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Bicyclobutonium Ions in Biosynthesis − Interconversion of Cyclopropyl-Containing Sterols from Orchids

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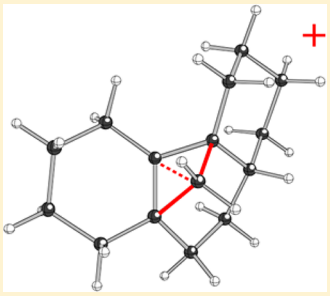
Supporting Information

ABSTRACT: Theoretical investigation of cyclopropane-to-cyclopropane rearrangements of sterols indicates a role for highly delocalized bicyclobutonium ions in biosynthesis.



INTRODUCTION

The interconversion of homoallyl, cyclopropylcarbinyl, cyclobutyl, and bicyclobutonium carbocations (Figure 1, top) has been of interest for more than half of a century.[1] Extensive work by Roberts, along with important studies by Schleyer, Saunders, Wiberg, Baldwin, Olah, Schindler, and others has led to the conclusion that the classical cyclobutyl cation is not a minimum (intermediate) in solution and the gas phase, whereas a bicyclobutonium ion with 3-center 2-electron bonding is.[1] Both C_1 and C_s symmetric versions have been implicated as minima (Figure 1, center). The curvature of the potential energy surface for the bicyclobutonium ion, like that for other nonclassical (i.e., carbonium) ions,[2] can, however, be altered by the attachment of substituents. A bicyclobutonium ion has been postulated as an intermediate en route to a bicyclobutane-containing fatty acid (Scheme 1), although further investigation is necessary to confirm this conjecture.[3] Related cations have also been invoked in isoprenoid coupling reactions.[4] Herein we describe the results of quantum chemical calculations[5] on a bicyclobutonium ion involved in the biosynthesis of complex, polycyclic terpenoids (Scheme 2).

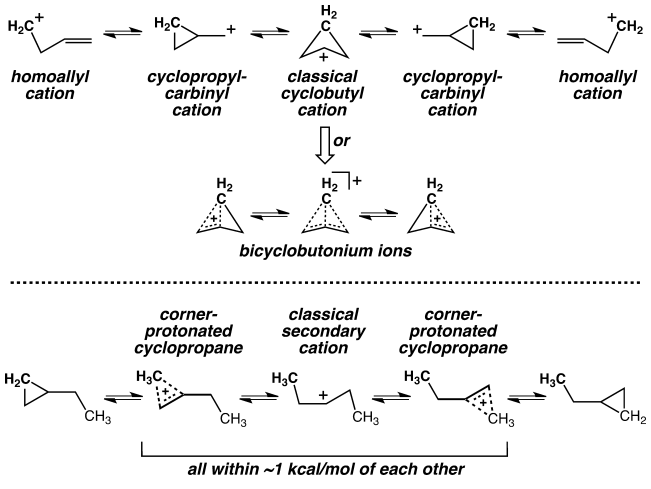
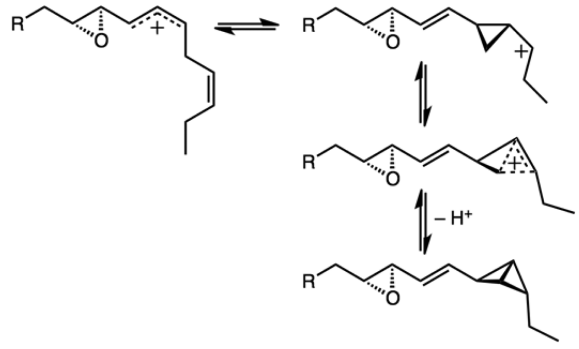


Figure 1. Top: Interconversion of a variety of $C_4H_7^+$ carbocations; although connected in this depiction by equilibrium arrows, some structures may constitute resonance forms and some may not be minima on the $C_4H_7^+$ potential energy surface. Bottom: Previously investigated mechanism[11] for interconversion of cyclopropanes in sterol side chains.

Scheme 1. Proposed Mechanism for Formation of a Bicyclobutane-Containing Fatty Acid [R = $(CH_2)_6CO_2CH_3$]



Cyclopropane rearrangements have long been studied in sterols, from *i*-cholesterol[6] to marine sterol biosynthesis.[7] The Asian orchid *Nervilia purpurea*, which contains side chain alkylated sterols more commonly encountered in marine

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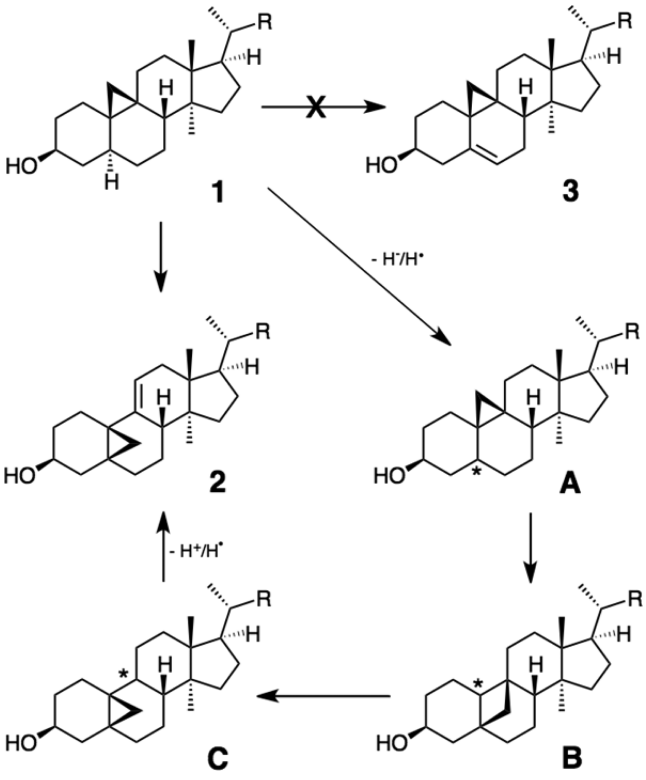
Scheme 2. Conversion of 1 to 2[a]



[a]The * indicates the position of either a carbocation or radical center.

sponges, also produces cyclopropyl sterol nuclei **1** and **2** (Scheme 2).[8] While **1** (pollinastanol) is a relatively common plant sterol that comes from the demethylation of cycloartenol, **2** is only found in this one orchid species. The biosynthesis of **2** from **1** may involve the action of a repurposed 5-desaturase.[9] The unrearranged product of 5-desaturation (**3**) is not known. Rearrangement of cyclopropylcarbinyl intermediate **A**, either as a carbocation or radical, could lead to an isomeric cyclopropylcarbinyl intermediate **C** and from there, after loss of a proton or hydrogen atom, to **2**. In the absence of an appropriately placed base or hydrogen atom acceptor this rearrangement might lead to nucleophilic capture and hence mechanism-based enzyme inhibition.[10] In this manner, both cyclopropyl sterols **1** and **2** could provide chemical defenses to the plant. Although this pathway is presently speculative, calculations could help to delimit its likelihood.

RESULTS AND DISCUSSION

The pathway from **A** to **2** can be formulated, as in Scheme 2, as two sequential 1,2-alkyl shifts with an intermediate cyclobutyl cation or radical. Herein we examine the feasibility of these mechanistic scenarios and provide evidence that a bicyclobutonium cation is actually the likely intermediate in this cyclopropane-to-cyclopropane rearrangement. Note that this mechanism differs from that examined previously for cyclopropane-to-cyclopropane rearrangements of sterol side chains (Figure 1, bottom), which involves initial protonation of a cyclopropane rather than desaturation of an adjacent methine group.[11]

The rearrangement of a model system for carbocation **A** (consisting of the A, B, and C rings of the sterol nucleus and fused cyclopropane) is shown in Figure 2;[5] although lacking the

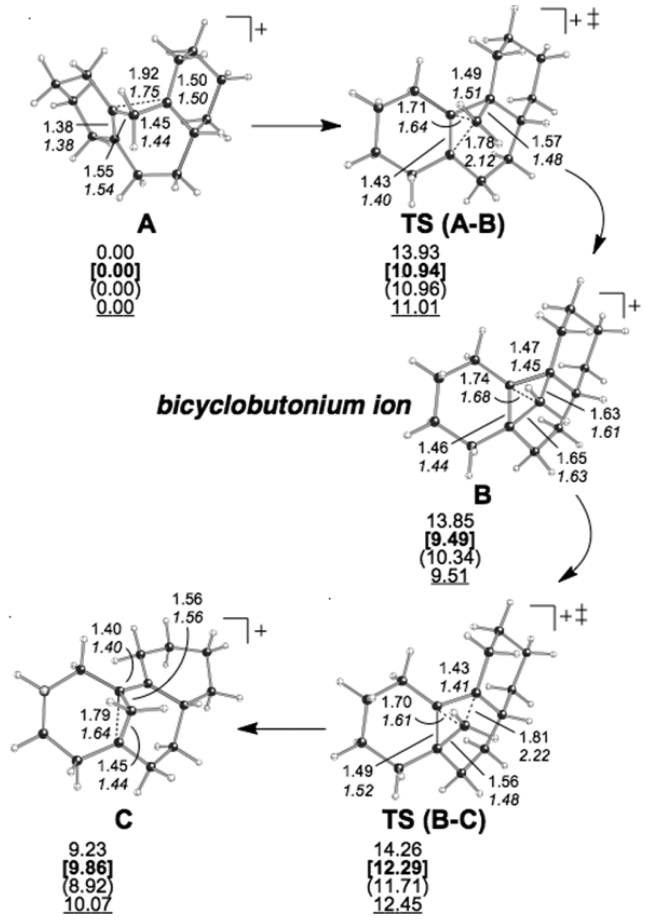


Figure 2. Rearrangement of **A** to **C** (* = +).[5] Selected distances in Å (B3LYP/6-31+G(d,p) in normal text, BB1K/6-31+G(d,p) in italics; results with other functionals are included in the Supporting Information). B3LYP/6-31+G(d,p) ZPE-corrected electronic energies in normal text, BB1K/6-31+G(d,p) ZPE-corrected electronic energies in bold and brackets, mPW1PW91/6-31+G(d,p) ZPE-corrected electronic energies in parentheses, MPWB1K/6-31+G(d,p) ZPE-corrected electronic energies underlined.

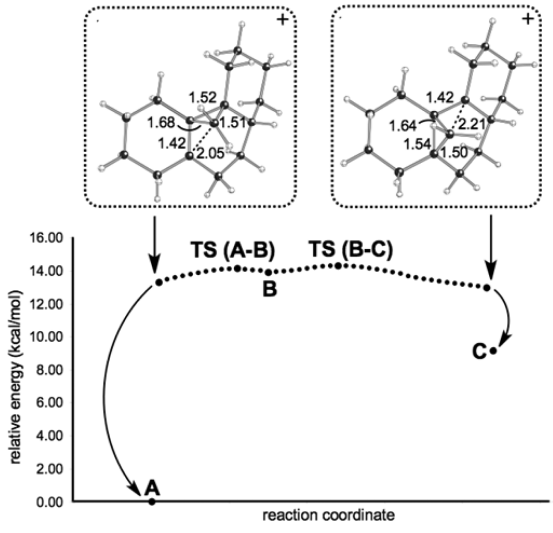


Figure 3. IRC plot (B3LYP/6-31G(d)) for **TS(A-B)** and **TS(B-C)**.[5] Energies are relative to that of **A** and do not include ZPE corrections (since these are not computed in an IRC calculation). The structures in boxes (not stationary points) appear along the reaction coordinate.

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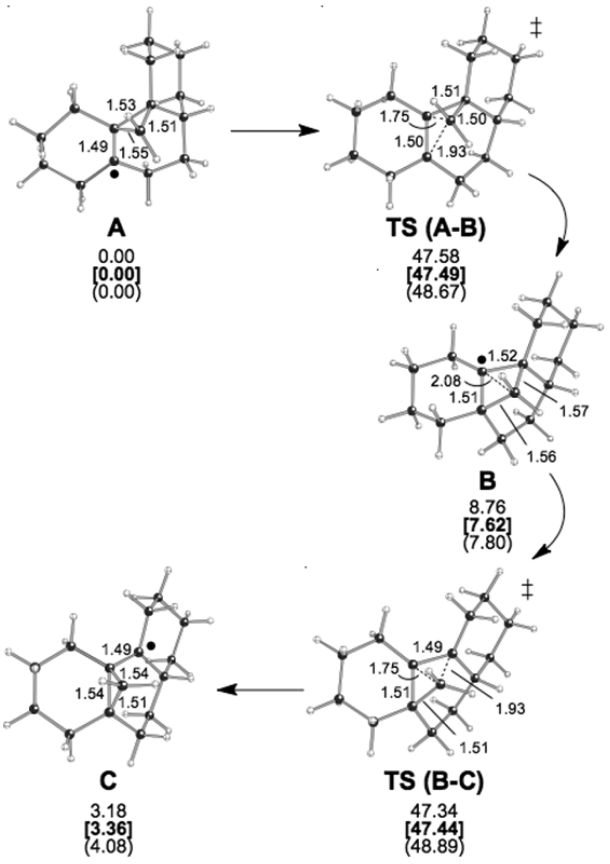

Figure 4. Radical rearrangement of **A** to **C** (* = •).[5] Selected distances in Å (B3LYP/6-31+G(d,p)). B3LYP/6-31+G(d,p) ZPE-corrected electronic energies in normal text, mPW1PW91/6-31+G(d,p)//B3LYP/6-31+G(d,p) single point energies in bold and brackets, MPWB1K/6-31+G(d,p)//B3LYP/6-31+G(d,p) single point energies in parentheses.

D ring and associated methyl groups, this model captures the conformation of the C ring in sterol **1**. Carbocation **A** is significantly delocalized at all levels examined, with bond lengths and angles consistent with it being a hybrid of a cyclopropylcarbinyl cation and a homoallylic cation. Similar structures have been observed as intermediates in other terpene-forming carbocation rearrangements.[12] Carbocation **A** can be transformed into carbocation **B** with a small barrier (<14 kcal/mol at all theoretical levels examined). Carbocation **B** can be transformed into carbocation **C**, which again resembles a hybrid of a cyclopropylcarbinyl cation and a homoallylic cation, with a very small barrier. Carbocation **B**, a bicyclobutonium ion, is predicted to have a central C···C bond distance of 1.67−1.74 Å, depending on the level of theory used, consistent with the delocalization expected for a bicyclic ion. This carbocation resides in a very shallow minimum (significantly less than 3 kcal/mol deep on either side of **B** with most levels of theory), i.e., all bond forming/breaking events in this rearrangement occur in a process that is close to concerted, albeit very asynchronous,[13] with a plateau in the vicinity of **B** and **C** (see intrinsic reaction coordinate [IRC] plot in Figure 3).[5g,h] Although cation **C** is approximately 9−10 kcal/mol higher in energy than carbocation **A**, the alkene derived from **C** (model of **2**) is only 3−4 kcal/mol higher in energy than that derived from **A** (model of **3**; B3LYP/6-31+G(d,p)), suggesting that both structures should be accessible; which one predominates would likely be a result of the positioning of the active site base, i.e., **A**, **B**, and **C** would likely be in equilibrium until deprotonation occurs.[14]

Structures and energetics for the **A**-to-**B**-to-**C** radical rearrangement are shown in Figure 4. Much less delocalization is observed for these structures (as indicated by the bond lengths shown), as are much higher barriers. Given that the overall barrier for this process is predicted to be >45 kcal/mol (at all levels of theory examined), this radical rearrangement is not likely to occur in a biological environment, even with enzymatic intervention.

■ CONCLUSIONS

Computations on the **A**-to-**B**-to-**C** cyclopropane-to-cyclopropane rearrangement indicate that a carbocation pathway is greatly favored over a radical pathway and that this carbocation pathway involves bicyclobutonium species. Again, a structure considered by many to be a physical organic curiosity is shown to be an energetically viable species in a biologically relevant context.[16]

■ ASSOCIATED CONTENT

Supporting Information

Coordinates and energies for all computed structures, IRC plots, full Gaussian citation. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(5) Calculations were performed with GAUSSIAN03 or GAUSSIAN09.[5a] Geometries were optimized using the B3LYP, BB1K, mPW1PW91, and MPWB1K methods with the 6-31+G(d,p) basis sets.[5b−f,i,j,o] All stationary points were characterized as minima or transition-state structures using frequency calculations at the same level. Intrinsic reaction coordinate (IRC) calculations were used for further characterization of transition-state structures.[5g,h] Single point energies with various methods, including MP2,[5k,l] are included in the Supporting Information.[5i] All reported energies include zero-point energy corrections (unscaled). The validity of these computational approaches for examining carbocation rearrangements relevant to biosynthesis is well-established.[5m] Structural images were created with *Ball&Stick*.[5n] (a) Frisch, M. J.et al., Gaussian, Inc.: Wallingford, CT, full reference in Supporting Information. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372−1377. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (d) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789. (e) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623−11627. (f) Tirado-Rives, J.; Jorgensen, W. L. *J. Chem. Theory Comput.* **2008**, *4*, 297−306. (g) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523−5527. (h) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363−368. (i) Matsuda, S. P. T.; Wilson, W. K.; Xiong, Q. *Org. Biomol. Chem.* **2006**, *4*, 530−543. (j) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 6908−6918. (k) Pople, J. A.; Raghavachari, K.; Schlegel, H. B.; Binkley, J. S. *Int. J. Quantum Chem., Quant. Chem. Symp.* **1979**, *S13*, 225−241. (l) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1988. (m) Tantillo, D. J. *Nat. Prod. Rep.* **2011**, *28*, 1035−1053. (n) Müller, N.; Falk, A. *Ball & Stick 4.0a12*, molecular graphics software for MacOS; Johannes Kepler University of Linz: Linz, Austria, 2004. (o) Zhao, Y.; Lynch, B. J.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 2715−2719.

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