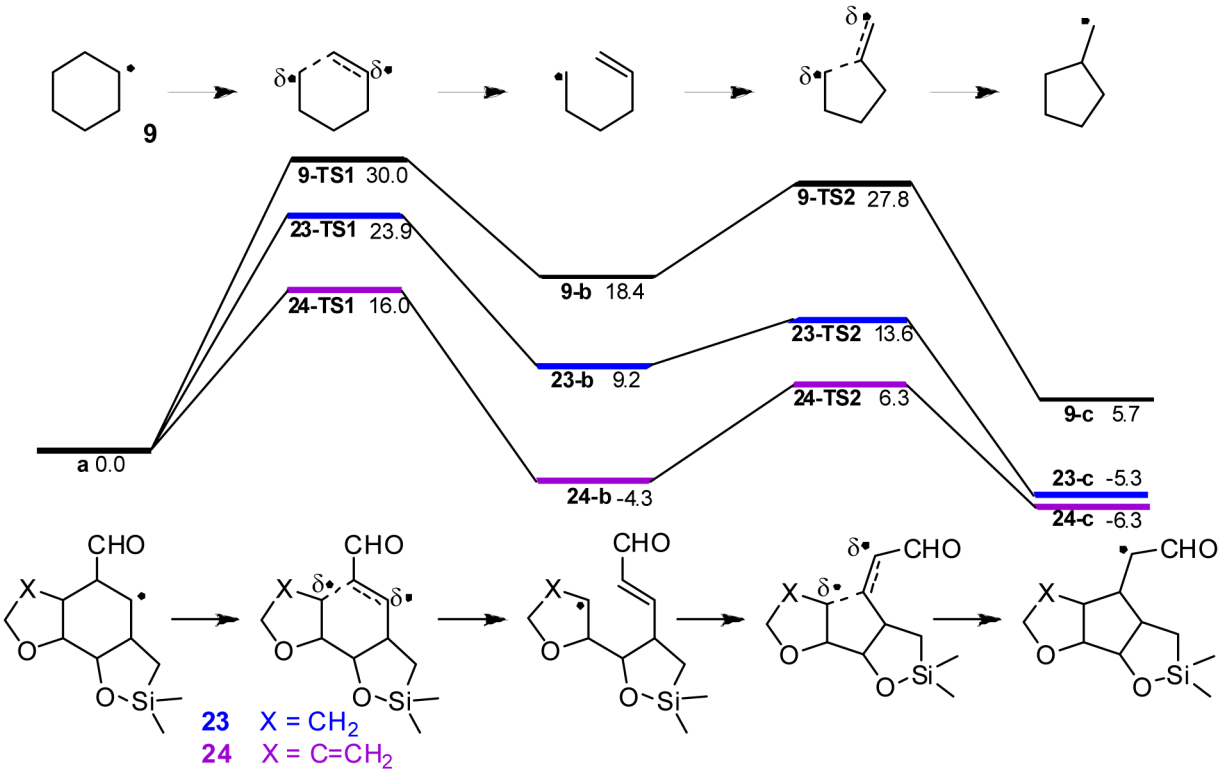


Figure 3.
Potential energy surface of rearrangement from cyclohexyl radical to cyclopentylmethyl radical for **23** and **24** (relative free energies at UB3LYP/6-31G(d) in kcal/mol).

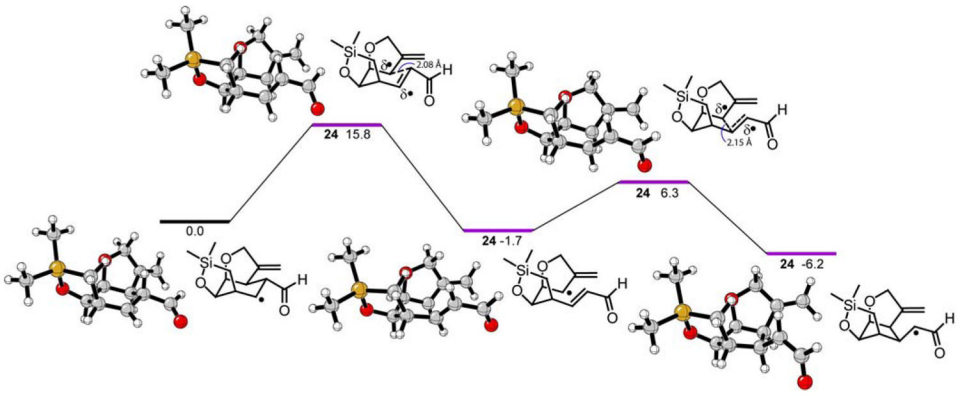


Figure 4.
Rearrangement of cyclohexyl radical to cyclopentylmethyl radical for model system **24** (relative free energies at UB3LYP/6-31G(d) in kcal/mol).

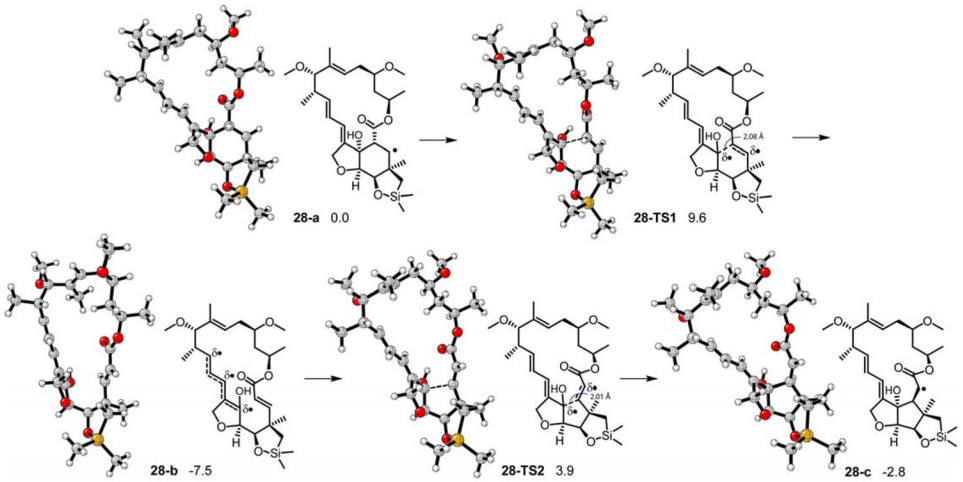
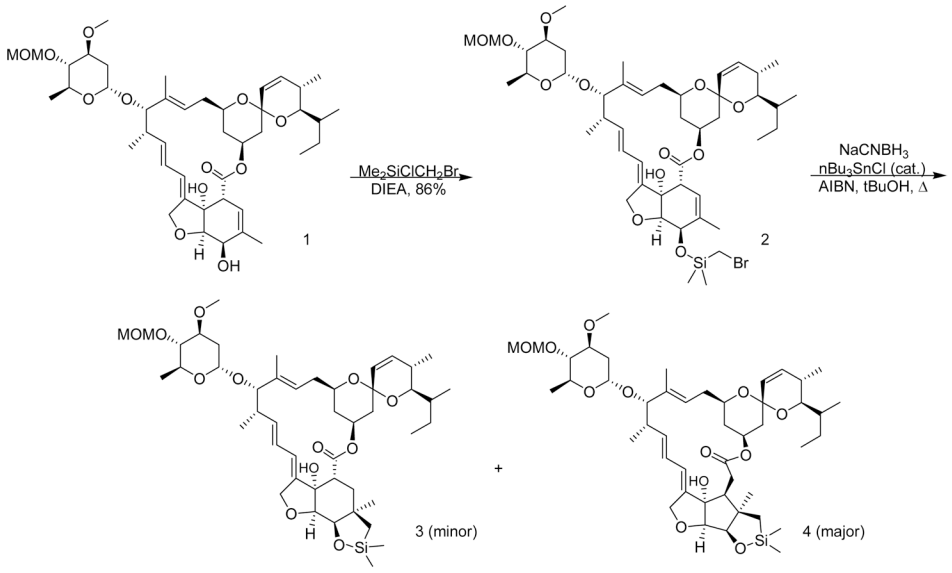
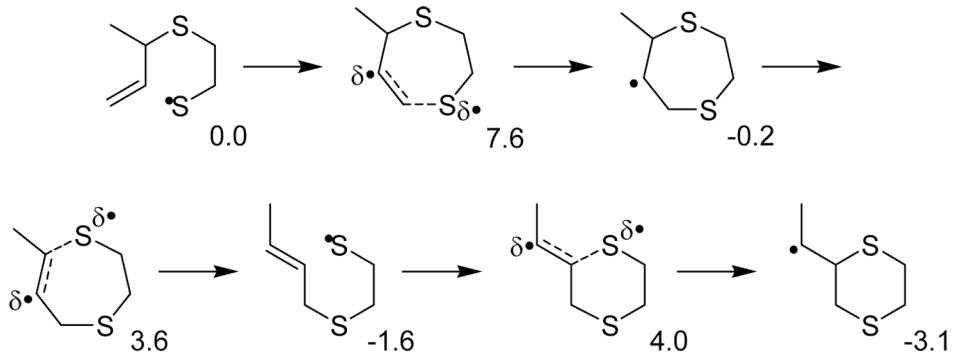


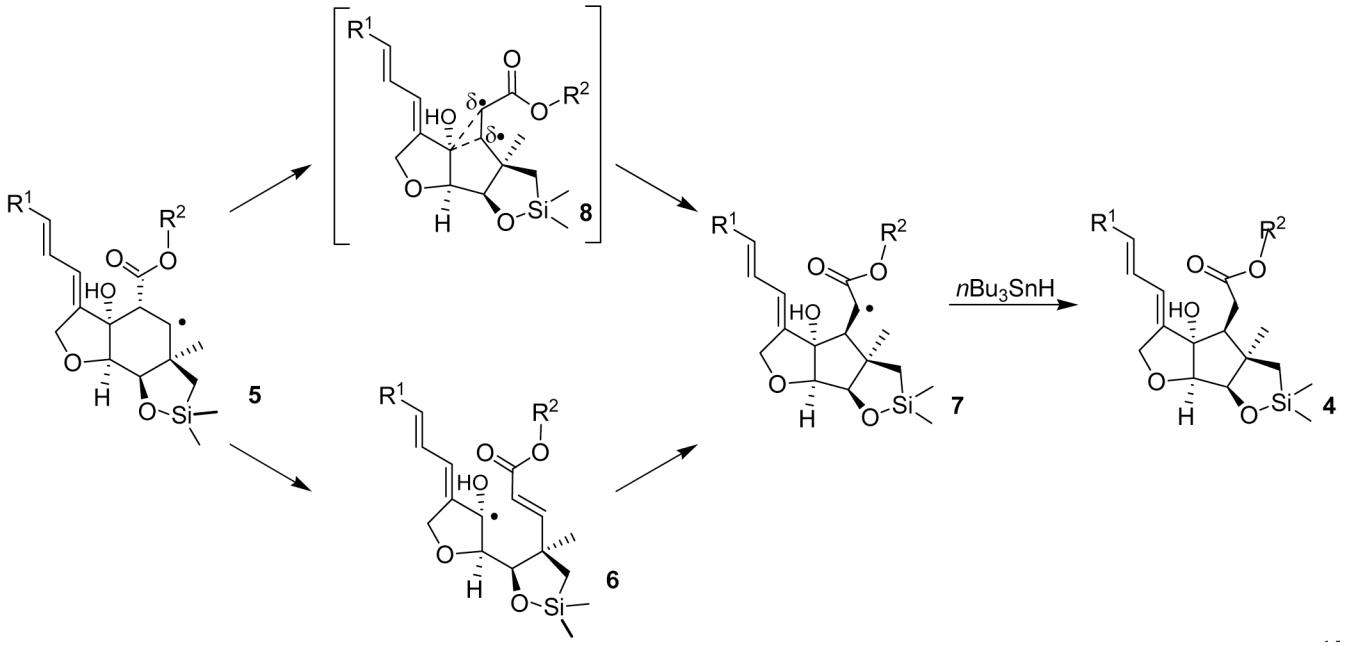
Figure 5.
Geometries and UB3LYP/6-31G(d)//UHF/3-21G(d) relative energetics (at 0K, in kcal/mol) for the rearrangement of cyclohexyl radical to cyclopentylmethyl radical for model system **28**.



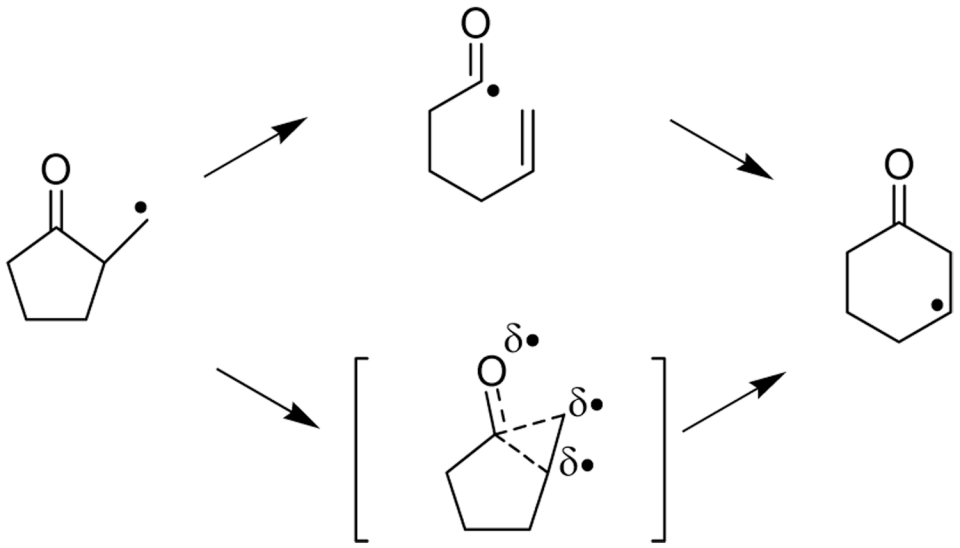
Scheme 1.
Formation of **3** (minor) and **4** (major) from reaction of **1**.



Scheme 2.
Radical rearrangement investigated by Surzur and UB3LYP/6-31G(d) free energies (kcal/mol)



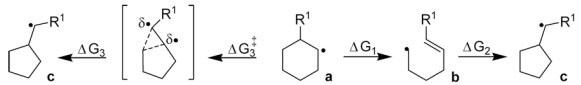
Scheme 3.
Possible paths for the rearrangement of a substituted cyclohexyl radical to a substituted cyclopentylmethyl radical.



Scheme 4.
Ring-cleavage versus 1,2-shift for formation of 2-cyclohexenone radical.

Table 1

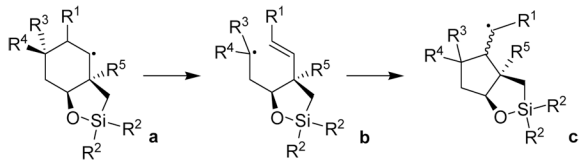
G3MP2B3 (UB3LYP/6-31G(d) in parenthesis) calculated free energies (relative to radical **a**) for rearrangements of cyclohexyl radicals by concerted and stepwise pathways.



compound	R^1	Transition State 1 ($\Delta G_1^{\ddagger}$)	Transition State 3 ($\Delta G_3^{\ddagger}$)	Radical b (ΔG_1)	Transition State 2	Radical c ($\Delta G_3 = \Delta G_1+\Delta G_2$)
9	−H	30.0 (30.6)	55.1 (63.0)	16.7 (18.4)	27.7 (27.8)	4.1 (5.7)
10	−CHO	28.3 (26.1)	44.7 (44.0)	14.3 (12.0)	20.9 (17.8)	−3.9 (−6.2)
11	$-CO_2Me$	26.6 (24.4)	48.6 (46.9)	13.7 (11.3)	21.3 (17.5)	−2.1 (−4.6)

Table 2

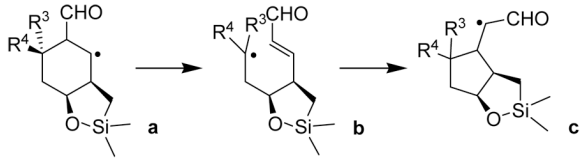
UB3LYP/6-31G(d) calculated free energies (relative to radical **a**) for the cyclohexyl radical rearrangement.



compound	Substituents					Radical b	Radical c
12-ax	R^1 = H,	R^2 = H,	R^3 = H,	R^4 = H,	R^5 = H	22.6	7.7
13-ax	R^1 = CHO,	R^2 = H,	R^3 = H,	R^4 = H,	R^5 = H	18.3	−5.4
14-ax	R^1 = H,	R^2 = Me,	R^3 = H,	R^4 = H,	R^5 = H	22.7	7.5
15-ax	R^1 = CHO,	R^2 = Me,	R^3 = H,	R^4 = H,	R^5 = H	18.0	−5.0
16-ax	R^1 = CHO,	R^2 = Me,	R^3 = OH,	R^4 = H,	R^5 = H	14.9	−2.4
17-ax	R^1 = CHO,	R^2 = Me,	R^3 = OH,	R^4 = Me,	R^5 = H	10.9	−1.4
17-eq	R^1 = CHO,	R^2 = Me,	R^3 = OH	R^4 = Me,	R^5 = H	6.8	−5.3
18-eq	R^1 = CHO,	R^2 = Me,	R^3 = OH,	R^4 = Me,	R^5 = Me	7.8	−5.8

Table 3

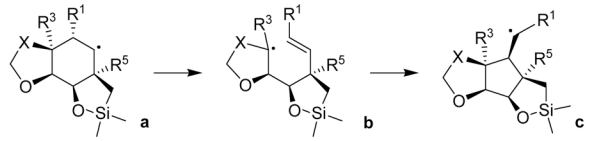
UB3LYP/6–31G(d) calculated free energies (relative to radical **a**) for rearrangements of siloxycycle substituted cyclohexyl radicals to cyclopentylmethyl radicals.



compound	Substituents		TS1	Radical b	TS2	Radical c
19-eq	R^3 = H,	R^4 = CH=CH_2	16.8	−2.3	8.7	−4.3
20-eq	R^3 = OH,	R^4 = CH=CH_2	14.5	−7.6	6.6	−4.0
21-eq	R^3 = H,	R^4 = (*E*)CH=CH-CH=CH_2	12.4	−6.7	2.3	−6.1
22-eq	R^3 = OH,	R^4 = (*E*)CH=CH-CH=CH_2	11.1	−11.0	1.6	−11.0

Table 4

UB3LYP/6–31G(d) calculated free energies (relative to radical **a**) for rearrangements of oxolane substituted cyclohexyl radicals to cyclopentylmethyl radicals.



compound	Substituents				TS1	b	TS2	c
23	R^1 = CHO,	R^3 = H,	X = CH_2,	R^5 = H	23.9	9.2	13.6	−5.3
24	R^1 = CHO,	R^3 = H, X = $C{=}CH_2$,	X = $C{=}CH_2$,	R^5 = H	16.0	−4.3	6.3	−7.3
25	R^1 = CHO,	R^3 = H,	X = (*E*) C=CH-CH=CH_2,	R^5 = H	13.3	−9.9	3.6	−7.4
26	R^1 = CHO,	R^3 = OH,	X = (*E*) C=CH-CH=CH_2,	R^5 = Me	10.8	−11.1	0.1	−7.0
27	R^1 = CO_2Me,	R^3 = OH,	X = (*E*) C=CH-CH=CH_2,	R^5 = Me	11.5	−12.8	1.4	−5.7