Electron Transfer Photochemistry of Homochrysanthemol: Intramolecular Nucleophilic Attack on the Cyclopropane Ring

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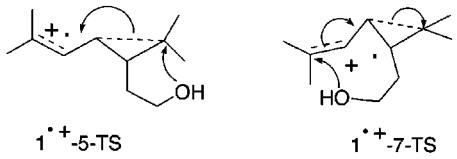
The electron-transfer photochemistry of homochrysanthemol, **1**, resulted exclusively in intramolecular "substitution" at the quaternary cyclopropane carbon, generating the five-membered cyclic ethers, **2** and **4**. The alternative "addition" to the terminal carbon of the double bond, which would result in seven-membered cyclic ethers, **3** and **5**, was not observed. Apparently, the five-membered transition state leading to **2** and **4** is significantly favored over the seven-membered one required for formation of **3** and **5**. These results stand in interesting contrast to the previously established reaction pattern of chrysanthemol, **8**, which is captured exclusively at the terminal vinyl carbon. The divergent regiochemistry of $\mathbf{1}^{\bullet+}$ and $\mathbf{8}^{\bullet+}$ (even though the tethers between vinylcyclopropane and alcohol functions differ only by a single CH_2 group) elucidates the principles governing the course of nucleophilic capture in radical cations.

Introduction

Radical cations of molecules containing strained ring moieties as well as olefinic fragments have been the focus of much interest in recent years,[1] including the conjugative and homoconjugative interactions between the two types of functions. Various substrates have been probed to delineate changes in the molecular geometry upon one-electron oxidation and to assess the spin and charge density distributions in the resulting radical cations.[2] Typically, the reactions of strained ring radical cations proceed with release of ring strain;[3,4] in some systems, this reaction is assisted by a nucleophile.[5−7]

Vinylcyclopropane radical cation, the simplest species containing an olefinic moiety and a cyclopropane ring, has only recently been characterized adequately.[7−11] The molecular ion of vinylcyclopropane rearranges to penta-1,3-diene radical cation in the gas phase.[8] Related rearrangements of two rigidly linked vinylcyclopropane systems in solution (sabinene to β-phellandrene; α-thujene to α-phellandrene) were interpreted as novel radical cation sigmatropic shifts.[9] The unsubstituted prototype reacted with nucleophiles by preferential (though not exclusive) capture at the cyclopropane ring.[10] In contrast, the *cis*-chrysanthemol radical cation, bearing an internal nucleophile, failed to react by capture of the quaternary cyclopropane carbon; instead, it underwent regiospecific intramolecular capture at the terminal carbon of the vinyl group.[11]

In this publication, we describe the intramolecular capture of a vinylcyclopropane radical cation, $\mathbf{1}^{\bullet+}$, in which the internal nucleophile is attached by an extended tether containing an additional methylene group. The intramolecular capture of $\mathbf{1}^{\bullet+}$ features the competition between a five-membered transition state ($\mathbf{1}^{\bullet+}$-5-TS) for attack at the cyclopropane carbon in S_N2 fashion and a seven-membered one ($\mathbf{1}^{\bullet+}$-7-TS) for attack at the terminal vinyl carbon, respectively, in S_N2' fashion.



$\mathbf{1}^{\bullet+}$-5-TS $\quad$ $\mathbf{1}^{\bullet+}$-7-TS

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Electron-Transfer Photochemistry of Homochrysanthemol

Irradiation of an electron acceptor sensitizer-*co*-sensitizer pair (**DCB**−**Phen**) in the presence of a donor such as **1** (**D**) leads to the generation of the radical cation ($\mathbf{D}^{\bullet+}$) and the sensitizer radical anion ($\mathbf{DCB}^{\bullet-}$; eq 1); $\mathbf{D}^{\bullet+}$ is captured by a nucleophile (e.g., CH_3OH; eq 2), and the resulting free radical reacts with the radical anion by aromatic substitution (eq 3).[12,13] In the system discussed here, the tethered alcohol function serves as an internal nucleophile, intercepting the positive charge density on the vinylcyclopropane radical cation.

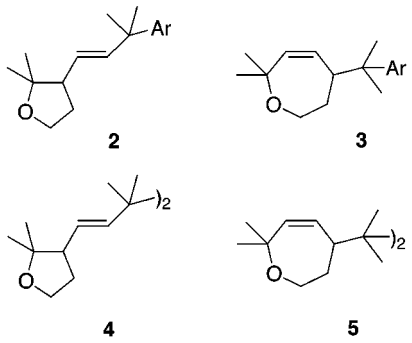
$$\mathbf{DCB/Phen} + \mathbf{D} \xrightarrow{h\nu} \mathbf{DCB}^{\bullet-} + \mathbf{D}^{\bullet+} + \mathbf{Phen} \quad (1)$$

$$\mathbf{D}^{\bullet+} + CH_3OH \rightarrow {}^{\bullet}[\mathbf{D}\text{-}OCH_3] + H^+ \quad (2)$$

$${}^{\bullet}[\mathbf{D}\text{-}OCH_3] + \mathbf{DCB}^{\bullet-} \rightarrow p\text{-}CN\text{-}C_6H_4\text{−}\mathbf{D}\text{-}OCH_3 + CN^- \quad (3)$$

Irradiation (350 nm) of an acetonitrile solution containing **DCB**, **Phen**, and **1** (a mixture of *cis*- and *trans*-isomers) led to the formation of two cyclic ethers, one bearing an aryl-substituted side chain (**2** or **3**), the other a related free-radical dimer (**4** or **5**), respectively, in a ratio of 3:1. The ^{1}H NMR chemical shifts establish certain structure elements. The first product (**2** or **3**) has two olefinic protons, $H_{1'}$ (5.34 ppm, dd, 15.53, 8.8 Hz) and $H_{2'}$ (5.66 ppm, d, 15.53 Hz). Two strongly deshielded (alkoxy) protons (3.81, 3.88 ppm, H_5) are coupled to two protons, (complex multiplets at 1.86, 2.09 ppm, H_4), which in turn are coupled to an allylic proton (2.43 ppm, dd, "q", 8.3, 8.3 Hz, H_3). In addition, two diastereotopic methyl groups (1.01, 1.22 ppm; 6H) appear upfield of two magnetically equivalent methyl groups (1.40 ppm, 6H).

The spectrum of the second product (**4** or **5**) is remarkably similar; only the signal of the two equivalent methyl groups is shifted to lower frequency (0.96 ppm). These data establish the connectivity of most carbons but fail to identify the ring size. The chemical shifts of alkoxy protons for five- and seven-membered cyclic ethers fall within a range, 3.5−3.8 ppm, too narrow to establish the ring size with any degree of confidence.[14,15] Thus, the alkoxy chemical shifts of the products fail to differentiate between the products formed via a five-membered and a seven-membered transition state.



The key to assigning the ring size of the cyclization products (and the site of nucleophilic attack) lies in the NMR signals of the two pairs of geminal methyl groups. The methyl pair originating in the three-membered ring remains adjacent to a chiral center regardless of the course of the reaction; they are expected to be magnetically distinct. The second pair, initially in the vinyl side chain, are attached to an allylic carbon, three C−C-bonds from the chiral center; they are most likely magnetically equivalent.

In the products potentially formed via the seven-center transition state ($\mathbf{1}^{\bullet+}$-7-TS), the two diastereotopic methyl groups are adjacent to the reactive free radical site. The different substituents introduced in this position will affect the chemical shifts for the methyl pair in the two products (**3** and **5**). On the other hand, the equivalent methyl groups will be five C−C bonds removed from the divergent substituents; their chemical shifts should experience little change.

In the product formed via a five-membered transition state ($\mathbf{1}^{\bullet+}$-5-TS), the diastereotopic methyl groups are attached to the tertiary alkoxy carbon of the cyclic ether, significantly distant from the coupling site of the allyl radical. Different substituents at the reactive site are not expected to affect their chemical shifts. Conversely, the two methyl groups originating in the vinyl side chain are connected directly to the carbon atom bearing either an aryl (**2**) or an alkyl group (**4**). These methyl signals should have substantially different chemical shifts for the two products, **2** and **4**.

The chemical shifts of the two diastereotopic methyl groups are identical for both isolated products and show a chemical shift difference, $\Delta\delta \sim 0.2$ ppm. These methyl groups must be close to the chiral center but far from the reactive site of the free radical intermediate. In contrast, the chemical shift of the equivalent methyl groups changes from 1.40 ppm in the aryl-bearing product to 0.96 ppm for the free-radical dimer. These methyl groups must be located close to the coupling site of the radical intermediate. These chemical shifts are incompatible with the seven-membered structures, **3** and **5**, and unambiguously identify the internal capture products as 2,2-dimethyl-3-(3-methyl-3-(*p*-cyanophenyl)-butenyl)tetrahydrofuran (**2**) and bis(3-methyl-1-(3-(2,2-dimethyltetrahydrofuranyl))-(*E*)-but-1-en-3-yl) (**4**). As an aside, we note that **4** has two chiral centers and likely exists as a mixture of diastereomers. However, this fact has no bearing on the primary mechanistic conclusion.

Discussion

The regiochemistry of the intramolecular capture of $\mathbf{1}^{\bullet+}$ is of significant interest. We will consider this feature in

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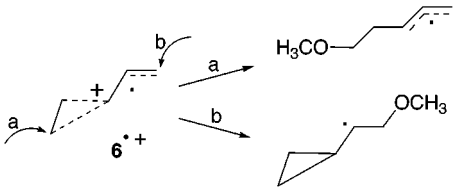
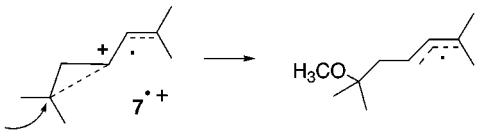
the light of the reactions of several terpenoid vinylcyclopropane radical cations with external nucleophiles[7,9] and in view of the intramolecular nucleophilic capture of various systems. The capture of vinylcyclopropane radical cations by external nucleophiles reveals several factors that may influence the regiochemistry of capture. Most importantly, the attack occurs at centers where both SOMO and LUMO have significant orbital coefficients, i.e., at a carbon bearing spin and charge density.[16,17] Once this electronic requirement is met, the attack is governed by thermodynamic factors; for example, it occurs with relief of ring strain and generates delocalized (allylic or benzylic) free radicals.[7,9]

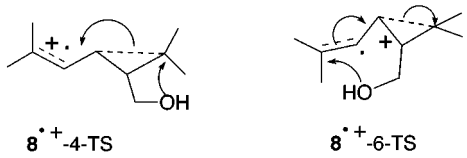
The unsubstituted prototype, vinylcyclopropane, $\mathbf{6}^{\bullet+}$, has significant orbital coefficients at the (degenerate) pair of secondary cyclopropane carbons and in the terminal vinyl position.[10] Radical cation, $\mathbf{6}^{\bullet+}$, is captured by external nucleophiles at both positions, giving rise to two different free-radical intermediates. However, attack at the cyclopropane ring is clearly preferred.[10]



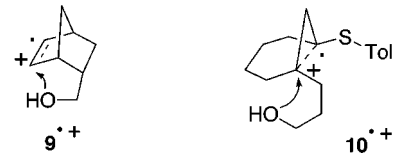
The degeneracy of the secondary carbons of $\mathbf{6}^{\bullet+}$ is removed by substitution at one of these carbons. For example, we have studied the electron-transfer photochemistry of a derivative of **6**, 2,2-dimethyl-1-(2-methyl-1-propenyl)cyclopropane (**7**). CIDNP effects observed during this reaction showed that the radical cation, $\mathbf{7}^{\bullet+}$, has spin density on both dimethyl-substituted carbons;[11] this conclusion was confirmed by ab initio calculations.[18−20] The dimethyl-substituted carbons also had strong orbital coefficients for both SOMO and LUMO (Figure 1). However, radical cation, $\mathbf{7}^{\bullet+}$, was captured by methanol exclusively at the quaternary cyclopropane carbon.[11]



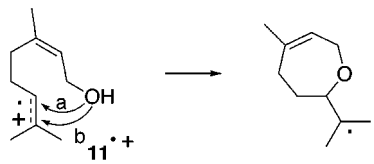
The calculated spin densities and orbital coefficients of $\mathbf{7}^{\bullet+}$ do not change significantly upon introduction of the tethered nucleophile: the results for *cis*-chrysanthemol radical cation, $\mathbf{8}^{\bullet+}$ (Figure 2), are very similar to those for $\mathbf{7}^{\bullet+}$. However, the reactions of $\mathbf{7}^{\bullet+}$ and $\mathbf{8}^{\bullet+}$ are significantly different: while the (intermolecular) capture of $\mathbf{7}^{\bullet+}$ occurs exclusively at the cyclopropane ring, the intramolecular capture of $\mathbf{8}^{\bullet+}$ involves only the terminal vinyl carbon.[11] Apparently, the four-membered transition state ($\mathbf{8}^{\bullet+}$-4-TS) required for attack on the cyclopropane ring is disfavored relative to a six-membered one ($\mathbf{8}^{\bullet+}$-6-TS). These findings suggest that intramolecular nucleophilic capture of radical cations, such as $\mathbf{1}^{\bullet+}$ or $\mathbf{8}^{\bullet+}$, may be governed by additional principles, such as ring strain in the transition state.



Several acyclic,[21−23] monocyclic,[11] or bicyclic[23−25] radical cations are captured intramolecularly by carboxylic acid[22] or alcohol functions.[11,22−25] For example, the radical cationic sites of $\mathbf{9}^{\bullet+}$ or $\mathbf{10}^{\bullet+}$ are captured by the internal alcohol functions via five-membered transition states.[22−24] The reactions involve either capture of a vacant p orbital ($\mathbf{9}^{\bullet+}$) or backside attack on a singly occupied Walsh orbital with "replacement" of a "free radical" ($\mathbf{10}^{\bullet+}$).



Two acyclic systems undergo intramolecular capture with formation of seven-membered rings. The radical cation ($\mathbf{11}^{\bullet+}$) of nerol or its dihydro derivative, citronellol radical cation, cyclize via seven-membered transition states (path a) and fail to form an eight-membered ring (path b).[23] Thus, both the $\mathbf{1}^{\bullet+}$-5-TS and $\mathbf{1}^{\bullet+}$-7-TS have precedent.



Nucleophilic attack generating a four-membered ring, to our knowledge, is observed only in the case of the bifunctional radical cation, $\mathbf{12}^{\bullet+}$, generated by C−C cyclization upon photoinduced electron transfer of nerol.[23] In other cases, capture via a four-membered transition state is avoided; in addition to the failure of $\mathbf{8}^{\bullet+}$ to form an oxetane ring, *cis*-verbenol, **13**, also failed to undergo intramolecular capture upon electron transfer.[26]

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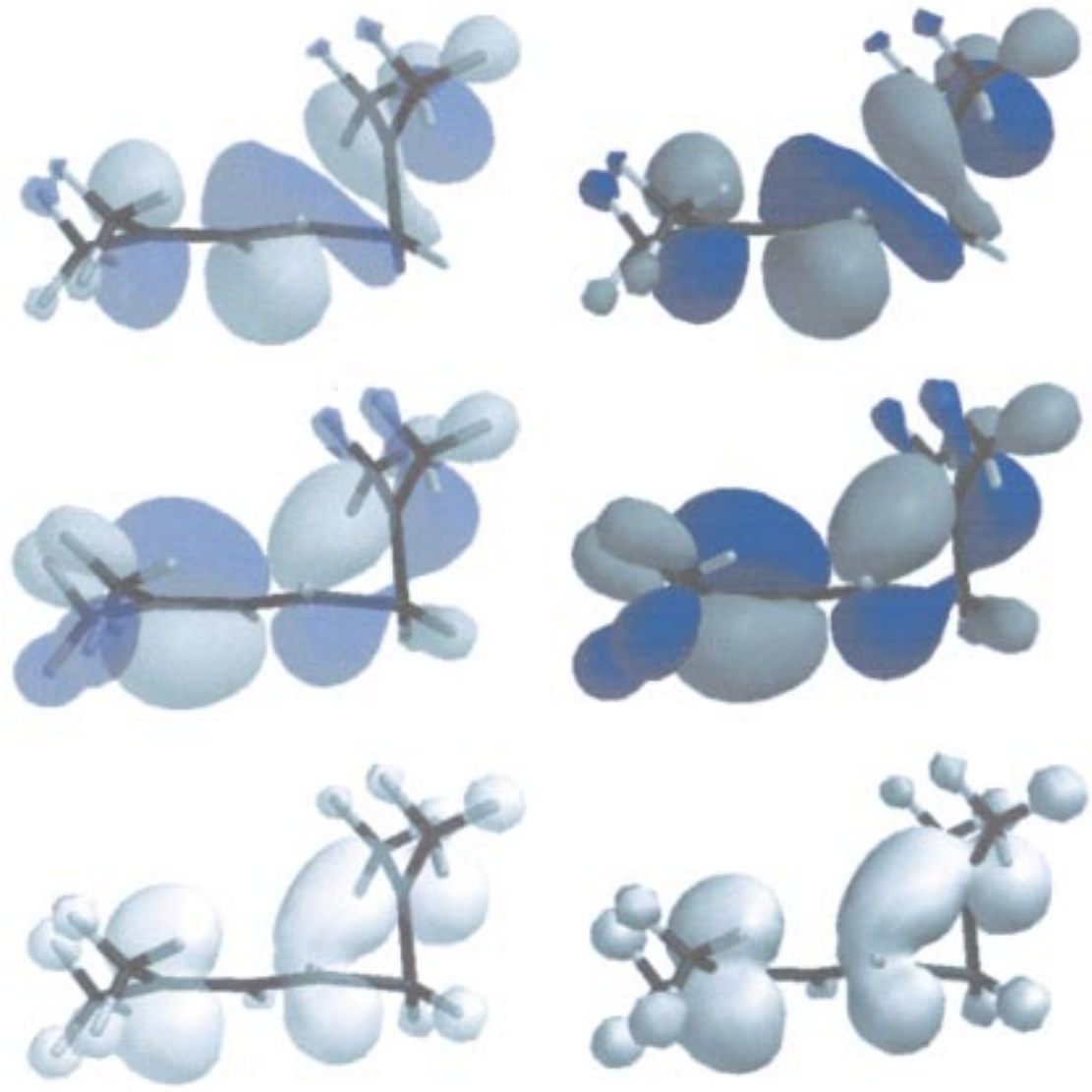
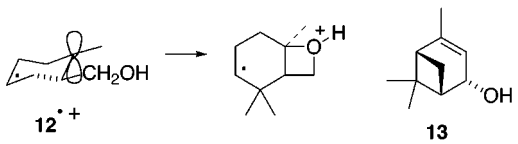


Figure 1. Pictorial representation of the spin density distribution of *anti*-2,2-dimethyl-1-(2-methyl-1-propenyl)cyclopropane radical cation (**7**$^{\bullet+}$) calculated by Spartan (bottom), its SOMO (center), and LUMO (top).



The sole cyclization involving a four-membered transition state involves capture of a vacant p orbital in **12**$^{\bullet+}$ by the tethered nucleophile; this reaction appears sterically less demanding than the backside S_N2-type attack "replacing" a free radical. This reaction appears to require a narrowly defined trajectory and should be particularly unfavorable in a rigid system such as **13**.

Compared to the various systems that either undergo cyclization (**9**−**12**) or fail to do so (**13**), the cyclizations of **1**$^{\bullet+}$ and its homolog, **8**$^{\bullet+}$, provide a consistent variation of structure elements. These systems allow for a meaningful comparison and, therefore, offer significant insight into the limiting requirements for the transition states of intramolecular nucleophilitic capture. The reactions of **1**$^{\bullet+}$ and **8**$^{\bullet+}$ differ in the size of the cyclic transition state and in the nature of the radical cationic site that is captured. Still, both **1**$^{\bullet+}$ and **8**$^{\bullet+}$ show pronounced regioselectivity; the failure to observe the isomers by GC or NMR suggests a preference of >20:1. Radical cation **8**$^{\bullet+}$ attacks the vinyl terminus exclusively via a six-membered transition state (**8**$^{\bullet+}$-6-TS); it avoids the four-membered transition state (**8**$^{\bullet+}$-4-TS) with attack on the cyclopropane ring. In contrast, the intramolecular capture of **1**$^{\bullet+}$ occurs at the quaternary cyclopropyl carbon. The hydroxyl group reacts in S_N2 fashion via a five-membered transition state (**1**$^{\bullet+}$-5-TS); it fails to capture the vinylic site via a seven-membered transition state (**1**$^{\bullet+}$-7-TS).

The preference of **1**$^{\bullet+}$ for the five-membered transition state, forming free radical **14**$^{\bullet}$, can be ascribed to favorable entropy as well as enthalpy factors. The release of strain upon cleaving the cyclopropane ring provides a significant driving force. The failure of **8**$^{\bullet+}$ to react via the four-membered transition state also may have two reasons: high angle strain in the transition state, and a trajectory of approach, which differs significantly from the ideal "backside" attack on the cyclopropane Walsh orbital. The short tether of **8**$^{\bullet+}$ holds the OH function well

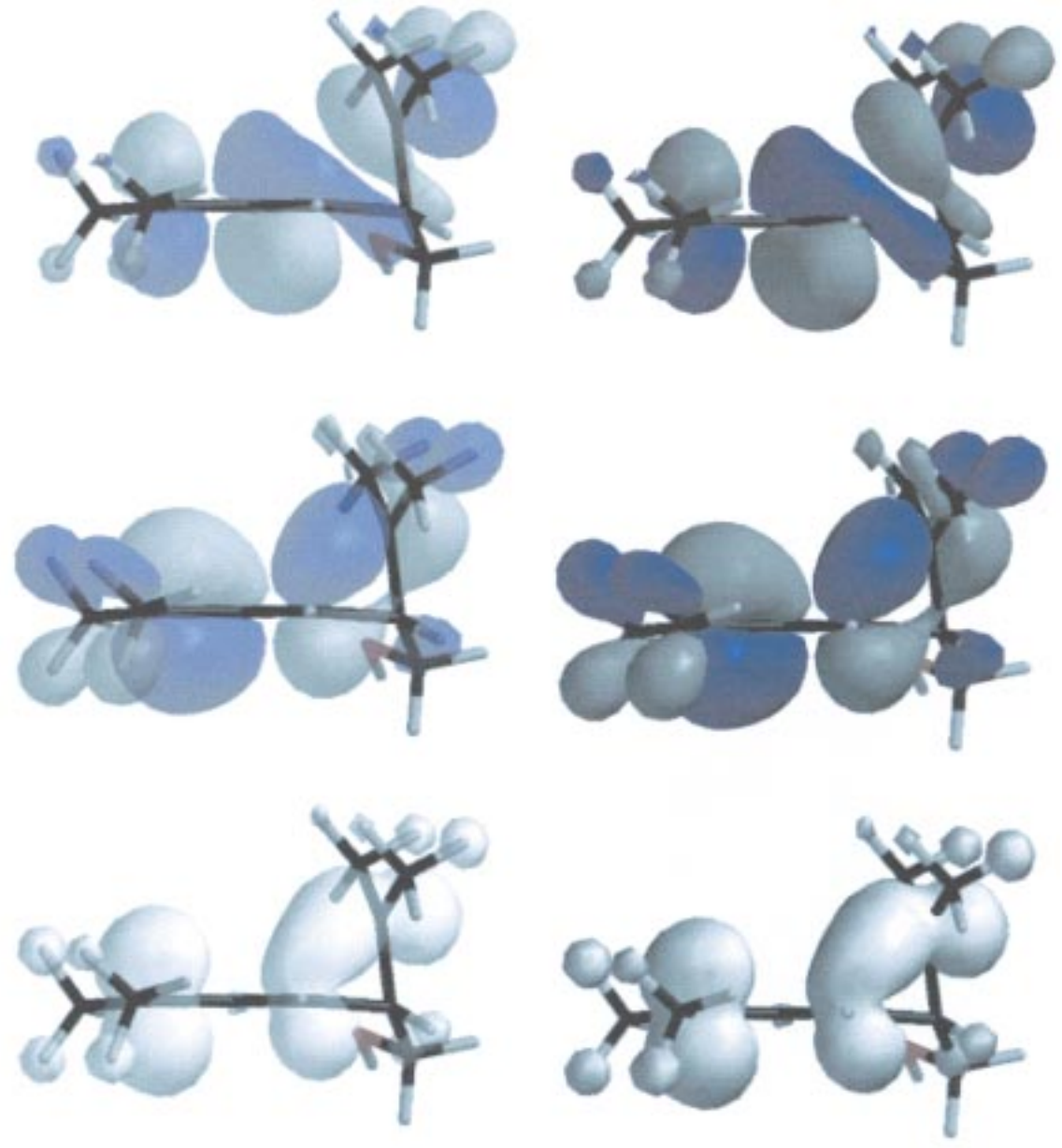
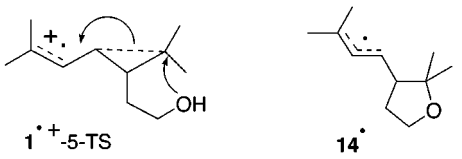
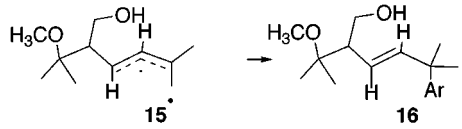


Figure 2. Pictorial representation of the spin density distribution of chrysanthemol radical cation (*cis*-**8**$^{\bullet+}$) calculated by Spartan (bottom), its SOMO (center), and LUMO (top).

below the plane of the cyclopropane carbons, far from the back lobe of the Walsh orbital, attack on which would "release" an allylic free radical.

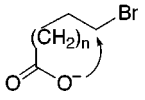


Once formed, the free radical intermediates, e.g., **14**$^{\bullet}$, may couple with **DCB**$^{\bullet-}$; subsequent loss of cyanide ion then generates NOCAS adducts, i.e., **2**. Alternatively, two radical intermediates combine at the planar vinyl terminus forming, for example, **4**. The regiospecific coupling at an apparently congested center, giving rise to **2** and **4**, is surprising only upon casual inspection; clearly, the alternative allyl center is more severely congested. A similar regiospecific reaction at a similarly congested allyl free radical was observed between **15**$^{\bullet}$ (formed via intermolecular capture of **8**$^{\bullet+}$ by methanol) and **DCB**$^{\bullet-}$; this reaction generated **16** exclusively.

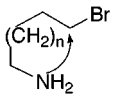


A comparison of the intramolecular capture of the radical cations, **1**$^{\bullet+}$ and **8**$^{\bullet+}$, with cyclization reactions occurring via intramolecular nucleophilic substitution reveals a correlation between the relative rates and the ring size of transition states and products. In intramolecular substitution reactions, such as a the displacement of a bromine by a carboxylate anion (forming a lactone) or by an amino group (leading to a cyclic amine), the

formation of products with five- (**17**, **18**, $n = 1$) and six-membered rings ($n = 2$) is clearly favored over four- or seven-membered rings (**17**, **18**, $n = 0$ or 3).[27−29]



17



18

In the case of the amino compound, **18**, formation of the six-membered ring ($n = 2$) is preferred over the four-membered ring ($n = 0$) by a factor of 1000; the rate for the formation of five-membered ring ($n = 1$) is 50000 times larger than that of the seven-membered one ($n = 3$).

In summary, the electron-transfer-induced cyclization of homochrysanthemol, **1**, and chrysanthemol, **8**, proceed via five- and six-membered transition states, respectively. Substrate **1** reacts by intramolecular "substitution" at the quaternary cyclopropane carbon, following the pattern set by the intermolecular reactions of various vinylcyclopropane radical cations. In light of these results, the failure of **8** to cyclize at the quaternary cyclopropane carbon must be ascribed to the unfavorable four-membered transition state required for this reaction. Apparently, the five-membered transition state used by $\mathbf{1}^{\bullet+}$ and the six-membered transition state used by $\mathbf{8}^{\bullet+}$ are significantly favored over the alternative ones. These results uniquely delineate the preferred cyclization pattern of intramolecular nucleophilic capture.

Experimental Section

Homochrysanthemol. (1,1-Dimethyl-2-(2-methyl-1-propenyl)-3-(2-hydroxyethyl)cyclopropane, **1**) was prepared by Arndt−Eistert homologation of chrysanthemic acid.[30] Thionyl chloride (0.25 mol, 29.75 g, 18.2 mL) was added slowly to a suspension of chrysanthemic acid (0.179 mol, 30 g, mixture of trans:cis ~9:1) in 100 mL of dry petroleum ether and stirred for 1 h. Excess thionyl chloride and solvent were removed under vacuum. The crude acid chloride was added to 300 mL of a diazomethane solution (in Et_2O:THF, prepared from DIAZALD (Aldrich, 0.6 mol)),[31] and stirred for 2 h; excess diazomethane and solvent were removed under vacuum.

The crude diazoketone was dissolved in 100 mL of dry methanol, 100 mL of silver benzoate catalyst solution [prepared from benzoic acid (0.25 mol, 30.53 g), NaOH (0.25 mol, 10.0 g), $AgNO_3$ (0.25 mol, 42.5 g) and 200 mL dry triethylamine][32] was added, and the mixture was refluxed for 2 h. The solvent was removed by short-path distillation, 200 mL of ether was added, and the mixture washed with dilute aqueous $NaHCO_3$, dried over K_2CO_3, and distilled to give 22 g of crude homochrysanthemic acid methyl ester ($bp_{0.6}$ 65−75 °C, 0.112 mol, 63% yield). Hydrolysis with aqueous KOH, reduction of the resulting acid with $LiAlH_4$ in Et_2O, and column chromatography on silica gel with petroleum ether furnished homochrysanthemol, **1** (10 g, 0.06 mol, 34% yield based on chrysanthemic acid).

Electron-Transfer Photochemistry of Homochrysanthemol. Acetonitrile solutions (50 mL) solutions containing 0.24 M **DCB** (1.54 g, 0.012 mol), 0.06 M **Phen** (0.534 g, 0.003 mol), and 0.24 M **1** (2.02 g, ~2.0 mL, 0.012 mol) were placed in a 30-mm i.d. tube and purged with argon for 15 min. The solution was then cooled to −10 °C (central cooling finger) and irradiated for 5.5 h at 350 nm.

Irradiation (350 nm) of an acetonitrile solution containing 0.24 M **DCB**, 0.048 M **Phen**, and 0.24 M homochrysanthemol (mixture of cis and trans, 77% conversion after 5.5 h) led to the formation of two products, a cyclic ether with an aryl-substituted side chain (**2**) and a related free-radical dimer (**4**), in yields of 65 and 20%, respectively.

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Supporting Information Available: NMR spectral assignments for the starting material, **1**, and products **2** and **4** (including ^{1}H NMR spectra of products **2** and **4**); Cartesian coordinates, calculated atomic energies, bond lengths, spin densities and hyperfine coupling constants (hfcs) for 2,2-dimethyl-1-(2-methyl-1-propenyl)cyclopropane radical cation (*anti*-$\mathbf{7}^{\bullet+}$), and *cis*- and *trans*-chrysanthemol radical cation (*cis*- and *trans*-$\mathbf{8}^{\bullet+}$). This material is available free of charge via the Internet at http://pubs.acs.org.

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