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Secondary Carbocations in the Biosynthesis of Pupukeanane Sesquiterpenes

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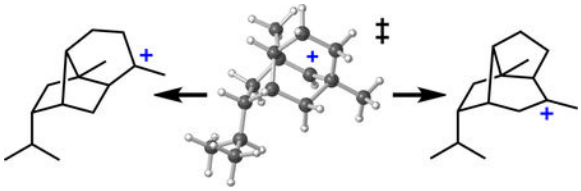
Abstract

The results of quantum chemical calculations on putative biosynthetic carbocation cyclization/rearrangements leading to pupukeanane and related sesquiterpenes indicate that a secondary carbocation proposed as an intermediate is not a minimum on the potential energy surface and instead resides in a region of the potential energy surface associated with a plateau containing multiple exit channels.

Graphic Abstract



INTRODUCTION

The formal s-bond frameworks of carbocations tend towards greater delocalization than those of carbanions, carbon-centered radicals and alkanes.[1–4] As a result, barriers for rearrangement reactions that involve the breaking of bonds involved in delocalized arrays (e.g., engaged in strong hyperconjugation[4]) can have very low barriers, and transition state structures (TSSs) for such rearrangements are frequently lacking in s-delocalization. For example, many secondary carbocations proposed as intermediates in cyclization/rearrangement reactions involved in the biosynthesis of terpene natural products have been shown not to be minima on potential energy surfaces (PESs), at least in the absence of enzymatic chaperons, occurring instead at other points on reaction coordinates, sometimes near TSSs (Figure 1).[5,6] Our ongoing studies on the scope and generality of this concept led us to examine the reactions shown in Scheme 1. It was proposed that cation **2**, formed from cyclization of cation **1**, could undergo a 1,2-alkyl shift to form either cation **3** or cation **4**. Cation **3** would be a biosynthetic precursor to neopupukeanane sesquiterpenes, while cation **4** would be a direct precursor to pupukeanane sesquiterpenes and an indirect precursor to

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SUPPORTING INFORMATION

Coordinates and energies for all computed structures, additional information on IRC calculations, full *Gaussian* reference.

abeopupukeanane sesquiterpenes (via cation **5**).[7] Based on previous experience, we suspected that one or both of secondary cations **3** and **4** might not be PES minima and set out to test this hypothesis using density functional theory (DFT) calculations.

METHODS

Computations were performed at the B3LYP/6–31+G(d,p),[8–10] B3LYP-D3/6–31+G(d,p)[11] and mPW1PW91/6–31+G(d,p)[12–13] levels of theory, using *Gaussian09*.[14] Identities of all stationary points (minima or transition state structures) were confirmed by frequency analysis and intrinsic reaction coordinate (IRC) calculations were performed on all transition state structures to confirm connectivity to products.[15,16] All energies shown are free energies at room temperature, except for those in the IRC plots, which are electronic energies. Three-dimensional molecular images were generated with *CylView*.[17]

RESULTS AND DISCUSSION

Secondary cation **3** is predicted to be a minimum at all levels used and is formed from cation **2** via a TSS that is similar in structure and energy to **2** (Figure 2). The formal secondary carbocation center in cation **3** benefits from hyperconjugation from two adjacent C–C bonds (1.59 and 1.70 Å; see Figure 2). Hyperconjugation with the 1.70 Å C–C bond has entered the realm of bridging (C–C–C angle <90°, consistent with cation **3** being described as nonclassical).[18-22]

Secondary cation **4** is predicted not to be a minimum at all levels used. With mPW1PW91/6–31+G(d,p), a TSS for concerted conversion of cation **2** to cation **5** was located (Figure 3). The TSS for this reaction, and nearby structures flanking it, resemble cation **4**. This reaction is another example of a concerted reaction with asynchronous 1,2-alkyl shifts.[23–25] With B3LYP/6–31+G(d,p) and B3LYP-D3/6–31+G(d,p), TSSs resembling cation **4** were also found, but these are connected, via IRC calculations, to cation **5** and, unexpectedly, cation **6** (Figure 4). The interconversion of cations **5** and **6** corresponds to a dyotropic rearrangement, several of which have been proposed to occur in terpene biosynthesis.[26] Structures on the shoulder on the side of the IRC pathway leading to **6** resemble the geometry expected for a TSS for a 1,2-alkyl shift that calculations are shown. Relative free energies from B3LYP-D3/6–31+G(d,p) (kcal/mol) are shown on each structure; energies for IRC points are electronic energies. All structures are cationic, but positive charge symbols are not shown, since charge is delocalized over multiple atoms.

Taken together, the results from the three levels of theory used are consistent with the following scenario. The portion of the PES near to cation **4** is somewhat flat and has at least three exit channels: to cations **2**, **5** and **6**. It is possible that there are two TSSs close to each other in structure and energy,[27,28] the initially formed TSS followed by the **5** ⇌ **6** TSS, i.e., there exists a post-transition state bifurcation (PTSB; Figure 5),[29,30] a contention that could be tested in the future using direct dynamics simulations.[31–34] Previous work has suggested that locating TSSs with similar structures at different levels of theory whose IRC pathways lead to different products is a marker for PTSBs.[27]

These results have implications for the biosynthesis of pupukeanane and related sesquiterpene natural products. First, sesquiterpenes with the pupukeanane skeleton would either result from coupled 1,2-shift/quenching reactions, as has been proposed for related systems,[35–37] or an enzyme would need to convert cation **4** to a minimum, i.e., increase its lifetime, via selective binding. Second, formation of abeopupukeanane sesquiterpenes would likely require a dynamical preference[31–34] – either inherent[38] or enzyme induced – for formation of cation **5** rather than cation **6**.

CONCLUSIONS

Putative biosynthetic carbocation cyclization/rearrangements leading to pupukeanane and related sesquiterpenes were examined using DFT calculations. The results of these calculations indicate that one of the secondary carbocations proposed as an intermediate is not a minimum on the PES and instead resides in a region of the PES associated with a plateau containing multiple exit channels or a PTSB. These examples add to the growing body of examples of such phenomena in biosynthetic carbocation chemistry, highlighting the complex chemistry of secondary carbocations – chemistry that differs greatly from that generally contained in the organic chemist's body of "general knowledge."

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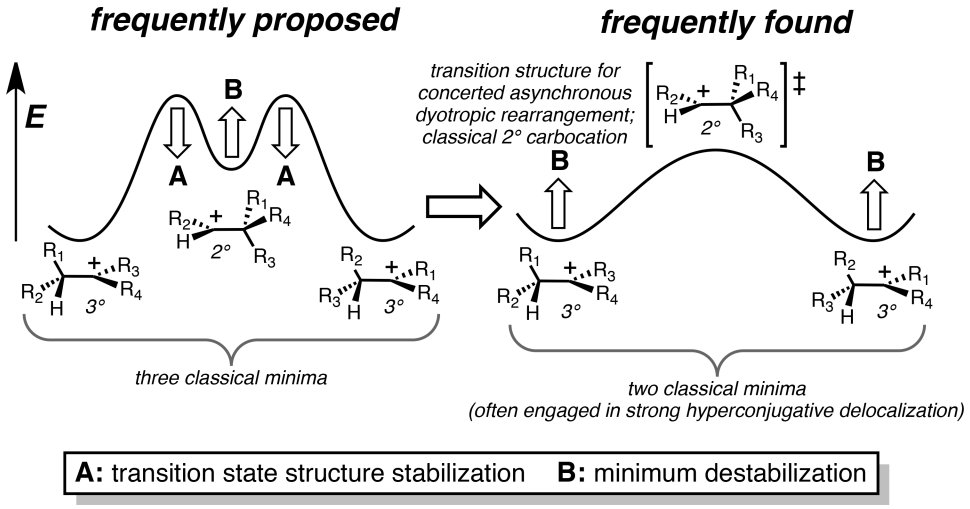


Figure 1.

Comparison between reaction coordinate for a stepwise carbocation rearrangement (left), which is often assumed, and a concerted rearrangement involving multiple asynchronous events (right), which is often observed. In the specific example shown, a reaction that might be formulated as two 1,2-shifts (of R_1 and then R_3) separated by a minimum (intermediate on the PES) is instead found to be a concerted process where the two 1,2-shifts occur sequentially but without an intervening minimum; instead the transition state structure for the concerted rearrangement (here a dyotropic rearrangement[26]) resembles the secondary cation formed after the first 1,2-shift.

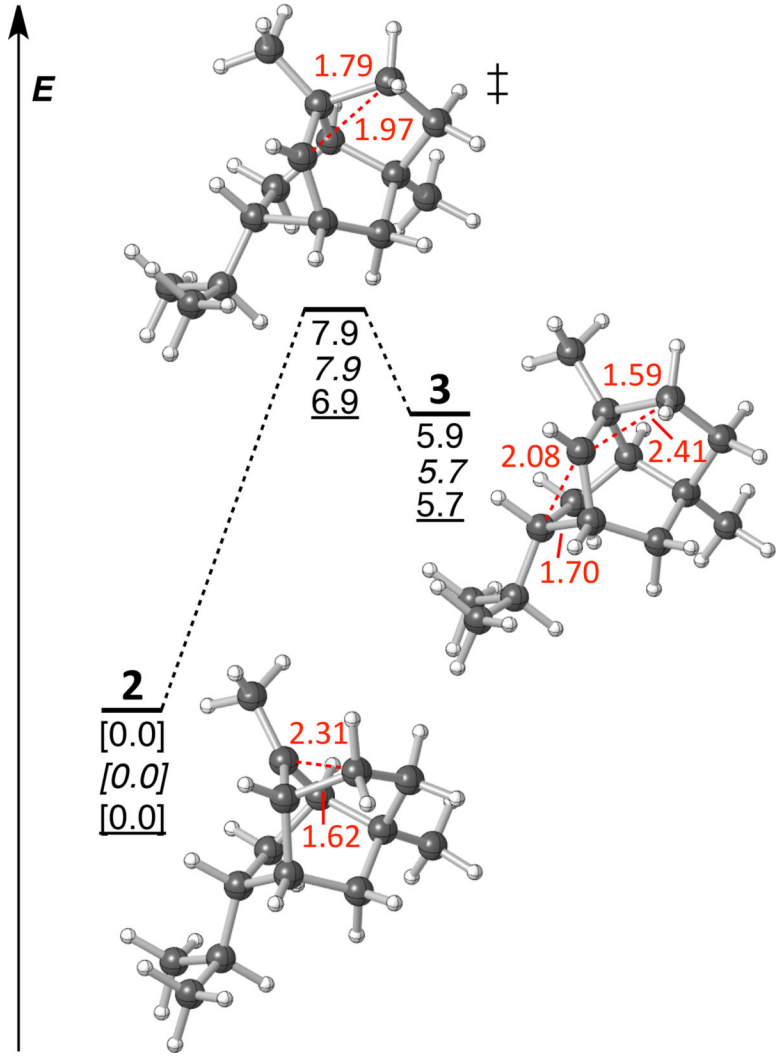


Figure 2.

Stationary points involved in the **2** → **3** rearrangement. Geometries (selected distances in Å) from B3LYP/6–31+G(d,p) calculations are shown. Relative free energies in kcal/mol from three levels of theory are shown: B3LYP/6–31+G(d,p) in plain text, B3LYP-D3/6–31+G(d,p) in italics, mPW1PW91/6–31+G(d,p) underlined. All structures are cationic, but positive charge symbols are not shown, since charge is delocalized over multiple atoms.

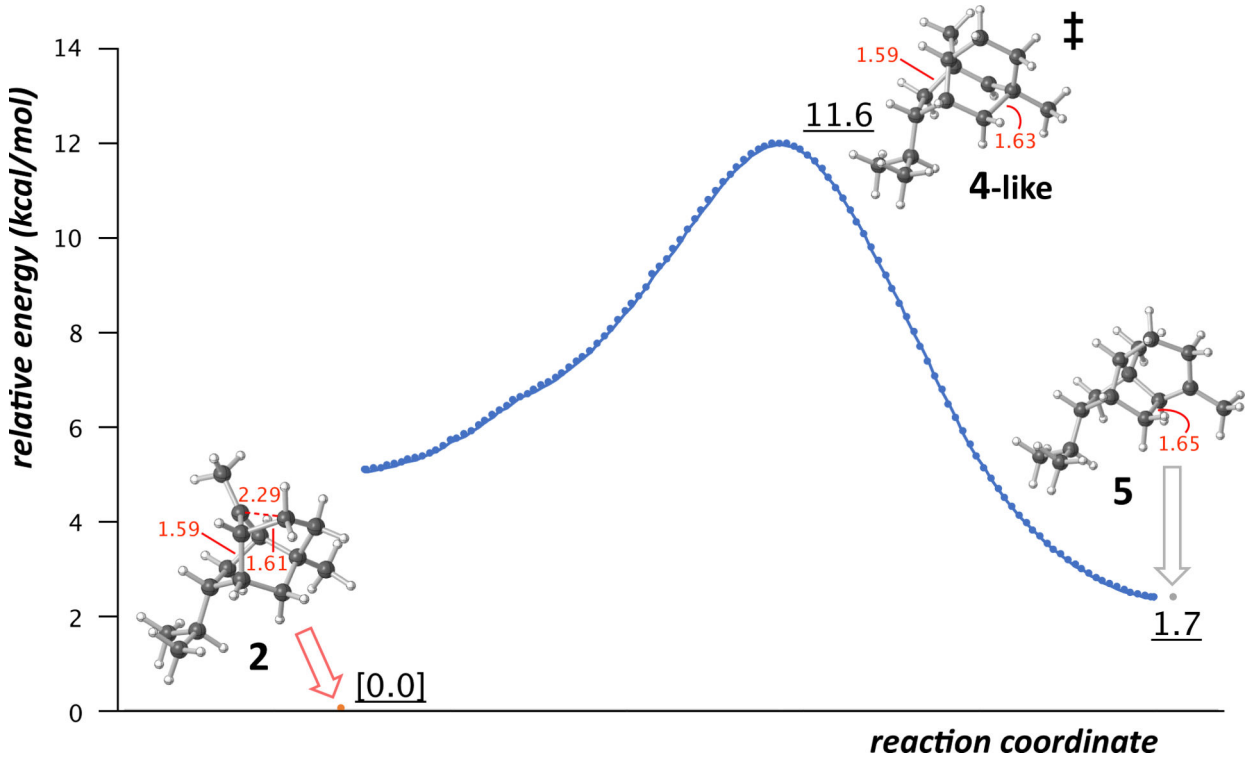


Figure 3.

Stationary points involved in the **2** → **5** rearrangement, along with IRC plot, obtained with mPW1PW91/6–31+G(d,p). Geometries (selected distances in Å) from mPW1PW91/631+G(d,p) calculations are shown. Relative free energies from mPW1PW91/6–31+G(d,p) (kcal/mol) are shown on each structure; energies for IRC points are electronic energies. All structures are cationic, but positive charge symbols are not shown, since charge is delocalized over multiple atoms.

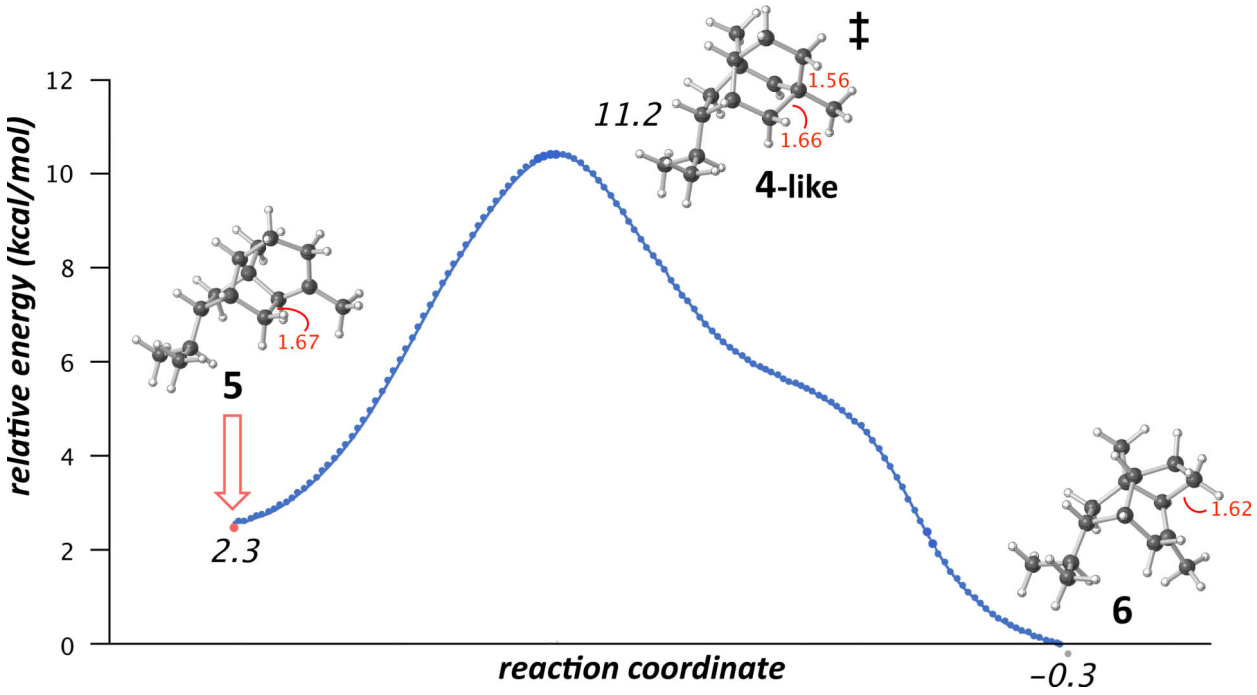


Figure 4.

Stationary points involved in the **5** → **6** rearrangement, along with IRC plot, obtained with B3LYP-D3/6–31+G(d,p). Geometries (selected distances in Å) from B3LYP-D3/6–31+G(d,p) calculations are shown. Relative free energies from B3LYP-D3/6–31+G(d,p) (kcal/mol) are shown on each structure; energies for IRC points are electronic energies. All structures are cationic, but positive charge symbols are not shown, since charge is delocalized over multiple atoms.

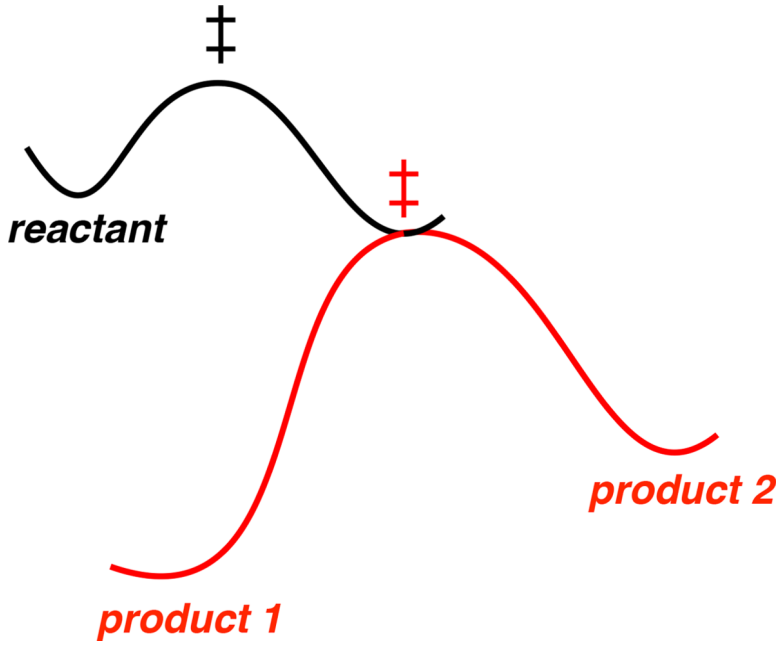
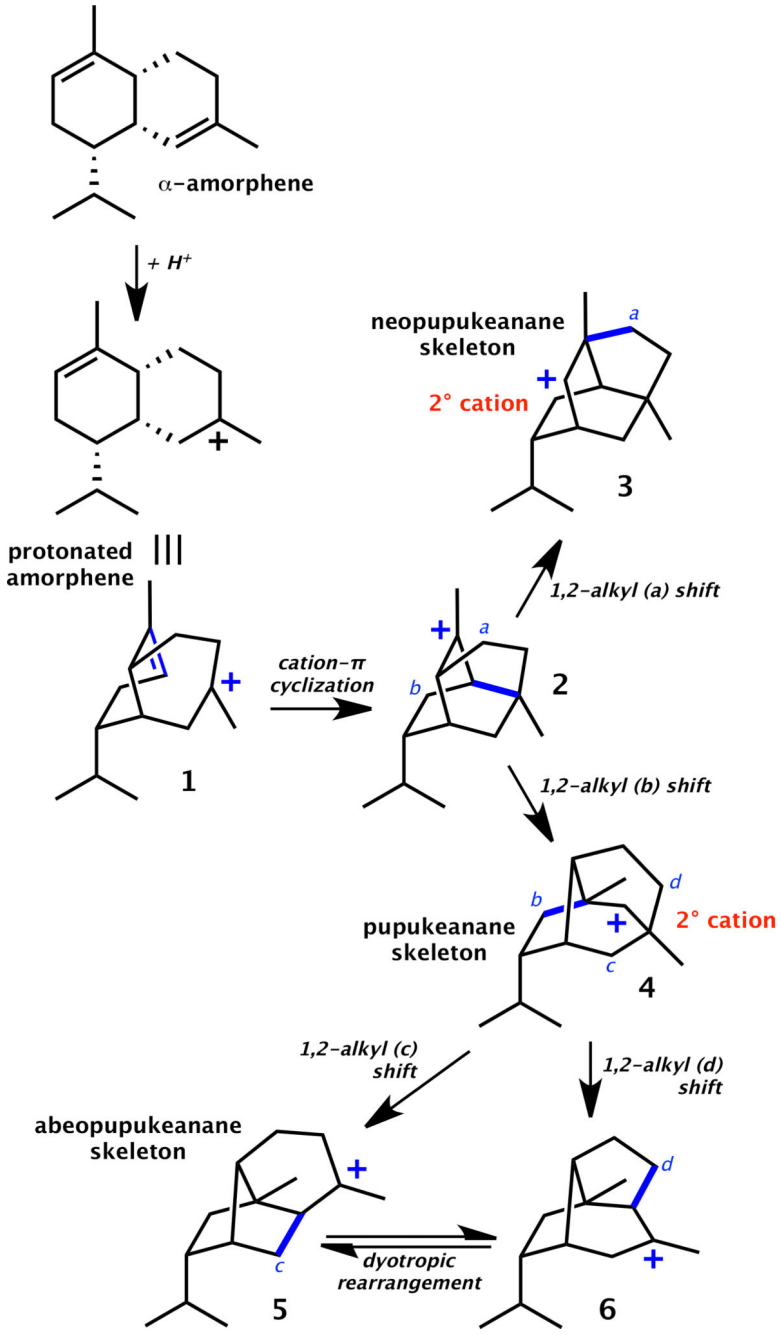


Figure 5.

Schematic representation of a PTSB. The reaction coordinate leading from reactant, through an initial TSS, toward products (black) bifurcates on the downhill slope following the first TSS. A second TSS can interconvert the two products, and the associated reaction coordinate for the product 1 ⇌ product 2 interconversion (red) is orthogonal to that associated with the first TSS (black).



Scheme 1.

Carbocations involved in proposed mechanisms for formation of pupukeanane and related sesquiterpene natural products. Newly formed σ-bonds in each structure are bolded and colored blue.