JOC *Article*

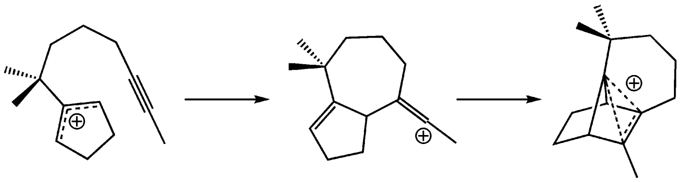
The Cationic Cascade Route to Longifolene

Gregory A. Ho, Dustin H. Nouri, and Dean J. Tantillo*

Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, California 95616

tantillo@chem.ucdavis.edu

Received February 26, 2005

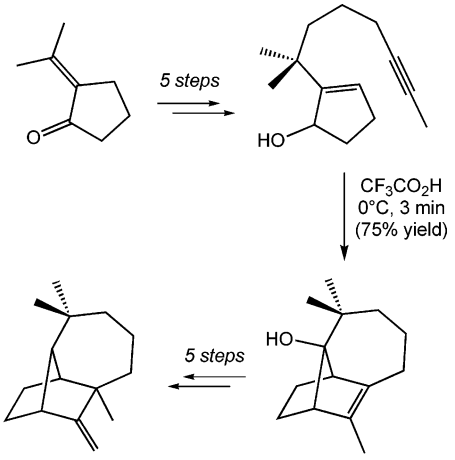


W. S. Johnson's total synthesis of the sesquiterpenoid longifolene is a classic example of the power of cationic polycyclizations for constructing complex molecular architectures. Herein we revisit the key polycyclization step of this synthesis using hybrid Hartree–Fock/density functional theory calculations and validate the feasibility of Johnson's proposed mechanism. We also explore perturbations to the 3-center 2-electron bonding array in a key intermediate that result from changing the polycyclic framework in which it is embedded.

Introduction

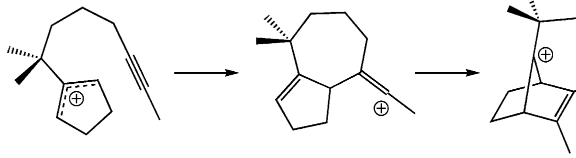
Biomimetic polycyclization reactions occupy a revered place in the history of synthetic organic chemistry[1] and still find favor today[2] due to their efficiency—such reactions often allow for the formation of several carbon–carbon bonds, rings, and stereocenters in a single transformation. One of the pioneers in this field was W. S. Johnson.[1,3] A prime example of his use of this strategy is the 1975 synthesis of longifolene (Scheme 1),[4] a classic synthetic target that has frequently served as a proving ground for innovative synthetic strategies.[5] Herein we revisit Johnson's elegant longifolene synthesis, subjecting it to the scrutiny of modern theoretical chemistry.

SCHEME 1



longifolene

SCHEME 2



1 **2** **3**

The key step in Johnson's longifolene synthesis was a cationic polycyclization cascade, which proceeded at low temperature (0 °C) in 75% yield.[4] It was proposed that this transformation involved the interconversion of allylic (**1**), alkenyl (**2**), and norbornenyl (**3**) cations (Scheme 2). Our theoretical studies address the feasibility of Johnson's putative mechanism. In addition, we explore the question of whether cation **3** is in fact a bridged, 3-center 2-electron species,[4,6–7] and we thoroughly investigate the

---

(1) For leading references, see: (a) van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152–158. (b) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9–17.

(2) For recent examples and leading references, see: (a) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564. (b) Zhang, J.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215–3216 (additional note: *Org. Lett.* **2002**, *4*, 3017). (c) Justicia, J.; Rosales, A.; Bunuel, E.; Oller-Lopez, J. L.; Valdivia, M.; Haidour, A.; Oltra, J. E.; Barrero, A. E.; Cardenas, D. J.; Cuerva, J. M. *Chem. Eur. J.* **2004**, *10*, 1778–1788. (d) Rosales, V.; Zambrano, J.; Demuth, M. *Eur. J. Org. Chem.* **2004**, 1798–1802. (e) Peterson, E. A.; Overman, L. A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943–11948. (f) de la Torre, M. C.; Sierra, M. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 160–181.

(3) Johnson, W. S. *A Fifty Year Love Affair with Organic Chemistry*; American Chemical Society: Washington, D.C., 1998.

(4) Volkmann, R. A.; Andrews, G. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1975**, *97*, 4777–4779.

10.1021/jo0503658 CCC: $30.25

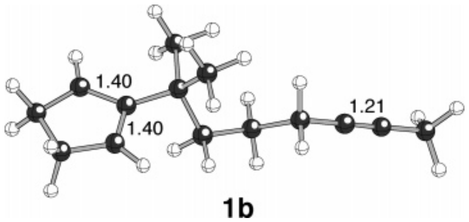
features in the polycyclic framework of longifolene and related species that influence the degree of delocalization in such structures.

Methods

All calculations were performed with GAUSSIAN03.[8] Geometries were optimized without symmetry constraints at the B3LYP/6-31G(d) level.[9] All structures were characterized by frequency calculations, and reported energies for gas-phase stationary points include zero-point energy corrections scaled by 0.9806.[10] Recent reports have discussed the appropriateness of using B3LYP for computing geometries and relative energies of delocalized carbocations.[7j,11] Intrinsic reaction coordinate (IRC) calculations were used to further characterize the nature of transition structures.[12] Single-point calculations on **1**−**3** and the transition structures connecting them were carried out using the CPCM method for treating solvation,[13] using water as the solvent. Structural drawings were produced using Ball & Stick (Müller, N.; Falk, A. *Ball & Stick V.3.7.6*, molecular graphics application for MacOS computers, Johannes Kepler University, Linz, 2000).

Results and Discussion

Our first task was to determine whether the mechanism outlined in Scheme 2 is energetically feasible. The energetics for this process, computed at the B3LYP/6-31G(d) level, both in the gas phase and in water, are shown in Figure 1, and the geometries of all stationary points (optimized in the gas phase) are shown in Figure 2. Once cation **1** folds into the correct conformation (extending the acyclic tail of **1** leads to a conformer, **1b**, that is 4.9 kcal/mol more stable than **1** in the gas phase), combination of its allyl cation and alkyne groups is quite facile. This leads to a structure, **2**, with a relatively long C−C single bond (1.60 Å), likely a result of hyperconjugation with the alkenyl cation. Subsequent attack of the alkene π-bond of **2** onto the empty p-orbital of its alkenyl cation is considerably more difficult. Nonetheless, the overall barrier from **1** is less than 20 kcal/mol, low enough that this mechanism could indeed be followed under the reaction conditions used by Johnson, especially given the expected facility and exothermicity of the initial cation formation step.[4,14]



1b

As shown in Figure 2, there is a fairly strong interaction between the alkene (C_b=C_c) and tertiary cation (C_a) in **3**. This is apparent in the C_b=C_c distance (lengthened to 1.40 Å), the short $C_{b,c}$---C_a distances (1.79 and 1.87 Å), and the $C_{b,c}$−C−C_a angles (76° and 73°, respectively), all of which indicate that the tertiary cation center bends toward the alkene to form a delocalized, nonclassical, norbornenyl cation.[15] Apparently, neither the fact that the cation center is tertiary nor the fact that an additional ring is appended to the norbornenyl framework in **3** prevent nonclassical cation formation. It is possible, however, that one or the other of these factors hinders

---

(5) (a) Corey, E. J.; Ohno, M.; Mitra, R. B.; Vatakencherry, P. A. *J. Am. Chem. Soc.* **1964**, *86*, 478−485. (b) Corey, E. J.; Ohno, M.; Mitra, R. B.; Vatakencherry, P. A. *J. Am. Chem. Soc.* **1961**, 8*3*, 1251−1253. (c) McMurry, J. E.; Isser, S. J. *J. Am. Chem. Soc.* **1972**, *94*, 7132−7137. (d) Oppolzer, W.; Godel, T. *J. Am.* Chem. Soc. **1978**, *100*, 2583−2584. (e) Oppolzer, W.; Godel, T. *Helv. Chim. Acta* **1984**, *67*, 1154−1167. (f) Attah-Poku, S. K.; Antczak, K.; Alward, S. J.; Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 1717−1721. (g) Schultz, A. G.; Puig, S. *J. Org. Chem.* **1985**, *50*, 915−916. (h) Kuo, D. L.; Money, T. *Can. J. Chem.* **1988**, *66*, 1794−1804. (i) Lei, B.; Fallis, A. *J. Am. Chem. Soc.* **1990**, *112*, 4609−4610. (j) Ho, T.-L.; Yeh, W.-L.; Yule, J.; Liu, H.-J. *Can. J. Chem.* **1992**, *70*, 1375−1384. (k) Lei, B.; Fallis, A. G. *J. Org. Chem.* **1992**, *70*, 1375−1384. (l) Lei, B.; Fallis, A. G. *J. Org. Chem.* **1993***, 58*, 2186−2195. (m) Karimi, S.; Tavares, P. *J. Nat. Prod*. **2003**, *66*, 52−53.

(6) For leading references on 3-center 2-electron nonclassical carbocations, see: (a) Grob, C. A. *Acc. Chem. Res*. **1983**, *16*, 426−431. (b) Brown, H. C. *Acc. Chem. Res.* **1983**, *16*, 432−440. (c) Olah, G. A.; Prakash, G. K. S.; Saunders: M. *Acc. Chem. Res.* **1983**, *16*, 440−448. (d) Walling, C. *Acc. Chem. Res.* **1983**, *16*, 448−454. (e) Brown, H. C. (with comments by Schleyer, P. v. R.) *The Nonclassical Ion Problem*; Plenum: New York, 1977.

(7) Nonclassical carbocations have been proposed as intermediates in various biological cation polycyclizations. For leading references, see: (a) Wessjohann, L. A.; Brandt, W. *Chem. Rev.* **2003**, *103*, 1625−1647. (c) Giner, J.-L.; Buzek, P.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1995**, *117*, 12871−12872. (d) Erickson, H. K.; Poulter, C. D. *J. Am. Chem. Soc.* **2003**, *125*, 6886−6888. (e) He, X.; Cane, D. E. *J. Am. Chem. Soc*. **2004**, *126*, 2678−2679. (f) Dewar, M. J. S.; Ruiz, J. M. *Tetrahedron* **1987**, *43*, 2661−2674. (g) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1393−1405. (h) For leading references to older proposals by Djerassi, Arigoni, and Eschenmoser, see: Giner, J.-L. *Chem. Res.* **1993**, *93*, 1735−1752. (i) Lee, J. K.; Houk, K. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1003−1005. (j) Gutta, P. Tantillo, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 2719−2723.

(8) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

(9) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372−1377. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789. (d) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623−11627.

(10) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502−16513.

(11) (a) Vrcek, I. V.; Vrcek, V.; Siehl, H.-U. *J. Phys. Chem. A* **2002**, *106*, 1604−1611. (b) Farcasiu, D.; Lukinskas, P.; Pamidighantam, S. V. *J. Phys. Chem. A* **2002**, *106*, 11672−11675.

(12) (a) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523−5527. (b) Fukui, K. *Acc. Chem. Res*. **1981**, *14*, 363−368.

(13) (a) Barone, V.; Cossi, M. J. *J. Phys. Chem. A* **1998**, *102*, 1995−2001. (b) Barone, B.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404−417. (c) Previous studies suggest that the geometries of various carbocations are similar in polar and nonpolar environments; see, for example: Schreiner, P. R.; Severance, D. L.; Jorgensen, W. L.; Schleyer, P. v. R.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1995**, *117*, 2663−2664. As a test, we reoptimized structure **3** with the CPCM-B3LYP/6-31G(d) method in water; the biggest changes to C−C bond lengths observed upon reoptimization were for the long bonds in the bridging unit which changed by <0.01 Å.

(14) (a) The initial loss of water and its recapture are not described herein. Transition structures for such processes are notoriously difficult to locate (if they exist at all), and both of these steps are likely to be fast. See, for example: Schreiner, P. R.; Schleyer, P. v. R.; Schaefer, H. F., III. *J. Org. Chem.* **1997**, *62*, 4216−4228 and references therein. Structures of the reactant and product alcohols are included in the Supporting Information, however. (b) Using the standard transition state theory approach, a free energy barrier of 20 kcal/mol corresponds to a half-life of well less than 1 h at 273 K.

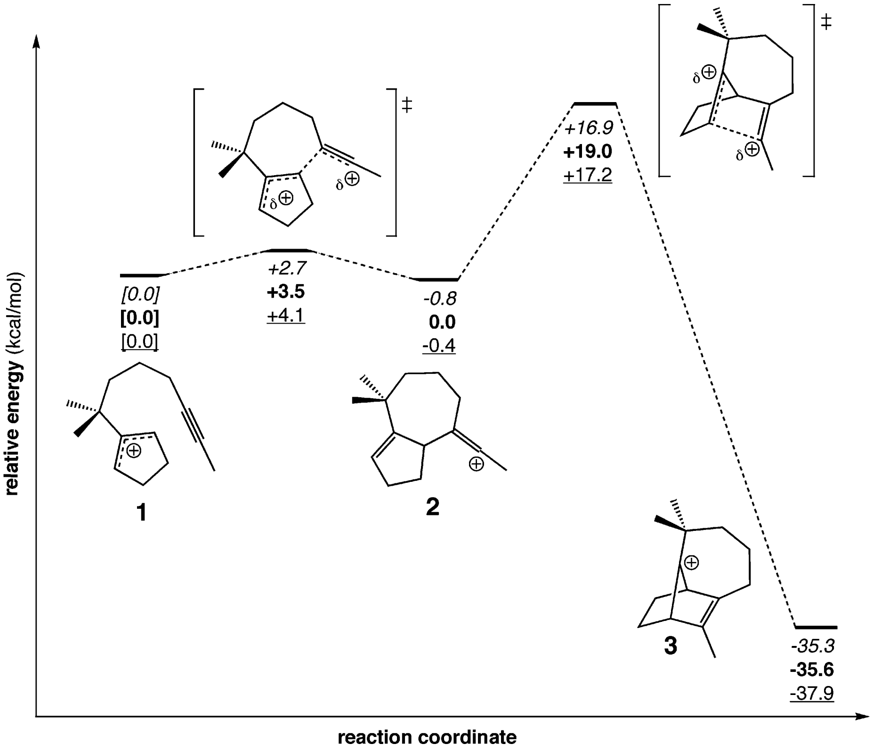


FIGURE 1. Relative energies (kcal/mol) of stationary points for the mechanism shown in Scheme 2 (B3LYP/6-31G(d) zero-point corrected energies in italics, B3LYP/6-31G(d) free energies at 0 °C in bold, and CPCM-B3LYP/6-31G(d) energies in water underlined).

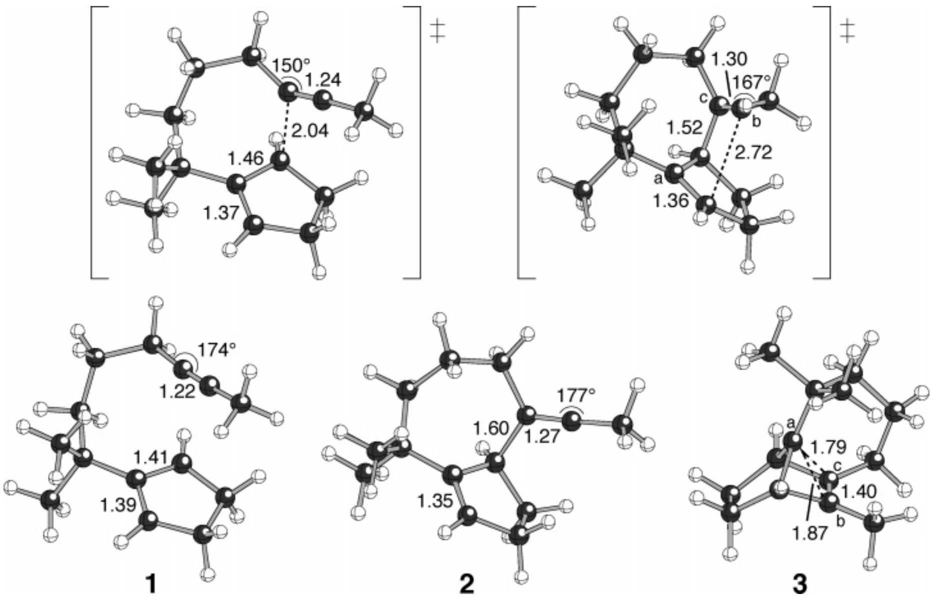
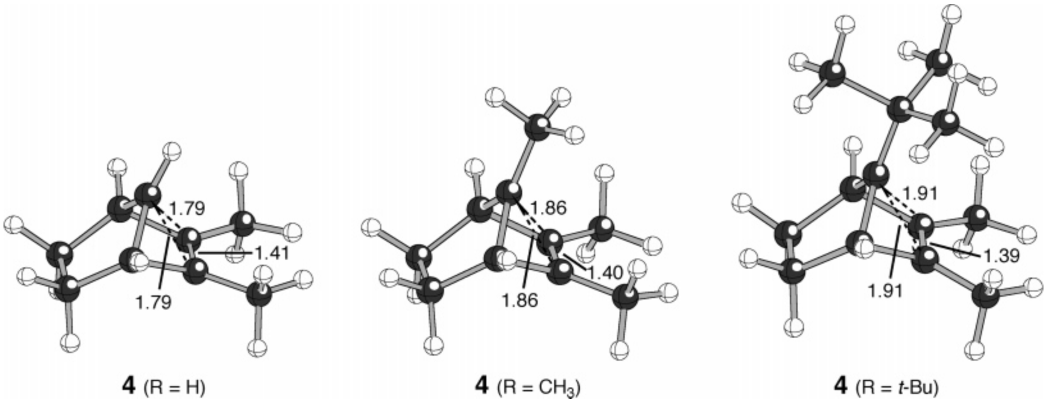


FIGURE 2. B3LYP/6-31G(d) geometries of intermediates and transition structures for the mechanism shown in Scheme 2. Selected distances are shown in Å. Several carbons are labeled (a−c) to emphasize the correspondence between **3** and the transition structure preceding it.

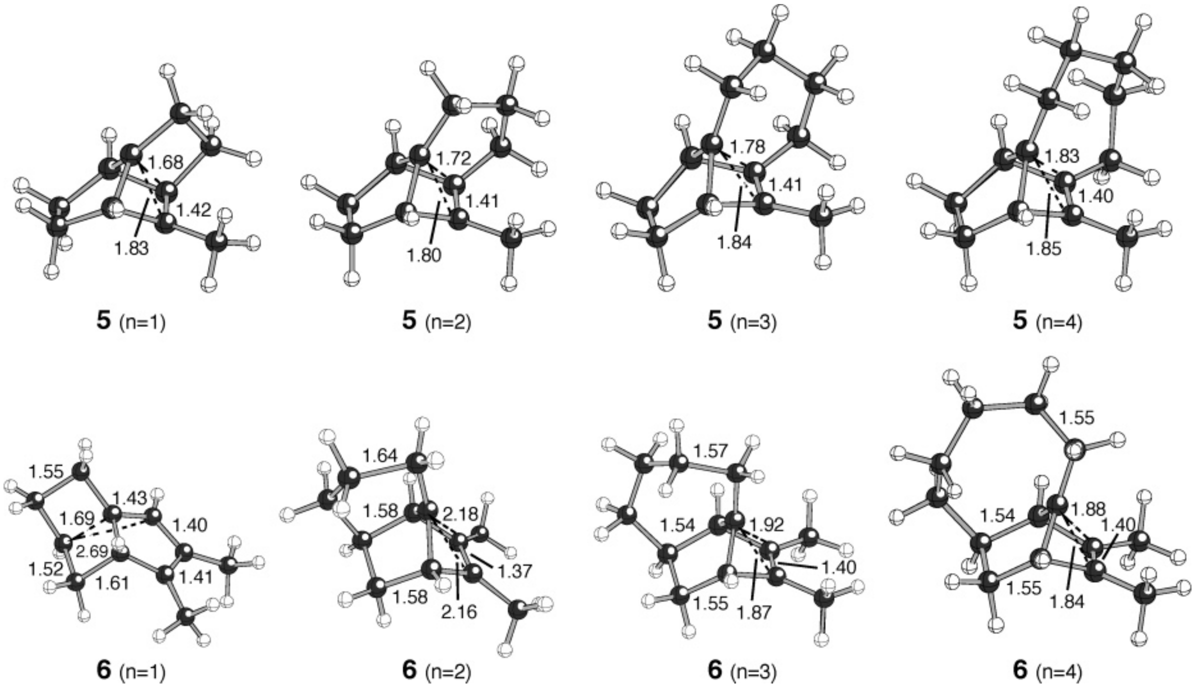
bridging but is overwhelmed by the other. We have examined a variety of related systems (Chart 1) to probe this issue.

Figure 3 shows the geometries of structures **4** (R = H, CH_3, *t*-Bu). In comparing the R = H[15e] and R = CH_3 structures, one can see that changing from a secondary carbocation to a tertiary one lessens the cation−alkene interaction, since this interaction is in competition with hyperconjugation between the cationic center and the methyl group. Replacing the methyl group by a *tert*-butyl group decreases the cation-alkene interaction further, most likely due to a combination of the slightly enhanced donating ability of C−C vs C−H σ−bonding orbitals[16] and the crowding of the *tert*-butyl group and the methyl groups attached to the alkene. Notice that the cation-alkene distances in **3** are shorter than those in **4** (R = *t*-Bu), suggesting that the cyclic tether in **3** actually serves to enhance the cation−alkene interaction.



4 (R = H) **4** (R = CH$_3$) **4** (R = *t*-Bu)

FIGURE 3. B3LYP/6-31G(d) geometries of cations **4**. Selected distances are shown in Å.



5 (n=1) **5** (n=2) **5** (n=3) **5** (n=4)

6 (n=1) **6** (n=2) **6** (n=3) **6** (n=4)

FIGURE 4. B3LYP/6-31G(d) geometries of cations **5** and **6**. Selected distances are shown in Å.

CHART 1

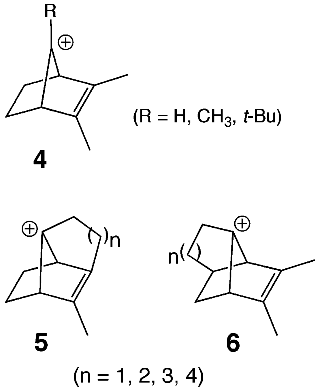


Figure 4 shows the geometries of structures **5** and **6** ($n = 1-4$). The **5** series demonstrates that the strength of the cation−alkene interaction (as judged by the cation−alkene distances) is somewhat dependent on the length of the tether, although in all cases cation−alkene interactions are observed. Not surprisingly, shortening the tether serves to force the alkene and cationic center into closer proximity. The **6** series reveals the effects of moving the tether to the side of the molecule opposite to the alkene. When the tether is long enough ($n = 3$ or 4), cation−alkene interactions are observed. However, as the tether length is reduced, stabilization of the cationic carbon through hyperconjugation with its three β-C−C bonds competes with stabilization by direct interaction

---

(15) For seminal and leading references, see: (a) Winstein, S.; Shatavsky, M.; Norton, C.; Woodward, R. B. *J. Am. Chem. Soc.* **1955**, *77*, 4183−4184. (b) Winstein, S.; Stafford, E. T. *J. Am. Chem. Soc.* **1957**, *79*, 505−506. (c) Woods, W. G.; Carboni, R. A.; Roberts, J. D. *J. Am. Chem. Soc.* **1962**, *84*, 4876−4882. (d) Gassman, P. G.; Fentiman, A. F., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 2549−2551. (e) Lustgarten, R. K.; Brookhart, M.; Winstein, S.; Gassman. P. G.; Patton, D. S.; Richey, H. G., Jr.; Nichols, J. D. *Tetrahedron* Lett. **1970**, *20*, 1699−1702. (f) Spurlock, L. A.; Mikuriya, Y. *J. Org. Chem.* **1971**, *36*, 1549−1553. (g) Olah, G. A.; Liang, G. *J. Am. Chem. Soc.* **1975**, *97*, 6803−6806. (h) Bremer, M.; Schotz, K.; Schleyer, P. v. R.; Fleischer, U.; Schindler, M.; Kutzelnigg, W.; Koch, W.; Pulay, P. *Angew. Chem.* **1989**, *101*, 1063−1065; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1042. (i) Laube, T. *Acc. Chem. Res.* **1995**, *28*, 399−405.

(16) See, for example: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: Chichester, 1976; p 85.

with the alkene. For **6** ($n = 1$), one of the hyperconjugated bonds actually breaks, producing a new architecture that resembles a cyclopentadiene interacting weakly with an appended secondary cation, that is itself stabilized though hyperconjugation.

Conclusions

Johnson's synthesis of longifolene was a triumph, not only demonstrating the ever growing prowess of organic synthesis but also showcasing the viability of enzyme-free carbocation polycyclizations. It also demonstrated that knowledge of and speculation on the biosynthesis of complex organic molecules can be a useful source of inspiration for synthesis design; this remains true today.[1,2] As shown herein, the allyl−alkenyl−norbornenyl polycyclization used for forming the longifolene core is energetically viable. This sequence results in a nonclassical norbornenyl cation, and our computations show that the cation−alkene interaction in this system is actually slightly enhanced by the presence of the alkyl tether. Although the strength of this interaction is somewhat sensitive to the length and orientation of the tether, the delocalized norbornenyl core is overall quite robust.

Acknowledgment. We gratefully acknowledge the University of California, Davis, the donors of the American Chemical Society Petroleum Research Fund, and the National Computational Science Alliance for support of this research.

Supporting Information Available: Coordinates and energies for all computed structures, along with IRC plots. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0503658