Viability of Nonclassical Carbocations Proposed as Intermediates in the Biosynthesis of Atiserene, Beyerene, Kaurene, and Trachylobane Diterpenes

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The results of quantum-chemical calculations aimed at assessing the viability of nonclassical carbocations proposed to be involved in the biosynthesis of atiserne, beyerene, kaurene, and trachylobane diterpenes are presented. While the proposed edge-protonated structure is much lower in energy than the proposed face-protonated structure, neither is predicted to be a viable intermediate energetically.

Introduction. – The carbocation cyclization/rearrangement mechanisms leading to atiserene, beyerene, kaurene (a biosynthetic precursor to steviol), and trachylobane diterpenes have been of interest for more than half a century [1]. Despite extensive theoretical studies revealing energetically viable pathways to these diterpenes (*Scheme*) [2], the intermediacy of several unusual carbocations **F**–**H** (*Fig. 1*) has still been advocated for in the recent literature [3]. Herein, we expand on our previous work to specifically address the energetic viability of carbocations **F**–**H**[1]).

Results and Discussion. – Computations on model systems corresponding to the portions of the natural products involved in rearrangements were used to estimate the relative energies of putative carbocations. Structures **1** and **2** (*Fig. 2*) correspond to the *ent*-kauranyl and *ent*-atiseranyl cations, **C** and **E**, respectively. These structures were fully optimized. The predicted energy difference between them, *ca.* 2 kcal/mol, is similar to that predicted previously for full-sized cations [2a]. Structure **1′**, for which one C(13)–H bond was constrained to a distance of 1.30 Å (similar to the depiction of this bond in **G**), is predicted, not surprisingly, to raise the energy of the carbocation by more than 10 kcal/mol.

Structures **4** and **4′** correspond to two forms of edge-protonated (C(13)–C(16)) *ent*-trachylobane, a differently protonated version of cation **H**. These structures are predicted to be similar in energy to **1′**. Protonation instead on the C(12)–C(16) bond leads to structures **5** and **5′**, the former of which opened significantly. Protonation on the C(12)–C(13) bond led to structures **6**–**8** of even higher energy (**8** is the fully optimized transition-state structure for the conversion of **1** to **2**).

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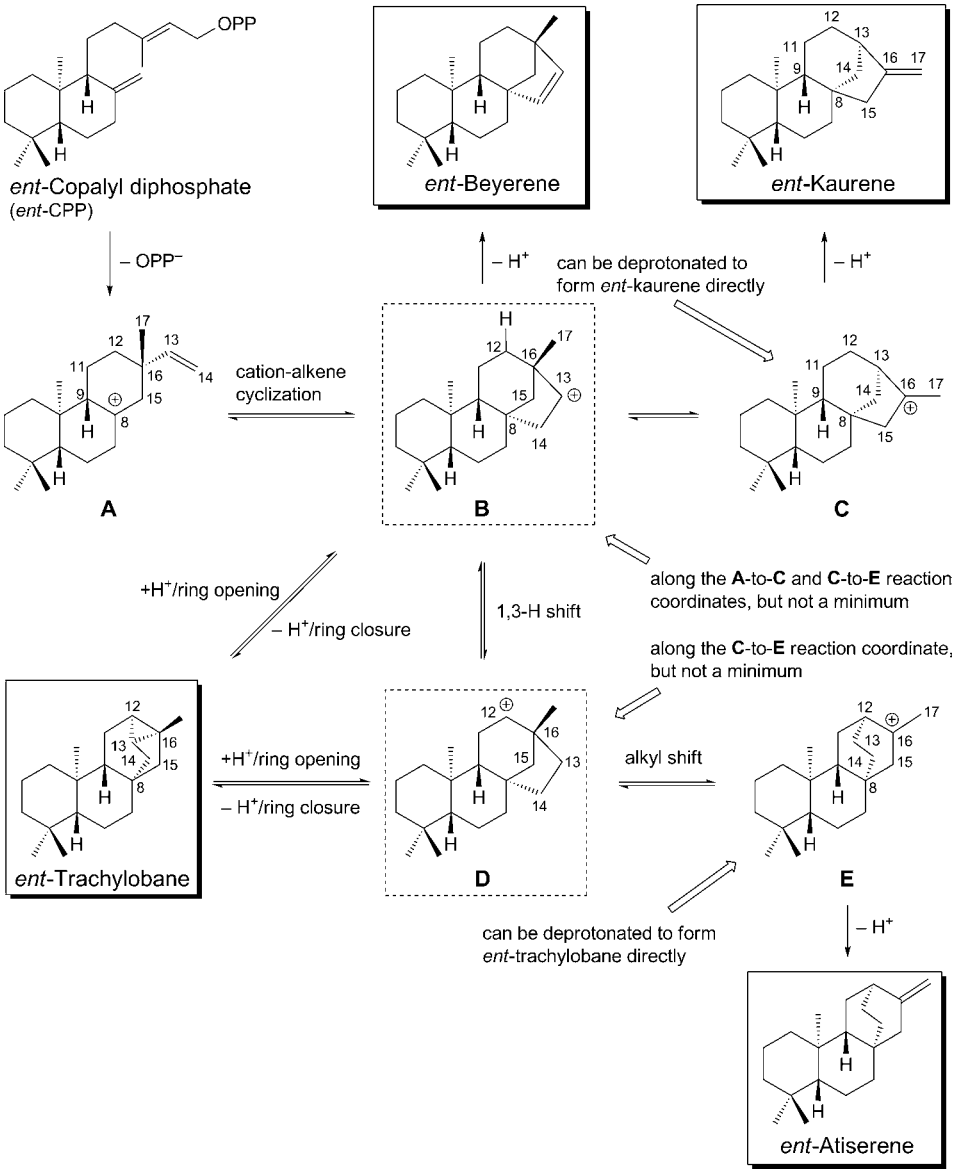
[1]) This is Part 8 in our series on diterpene-forming carbocation rearrangements. For Part 7, see [4].

Scheme



Cation **H** is formulated as a face-protonated, rather than edge-protonated, cyclopropane, however. Structure **9** shows that face protonation leads to a structure that is very high in energy, even if one allows for C–C bonds to lengthen (**9′**). Even if the energies predicted by these calculations were off by tens of kcal/mol (and there is no

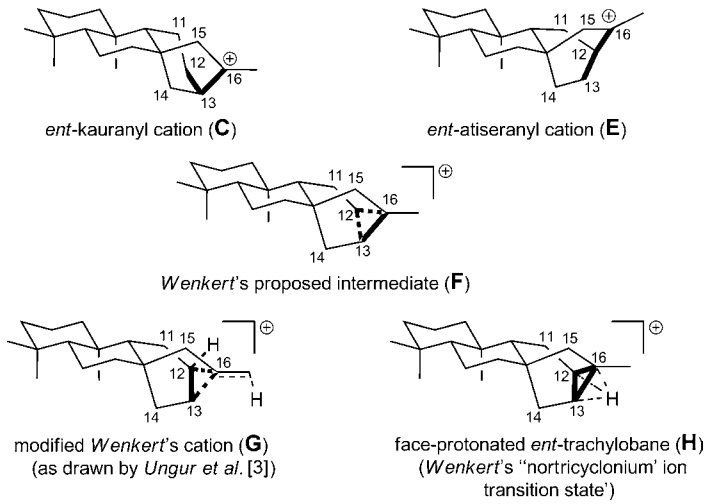


Fig. 1. *Several unusual carbocations*

reason to assume that they are), we can confidently rule out cation **H** as a viable intermediate.

Is cation **G**, or its slightly reformulated version **F**, energetically accessible? Structure **10** (*Fig. 3*) is a model of cation **G**. This structure is predicted to be more than 30 kcal/mol higher in energy than structure **1**. Allowing the C(16)–C(17) bond to relax leads to a species that more closely resembles cation **F**, but this leads to only a small decrease of energy. Consequently, we can also rule out cations **F** and **G** as viable intermediates.

Conclusions. – The results of quantum-chemical calculations indicate that proposed σ-delocalized carbocations **F**–**H** are not energetically viable. The mechanism depicted in the *Scheme* remains the most plausible on energetic grounds for the formation of atiserene, beyerene, kaurene, and trachylobane.

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Experimental Part

Computational Methods. All calculations were performed with Gaussian 03 or Gaussian 09 [5]. All geometries were optimized using the B3LYP/6-31 + G(d,p) method [6][7], and all stationary points were characterized by frequency calculations. Structural drawings were produced using *Ball & Stick* [8]. The results of calculations on cations **C**–**E** with the attached COOH group present in the natural products from [3] indicated that the COOH group has little effect on the rearrangement chemistry and carbocation structures.

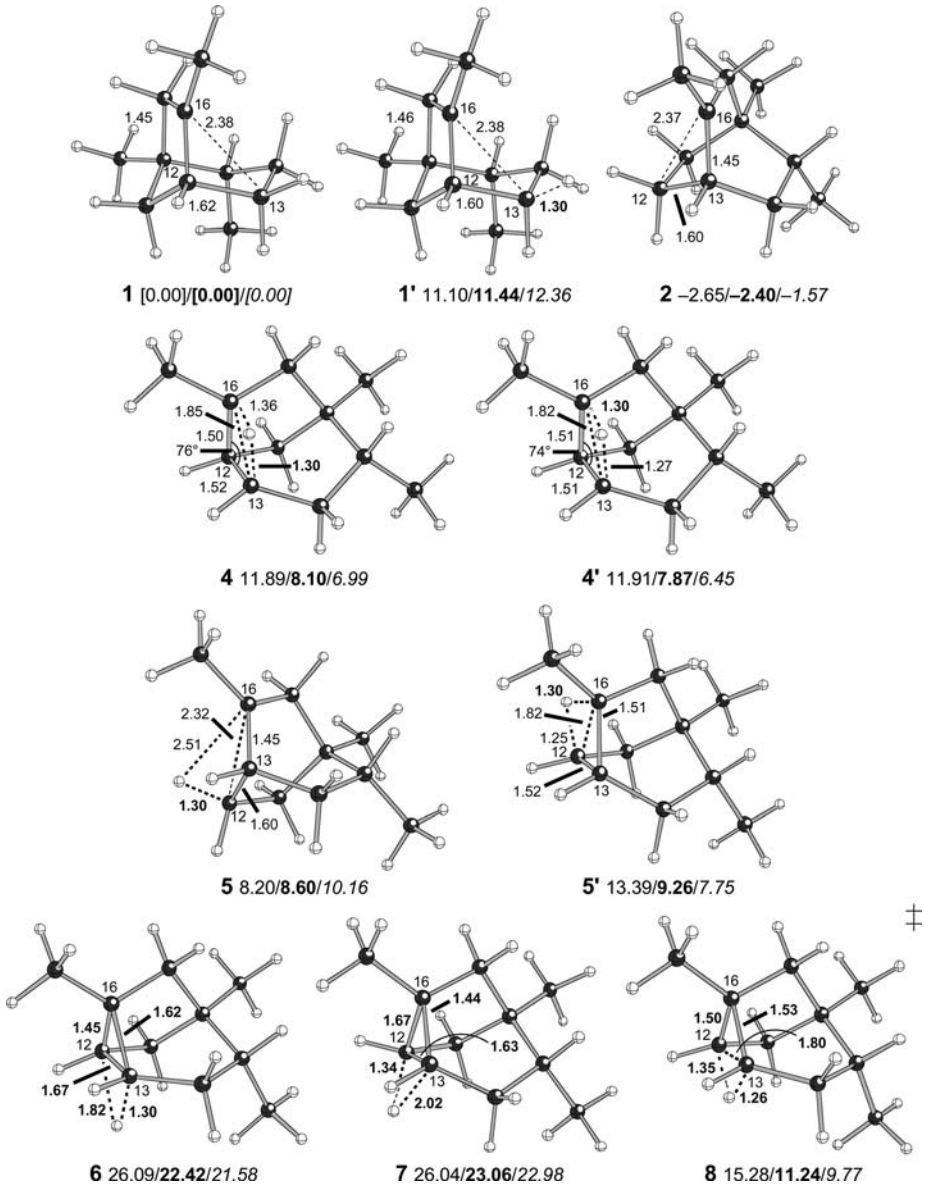

Fig. 2. *Computed* (B3LYP/6-31 + G(d,p)//B3LYP/6-31 + G(d,p)) *geometries* (selected distances in Å) *and energies* (kcal/mol; zero-point energy corrections not included, since many structures are constrained; mPW1PW91/6-31 + G(d,p)//B3LYP/6-31 + G(d,p) in bold, MPWB1K/6-31 + G(d,p)//B3LYP/6-31 + G(d,p) in italics) *of model cations* **1**–**9**. All energies are relative to that of structure **1**. Structures are rotated by *ca.* 180° relative to the depictions in *Fig. 1*. All distances highlighted in bold were constrained to the lengths shown during structure optimization.

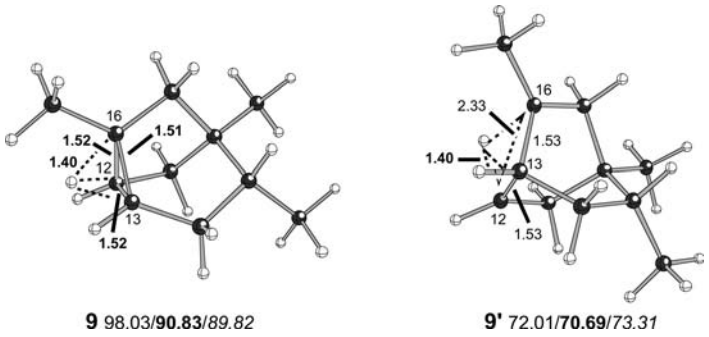

Fig. 2 (cont).

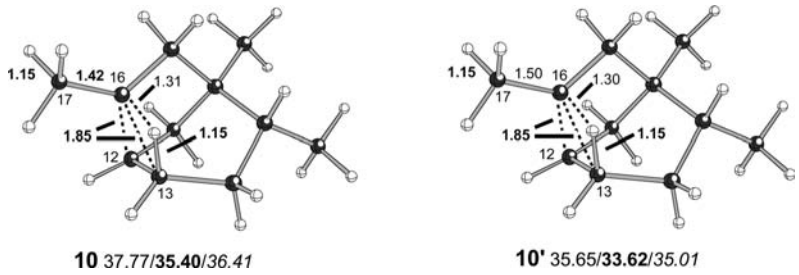

Fig. 3. *Computed* (B3LYP/6-31 + G(d,p)//B3LYP/6-31 + G(d,p)) *geometries* (selected distances in Å) *and energies* (kcal/mol; zero-point energy corrections not included, since structures are constrained; mPW1PW91/6-31 + G(d,p)//B3LYP/6-31 + G(d,p) in bold, MPWB1K/6-31 + G(d,p)//B3LYP/6-31 + G(d,p) in italics) *of model cations* **10** and **10′**. Energies are relative to that of structure **1** (*Fig. 2*). Structures are rotated by *ca.* 180° relative to the depictions in *Fig. 1*. All distances highlighted in bold were constrained to the lengths shown during structure optimization.

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