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Biomimetic rearrangement of the 2-cyclopentyl-2-propyl cation

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ABSTRACT: In order to investigate the mechanism of the five-membered ring enlargement in carbocation intermediates in steroid biosynthesis, the rearrangement processes in a model carbocation, the 2-cyclopentyl-2-propyl cation **5**, were followed by means of ^{1}H and ^{13}C NMR spectroscopy. Carbocations **5A** and **5B** were prepared in SbF_5–SO_2ClF–SO_2F_2 from the corresponding alcohol precursors. At about −100 °C a ring enlargement process takes place to give the 1,2-dimethylcyclohexyl cation **7**. Quantum chemical calculations of model carbocation structures **5A, 5B, 6** and **7** were carried out at the HF/6–31G(d) and B3LYP/6–31G(d) levels of theory. Copyright © 2000 John Wiley & Sons, Ltd.
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KEYWORDS: carbocations; rearrangement; ring expansion; NMR spectroscopy; quantum-chemical DFT calculations

It is well established that all steroid hormones and triterpenoids arise from 2,3-epoxysqualene in enzymatic cyclization reactions.[1] The six-membered C ring of the steroid structure is obtained by expansion of the initially formed five-membered ring of the tricyclic cation **1** (Scheme 1).[2] During the biosynthesis of phytosterols, the products arise from a common cation intermediate, the dammarenyl cation **3** (Scheme 1). The key step again is the expansion of the five-membered ring, which results in the formation of the baccharenyl cation **4**.[3] Jenson and Jorgensen have rationalized by quantum chemical calculations the formation and expansion of the five-membered C ring.[4]

To obtain a closer insight into the ring expansion reaction in this work we investigated suitable model carbocations in superacid media using NMR spectroscopy. The 2-cyclopentyl-2-propyl cation **5A** (see Scheme 2) is a simple model suitable for investigating the rearrangement of the tricyclic cation **1** and the dammarenyl cation **3**, as emphasized with thick bonds in Scheme 1. The cation **5** was prepared by the molecular beam method[5] in SbF_5–SO_2F_2–SO_2ClF from the alcohol precursor either 2-cyclopentyl-2-propanol or 1-(2-propyl)cyclopentanol.

There are five resonances in the ^{13}C NMR spectrum at −120 °C, which is consistent with the clean formation of only carbocation **5**. The NMR chemical shifts at −120 °C are δ (ppm) 329.73 (C-1, d) 66.86 (C-1, d) 58.33 (C-2, t), 26.71 (C-3, t) and 21.03 (C-2, q). These shifts are temperature dependent, showing that the cation undergoes a rapid non-degenerate hydride shift between the 2-cyclopentyl-2-propyl cation **5A** and the 1-(2-propyl)-cyclopentyl cation **5B**. The relative shieldings of the carbons C-2 and C-2′ next to the carbocation centers C-1 or C-1′, respectively, indicate that the equilibrium favors the isomer **5B** which has the charge located on the endocyclic carbon C-1. The signal for the methylene carbons C-2 are shifted significantly more downfield than those for the methyl groups C-2′. This result is in accord with earlier conclusions by Okazava and Sorensen[6] and M. Saunders (Yale University, unpublished results)[7] that structure **5B** is more stable than structure **5A**.

At about −100 °C four new signals appear in the ^{13}C NMR spectrum and the averaged peaks for **5A/5B** gradually disappear (Fig. 1), indicating that an additional rearrangement process takes place. After about 45 min, the spectrum consists of four signals only, at δ (ppm) 197.22, 57.22, 36.24 and 27.43. The chemical shifts of these signals are not temperature dependent. The spectrum is consistent with the formation of the 1,2-dimethylcyclohexyl cation **7**, in which a rapid degenerate hydride shift occurs over a low barrier [$\Delta G^{\ddagger}$ =

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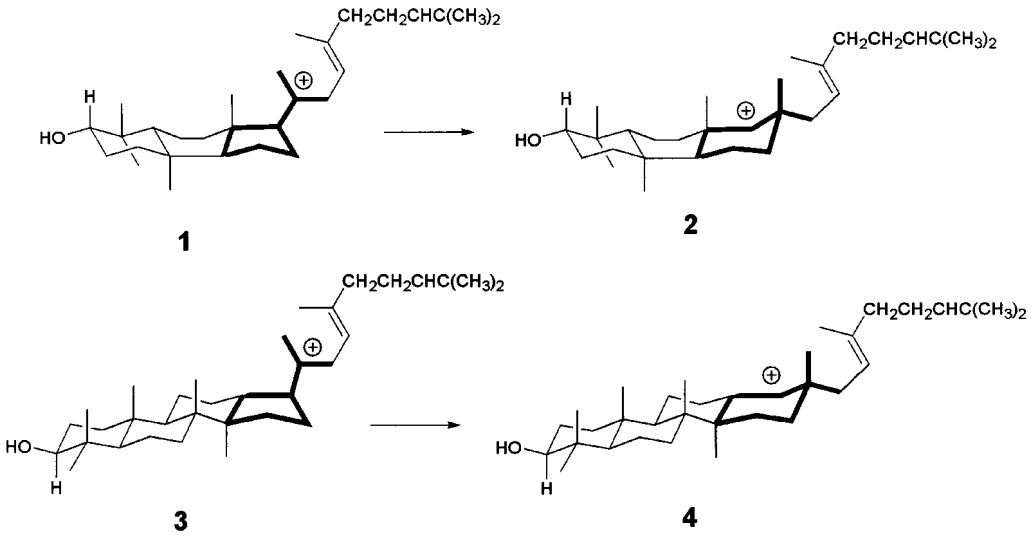

Scheme 1

3.7 kcal mol^{-1} (1 kcal = 4.184 kJ) at −136 °C].[8] The formation of carbocation **7** can be rationalized by the mechanism suggested in Scheme 2. Expansion of the five-membered ring of the carbocation isomer **5A** yields the 2,2-dimethylcyclohexyl cation **6**. Sequentially a 1,2-methyl shift transforms the secondary carbocation **6** into the tertiary carbocation **7**.

The rate of the formation of carbocation **7** was followed by means of ^{1}H NMR spectroscopy. The disappearance of the methyl groups in **5A/5B** (δ = 2.22 ppm) and the concomitant appearance of the methyl groups of cation **7** (δ = 2.45 ppm) was monitored by recording ^{1}H NMR spectra at given time intervals (Fig. 2). The first-order reaction rate obtained at −99 °C is $k_{obs} = (2.6 \pm 0.2) \times 10^{-4}$ s^{-1}. Taking into account that carbocation **5A** is formed in the rapid pre-equilibrium **5B/5A**, the observed rate constant is $k_{obs} = K_{eq}k_2$, where K_{eq} represents the equilibrium constant **5B/5A**, and k_2 is the rate constant of the ring expansion reaction. The equilibrium constant K_{eq}(**5A/5B**) = 0.095 at −99 °C (Kronja O, Vrček V. and Siehl H.-U. oral presentation at the 7th European Symposium on Organic Reactivity, ESOR-7, Ulm, Germany, 1999). Thus the rate constant of the rearrangement process from **5A** to **7** at −99 °C is $k_2 = 2.7 \times 10^{-3}$ s^{-1} and the free energy of activation is $\Delta G^{\ddagger}_{(-99°C)} = 12.0$ kcal mol^{-1}.

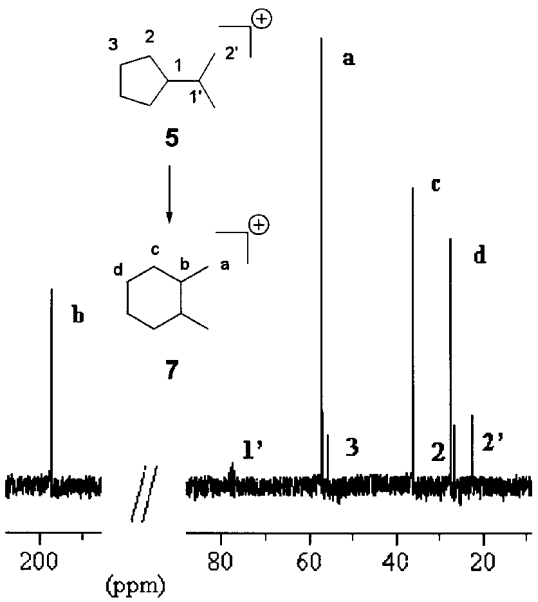

Figure 1. ^{13}C NMR spectrum showing the rearrangement of carbocation **5A/5B** to **7** in SbF_5–SO_2C1F–SO_2F_2 solution after 30 min at −99 °C

Quantum chemical calculations were carried out for model structures **5A, 5B, 6** and **7** at the HF/6–31G(d) and B3LYP/6–31G(d) levels of theory using the Gaussian 94 program suite.[9] B3LYP/6–31G(d)-optimized structures and selected geometric parameters for carbocations **5** and **7** are shown in Fig. 3. Frequency calculations for **5A, 5B** and **7** at the same level give no imaginary frequencies (N_{Imag} = 0), confirming that these structures are local minima on the energy surface. The carbocation structure **5B** was found to be 1.5 kcal mol^{-1} [B3LYP/6–31G(d)] more stable then **5A**. This confirms the interpretation of the experimental results that the positive charge is favored on the endocyclic carbon. Four local minimum structures **7a–d**, which are stereochemically distinct chair conformations, were found for the 1,2-dimethylcyclohexyl cation **7**. These structures are analogous to the two isomeric chair structures found for the lower homologous 1-methyl-1-cyclohexyl cation.[10] The carbocation structures **7a** and **b** both have 'axially' oriented carbocation p-orbitals. In **7a** the methyl group at C-2 is in an equatorial position and in **7b** the methyl group at C-2 is in an axial position. The two other structures, **7c** and **d**, both have an 'equatorially' oriented carbocation p-orbital, **7c** has the methyl at C-2 in an equatorial position and **7d** in

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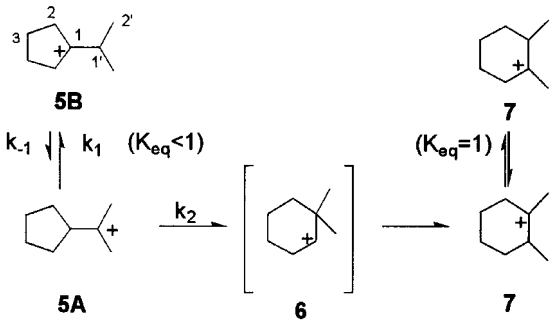

Scheme 2

an axial position. The most stable structure is **7c**, which is 2.5 kcal mol^{-1} [B3LYP/6–31G(d)] more stable than the least stable conformer **7a** (Table 1). The conformations **7a**–**d** of the 2-dimethylcyclohexyl cation are 0.7–4.7 kcal mol^{-1} more stable than calculated for the carbocation structures **5A** and **5B** (Table 1). The secondary 2-dimethylcyclohexyl cation **6** was located as a local minimum at the HF/6–31G(d) level, 8.8 kcal mol^{-1} less stable than **5A**. However, on geometry optimization at the B3LYP/6–31G(d) level, this structure converged to the tertiary carbocation structure **7**, hence the HF optimized structure of **6** is not a local minimum at the DFT level of theory.

It appears that the mechanism of the five- to six-membered ring expansion in the enzymatic biosynthesis of steroids and in the biomimetic model reaction are comparable. The structure of the model cation **6** is closely related to the secondary cation **2** and the baccharenyl cation **4**, which arise under enzymatic conditions (Scheme 1). Unlike the model cation **6**, the secondary cations **2** and **4** enjoy additional stabilization of the positive charge, either by internal interaction with the

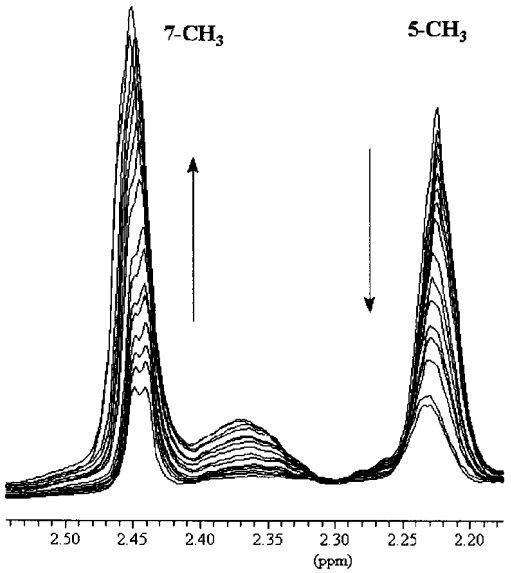

Figure 2. Time-dependent ^{1}H NMR spectra of the rearrangement of **5A/5B** to **7** at −99 °C showing the disappearance of the methyl group signal in **5A/5B** and the appearance of the methyl group signal in **7**

Table 1. Relative energies for carbocations **5A, 5B, 6** and **7a**–**d**

	ΔE/(kcal/mol^{-1})	
Carbocation	HF/6–31G(d)	B3LYP/6–31G(d)
5A	4.9	3.2
5B	1.6	4.7
6	13.7	—
7a	0.8	2.5
7b	0.1	1.9
7c	0	0
7d	1.3	1.4

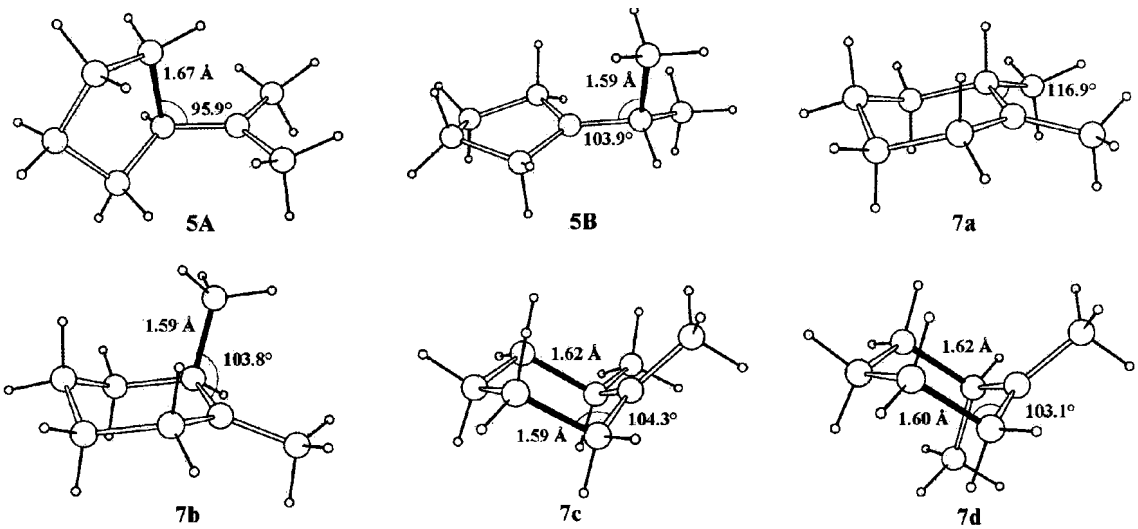

Figure 3. B3LYP/6–31G(d)-optimized geometries for carbocations **5A, 5B** and **7a**–**d**. C—C bonds elongated from hyperconjugative interaction with the carbocation p-orbital are shown with thick lines

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π-electrons of the remoted double bond[11,12] or by external interactions with π-electrons of aromatic amino acid residues of the enzyme.[13]

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Coordinates in *xyz* format for the optimized geometries of structures **5A, 5B** and **7a–d** [B3LYP/6–31G(d)] are available as supplementary data at the epoc website at http://www.wiley.com/epoc/.

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REFERENCES

1. Abe I, Rohmer M, Prestwich GD. *Chem. Rev.* 1993; **93**: 2189–2206, and references cited therein.
2. Corey EJ, Virgil SC, Cheng H, Baker CH, Matsuda SPT, Singh V, Sarshar S. *J. Am. Chem. Soc.* 1995; **117**: 11819–11821.
3. (a) Corey EJ, Virgil SC. *J Am. Chem. Soc.* 1991; **113**: 4025–4026; (b) Corey EJ, Virgil SC. *J Am. Chem. Soc.* 1982; **104**: 6480–6481.
4. Jenson C, Jorgensen WL. *J. Am. Chem. Soc.* 1997; **119**: 10846–10854.
5. (a) Saunders M, Vogel P. *J. Am. Chem. Soc.* 1971; **93**: 2559–2561; (b) Lenoir D, Siehl H-U *Houben–Weyl: Methoden der Organischen Chemie*, vol. E19C. Georg Thieme: Stuttgart, 1990; 26–32.
6. Okazava NE, Sorensen TS. *Can J. Chem* 1982; **60**: 2180–2193.
7. Lloyd JR, PhD Thesis, Yale University, 1978.
8. Saunders M, Kates MR. *J. Am. Chem. Soc.* 1978; **100**: 7082–7083.
9. Frisch MJ, Trucks GW, Schlegel HB, Gill PMW, Johnson BG, Robb MA, Cheeseman JR, Keith T, Petersson GA, Montgomery JA, Raghavachari K, Al-Laham MA, Zakrzewski VG, Ortiz JV, Foresman JB, Cioslowski J, Stefanov BB, Nanayakkara A, Challacombe M, Peng CY, Ayala PY, Chen W, Wong MW, Andres JL, Replogle ES, Gomperts R, Martin RL, Fox DJ, Binkley JS, Defrees DJ, Baker J, Stewart JP, Head-Gordon M, Gonzalez C, Pople JA. *Gaussian 94, Revision E. 1*. Gaussian: Pittsburgh, PA, 1995.
10. Rauk A, Sorensen TS, Maerker C, Carnerio JW de M, Sieber S, Schleyer PvR. *J. Am. Chem. Soc.* 1996; **118**: 3761–3762.
11. Borčić S, Kronja O, Humski K, Miletić S. *Croat. Chem. Acta* 1996; **69**: 563–568.
12. Orlović M, Borčić S, Humski K, Kronja O, Imper V, Polla E, Shiner VJ Jr. *J. Org. Chem.* 1991; **56**: 1874–1878.
13. (a) Dougherty DA. *Science*, 1996; **271**: 163–167; (b) Miklis PC, Ditchfield R, Spencer TA. *J. Am. Chem. Soc.* 1998; **120**: 10482–10489; (c) Pale-Grosdemange C, Feil C, Rohmer M, Poralla K. *Angew. Chem.* 1998; **110**: 2355–2357.

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