Mechanism of Cyclopropane−Cyclopropane Rearrangements in Marine Sterol Biosynthesis: Ab Initio Calculations on Protonated Ethylcyclopropane

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Long known to be important in sterol biosynthesis,[1] carbocation rearrangements are believed to account for the unusual cyclopropane rings in the side chains of sterols of marine origin.[2] Unprecedented protonated cyclopropane to protonated cyclopropane rearrangement mechanisms were proposed. These are now supported by ab initio calculations on the basic model system which reveal a very flat potential energy surface for the degenerate rearrangement of protonated ethylcyclopropane (Figure 1).

Marine sponges of the order Haplosclerida contain an assortment of sterols bearing cyclopropyl rings in their side chains (Figure 2, **1**, **2**). A biosynthetic theory based on structural considerations was put forward by Proudfoot and Djerassi which postulated the protonated cyclopropane form of dihydrocalysterol as a central intermediate (Figure 2, **3**).[3] This intermediate (**3**) is formed not by enzymatic protonation of dihydrocalysterol (**1**)[4] but, unexpectedly, during the metalloenzyme-catalyzed dehydrogenation of clionasterol (**4**).[5] The initial secondary carbocation thought to be generated at C-23 (**5**) can give rise to the requisite protonated cyclopropane (**3**) by ring closure. According to the biosynthetic theory, the protonated dihydrocalysterol (Figure 2, **3**), once formed, can give rise to a new protonated cyclopropane (**6**) through a backside nucleophilic attack of a methyl group on the protonated cyclopropyl ring. Simple deprotonation of the protonated cyclopropane intermediates leads to the observed products (**1**, **2**). This same novel rearrangement also explains the formation of other isomeric cyclopropyl sterols found in these sponges. This mechanism is attractve since it accounts for the complex stereochemical interrelationships of these sterols.

Isotopic labeling experiments support this biosynthetic scheme.[3b,4] However, although the hypothetical mechanism accounts for the facts concisely, it has remained uncertain whether the reaction actually takes place via the proposed protonated cyclopropane to protonated cyclopropane rearrangement or via another, less appealing, but perhaps less unusual, nonconcerted mechanism. Ab initio calculations were carried out in order to shed light on this question.

The simplest model degenerate rearrangement would convert one ethylcyclopropane (Figure 3, **7**) into another (**7′**) via the intermediacy of the equivalent protonated cyclopropanes (**8** and **8′**) as well as the 3-pentyl cation (**9**). At all levels of ab initio theory examined (HF/6-31G*, MP2fc/6-31G*, MP2fc/6-31G**, Becke3LYP/6-31G* optimizations, and MP4sdtq/6-31G**//MP2/6-31G**), carbocations **8** and **9** are both minima of nearly the same energy and are separated by a very low barrier.[6] Hence, the potential energy surface is very flat and the

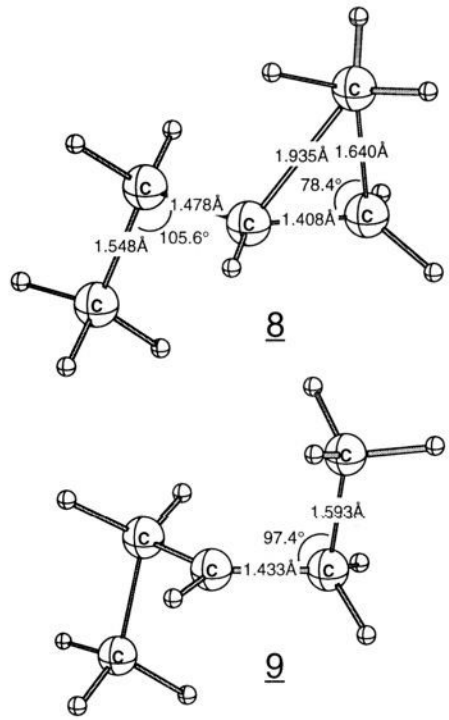

Figure 1. Calculated structures of intermediates in the degenerate rearrangement of protonated ethylcyclopropane.

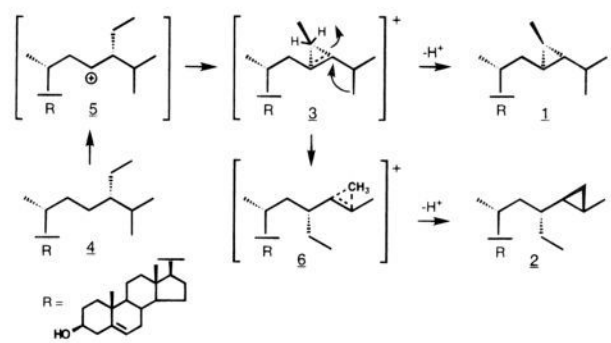

Figure 2. Biosynthesis of cyclopropyl marine sterols.

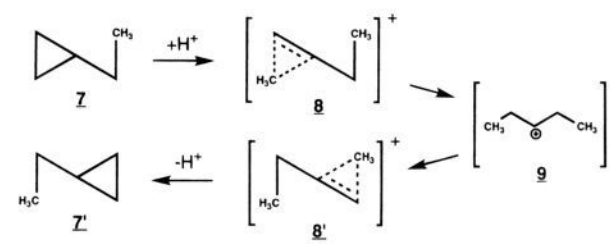

Figure 3. Degenerate rearrangement of protonated ethylcyclopropane.

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(1) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.

(2) For a review of marine sterol biosynthesis, see: Giner, J.-L. *Chem. Rev.* **1993**, *93*, 1735. Of related interest, see: White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 6224.

(3) (a) Proudfoot, J. R.; Djerassi, C. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1283. (b) Proudfoot, J. R.; Catalan, C. A. N.; Djerassi, C.; Sica, D.; Sodano, G. *Tetrahedron Lett.* **1986**, *27*, 423. (c) Proudfoot, J. R.; Li, X.; Djerassi, C. *J. Org. Chem.* **1985**, *50*, 2026.

(4) Doss, G. A.; Proudfoot, J. R.; Silva, C. J.; Djerassi, C. *J. Am. Chem. Soc.* **1990**, *112*, 305.

(5) (a) Giner, J.-L.; Silva, C. J.; Djerassi, C. *J. Am. Chem. Soc.* **1990**, *112*, 9626. (b) Silva, C. J.; Giner, J.-L.; Djerassi, C. *J. Am. Chem. Soc.* **1992**, *114*, 295.

(6) *E* (HF/6-31G*): **8** = −195.459 70 au, **9** = −195.459 69 au. *E* (MP2fc/6-31G*): **8** = −196.092 19 au, **9** = −196.090 92 au, TS(C1) −196.090 87 au. *E* (MP2fc/6-31G**): **8** = −196.177 96 au, **9** = −196.176 34 au. *E* (MP4sdtq/6-31G*//MP2fc/6-31G**): **8** = −196.173 50 au, **9** = −196.173 76 au. *E* (Becke3LYP/6-31G*): **8** = −196.851 21 au, **9** = −196.851 27 au. ZPE (Becke3LYP/6-31G*): **8** = 93.28 kcal/mol, **9** = 93.40 kcal/mol.

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interconversion of **8** and **8′** is much more rapid than other rearrangements which are known to occur in $C_5H_{11}^+$ cations (particularly from the work of Saunders) and to have higher barriers.[7] Under stable ion conditions, the tertiary pentyl cation is the most stable $C_5H_{11}^+$ isomer, but degenerate rearrangements (which scramble the hydrogens and carbons) are observable by dynamic NMR. Both secondary carbocations and protonated cyclopropanes are implicated mechanistically.[7] Experimental and computational results of Wiberg and Kass show that protonation of alkyl-substituted cyclopropanes at unsubstituted carbons is preferred somewhat.[8]

The ab initio structures (Figure 1) reveal why **8** and **9** interconvert so easily: both have nearly the same geometries! Due to the strong double hyperconjugation involving both methyl groups in **9** (C_2 symmetry), the C-1, C-2, C-3 angle is only 97°. (Close analogies are found in the structures of the propyl (C_2)[9] and cyclopentyl (C_2)[10] cations.) In **8**, the corresponding CCC angle is 78.4°, due to unsymmetrical substitution of protonated cyclopropane. The C_1 2-butyl cation structure[11] provides a direct analogy. The "top−bottom" mechanism of the nonamethylcyclopentyl cation automerization provides a nice experimental example of preferred backside methyl group rearrangement.[12]

As is evident from such low activation barriers, protonated cyclopropane to protonated cyclopropane rearrangements can take place very rapidly under the enzymatic conditions of a marine sponge dehydrogenase. This unexpected chemical reaction found in nature may reflect the short lifetimes of the carbocations involved in the proposed biosynthetic mechanism.

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(7) (a) Saunders, M.; Rosenfeld, J. *Acc. Chem. Res.* **1973**, *6*, 53. (b) Saunders, M.; Jimenez-Vazquez, H. A. *Chem. Rev.* **1991**, *91*, 375.

(8) Wiberg, K. B.; Kass, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 988.

(9) (a) Koch, W.; Liu, B.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 3479. (b) Koch, W.; Schleyer, P. v. R.; Buzek, P.; Liu, B. *Croat. Chem. Acta* **1992**, *65*, 655.

(10) Schleyer, P. v. R.; Carneiro, J. W. d. M.; Koch, W.; Raghavachari, K. *J. Am. Chem. Soc.* **1989**, *111*, 5475.

(11) (a) Sieber, S.; Buzek, P.; Schleyer, P. v. R.; Koch, W.; Carneiro, J. W. d. M. *J. Am. Chem. Soc.* **1993**, *115*, 259. (b) Buzek, P.; Schleyer, P. v. R.; Sieber, S.; Koch, W.; Carneiro, J. W. d. M.; Vancik, H.; Sunko, D. E. *J. Chem. Soc., Chem. Commun.* **1991**, *10*, 671. (c) Carneiro, J. W. d. M.; Schleyer, P. v. R.; Koch, W.; Raghavachari, K. *J. Am. Chem. Soc.* **1990**, *112*, 4046.

(12) (a) Mayr, H.; Koschinsky, R. *J. Am. Chem. Soc.* **1989**, *111*, 2305. (b) Sorensen, T. S.; Whitworth, S. W. *J. Am. Chem. Soc.* **1990**, *112*, 6647.