Nonclassical Carbocations

Proton Sandwiches: Nonclassical Carbocations with Tetracoordinate Protons[**]

*Pradeep Gutta and Dean J. Tantillo**

Nature makes an astonishing array of complex terpenoid natural products from only a few simple achiral, acyclic precursors such as farnesyl pyrophosphate.[1] Still, many details of terpenoid cyclization mechanisms are unknown. One outstanding issue is whether nonclassical carbocations are involved in these mechanisms,[1,2] and if so, then when, where, and why? During our ongoing theoretical studies on the mechanisms of terpenoid cyclizations, we encountered the unusual carbocation **1** (Figure 1).[3,4] In this complex cation, a formally tetracoordinate proton is seemingly suspended between two C=C bonds on opposite sides of a cyclooctadiene ring.

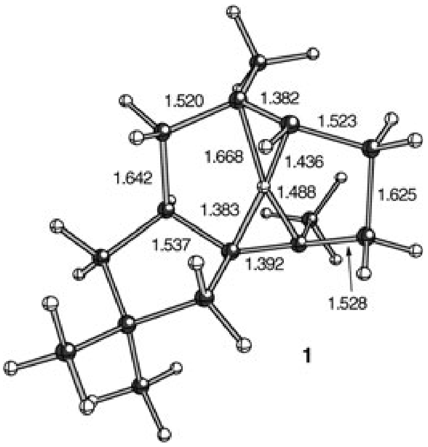

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Figure 1. Optimized (B3LYP/6-31+G(d,p)) geometry of cation **1** (C black, H white). Selected bond lengths (Å) are shown.

Intrigued by this structure, we set out to explore simpler related species to see how common this structural motif might be. Initially we explored models based on 1,5-cyclooctadiene (**2**; Figure 2). Addition of a proton between its two C=C bonds followed by geometry optimization (using either B3LYP/6-31+G(d,p) or MP2/6-31+G(d,p)) led to cation **3** (Figure 3).[4] The geometry of cation **3**, which is D_2-symmetric,

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Supporting information, which includes coordinates and energies for all structures, for this article is available on the WWW under http://www.angewandte.org or from the author.

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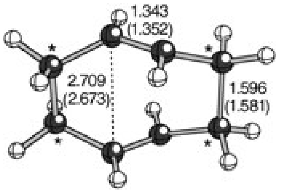
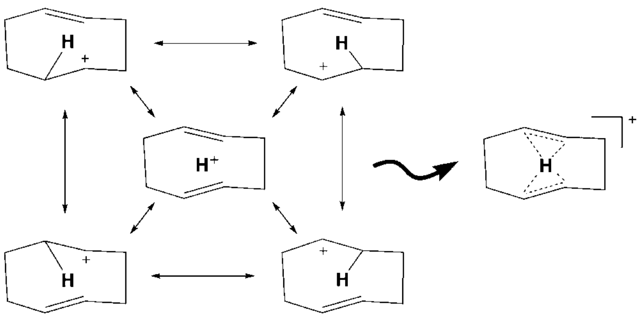


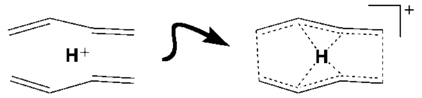
Figure 2. Structure of cyclooctadiene **2**. Selected bond lengths and distances (Å; B3LYP/6-31+G(d,p) (MP2/6-31+G(d,p) in parentheses)) are shown. ⋆ indicates carbon atoms of doubly allylic bonds.

is quite similar to the core of **1**.[5] The central proton of **3** is shared evenly by all four "alkene" carbon atoms at a distance of 1.48 Å (B3LYP level) or 1.46 Å (MP2 level) from each;[6] C···H distances in both cyclic[7] and acyclic[8] three-center, two-electron $[\mathrm{C{\cdots}H{\cdots}C}]^+$ cations are less, typically around 1.3 Å. The double bonds in **2** appear to be well-preorganized to chelate a proton and are lengthened upon doing so as they share their electron density with the sandwiched proton. Overall, cation **3** can be viewed as a hybrid of the resonance structures shown in Scheme 1, a very unusual flavor of nonclassical cation[9] that boasts a five-center, four-electron bonding array.



Scheme 1. Resonance structures for cation **3**.

Interestingly, both doubly allylic bonds (between carbon atoms marked with asterisks in Figure 2) of **2** are slightly lengthened upon addition of the proton, which indicates that they may help stabilize the four equivalent resonance structures shown in Scheme 1.[10] If the limiting resonance structure, which is shown at the left of Scheme 2 and consists of a proton sandwiched between two butadienes, is a significant contributor, then we arrive at the very unusual resonance hybrid shown at the right of Scheme 2, a nine-center, eight-electron species.[11,12]



Scheme 2. Additional resonance structure (left; a proton sandwiched between two butadienes) and resulting resonance hybrid (right; a nine-center, eight-electron species) for **3**.

Let us now consider the distribution of charge throughout the molecule. Computed atomic charges[13] are shown in Figure 4a and the electrostatic potential of **3**,[14] mapped onto a surface that approximates the van der Waals surface of this species, is shown in Figure 4b. The central proton is the most positive atom in **3**, but positive charge is still delocalized over the molecule. In addition, it appears that access to the central proton is somewhat limited. The computed chemical shift of the central proton is also quite unusual with $\delta = +13.45$ ppm (GIAO/B3LYP/6-31+G(d,p) level) or $\delta = +13.33$ ppm (GIAO/MP2/6-31+G(d,p) level).[15,16] These chemical shift values are quite unlike those observed experimentally and computationally for protons in stable three-center, two-electron $[\mathrm{C{\cdots}H{\cdots}C}]^+$ cations, which typically range from $\delta = -7$ to -3 ppm.[8,17] Clearly, whereas the hydrogens in $[\mathrm{C{\cdots}H{\cdots}C}]^+$ cations are quite electron-rich (hydride-like), the hydrogen in cation **3** is quite electron-deficient.

One qualitative approach to constructing the molecular orbitals of the nine-center array in **3** is to build them from combinations of the π orbitals of butadiene and the s orbital of a proton. This leads to the orbitals shown at the center of Figure 4c. This qualitative picture is also reflected in the Kohn–Sham orbitals[18] from our B3LYP/6-31+G(d,p) calculations which are shown on the outside of Figure 4c. Wiberg bond indices[13c] for the C···H bonds, partial C⩵C double bonds, and doubly allylic C–C bonds are 0.21, 1.65, and 0.94, respectively, and these values are most consistent with the five-center, four-electron picture described above (see Scheme 1).

What are the limits on forming cations such as **3**?[12] Although cation **3** is highly delocalized, protonation of cyclooctadiene **2** on the "outside" actually leads to a more stable isomer, **4** (Figure 5).[19a] Structure **4** is approximately 40 kcal mol^{-1} lower in energy than **3** (39.6 and 40.3 kcal mol^{-1} at the B3LYP/6-31+G(d,p) and MP2/6-31+G(d,p) levels, respectively), perhaps, at least in part, because **4** allows an alternative nonclassical (three-center, two-electron) bonding array to form. The barrier for rearrangement of **3** to **4**, via the transition-state structure shown in Figure 6,[4b] is computed to be 2.8 kcal mol^{-1} at the B3LYP/6-31+G(d,p) level and

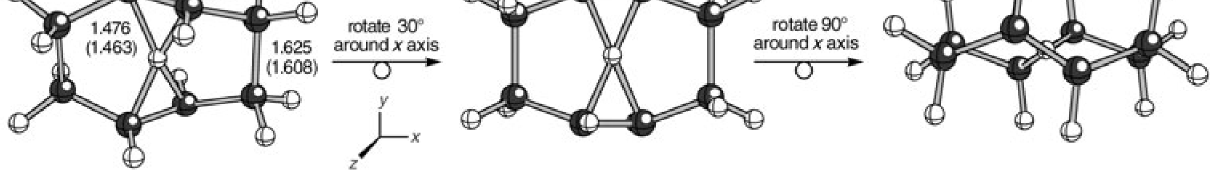


Figure 3. Three views of cation **3**. Selected bond lengths (Å; B3LYP/6-31+G(d,p) (MP2/6-31+G(d,p) in parentheses)) are shown.

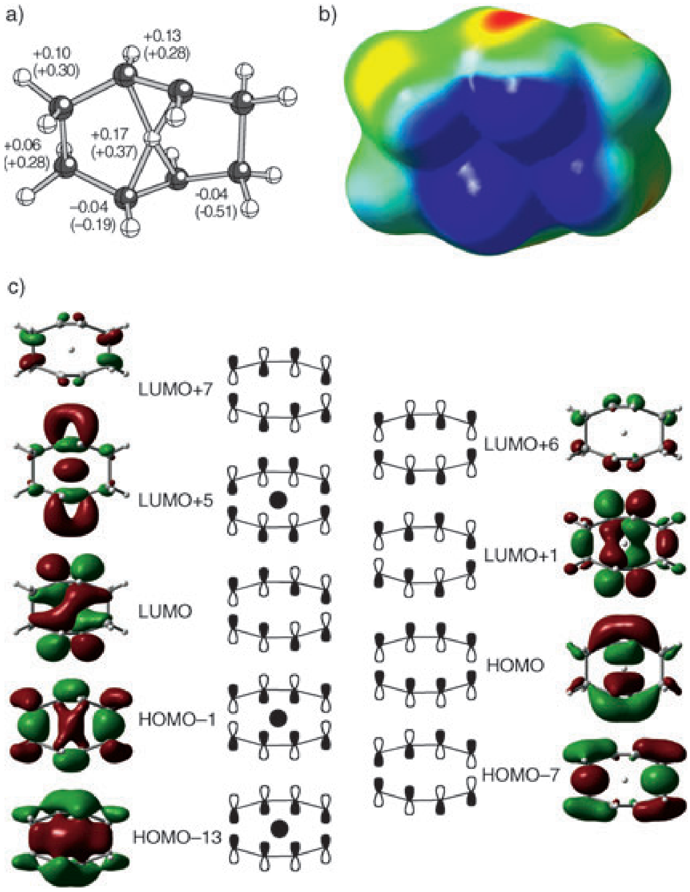


Figure 4. a) Computed atomic charges (B3LYP/6-31 + G(d,p): CHelpG (NBO in parentheses)[13]), b) electrostatic potential surface constructed from the B3LYP density (blue is most positive and red is least positive), and c) qualitative and computed (B3LYP/6-31 + G(d,p), isovalue = 0.04) molecular orbitals corresponding to the "butadienes + H" picture of bonding discussed in the text for cation **3**. Relative sizes of component atomic orbitals are not considered in the qualitative picture.

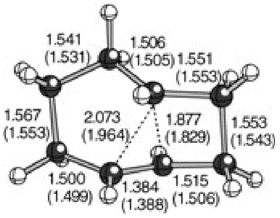


Figure 5. Computed geometry of the "out" protonated isomer **4**. Selected bond lengths and distances (Å; B3LYP/6-31 + G(d,p) (MP2/6-31 + G(d,p) in parentheses)) are shown.

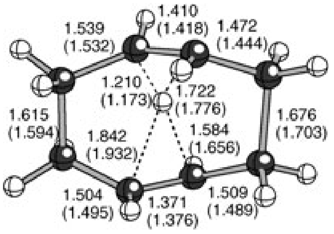


Figure 6. Computed geometry of the transition state for the isomerization of **3** to **4**. Selected bond lengths and distances (Å; B3LYP/6-31 + G-(d,p) (MP2/6-31 + G(d,p) in parentheses)) are shown.

8.5 kcal mol^{-1} at the MP2/6-31 + G(d,p) level.[19b] Note that, as expected for a very exergonic reaction, this is an early transition state, dominated by shifting of the proton. Note also that one of the doubly allylic bonds lengthens, which is indicative of hyperconjugative stabilization of the positive charge that builds up in its vicinity as the proton moves away from its central position. Whether or not suitably substituted systems that favor "in-protonation" or protect such "in-protonated" structures can be contrived is an open question.[20,21]

The propensities of other 1,5-cyclooctadiene isomers to form cations such as **3** were also explored.[12] First, there is another conformer of (*E*,*E*)-**2**. This structure, shown at the top of Figure 7, is less stable than **2** by 6.5 kcal mol^{-1} at the B3LYP/6-31 + G(d,p) level and 7.9 kcal mol^{-1} at the MP2/6-31 + G(d,p) level, and its two C=C bonds are parallel rather than "crossed" as they are in **2**. This arrangement is also suitable for sandwiching a proton, and C_{2h}-symmetric structure **5** is the energy-minimized structure of the resulting carbocation (Figure 8). Analogous delocal-

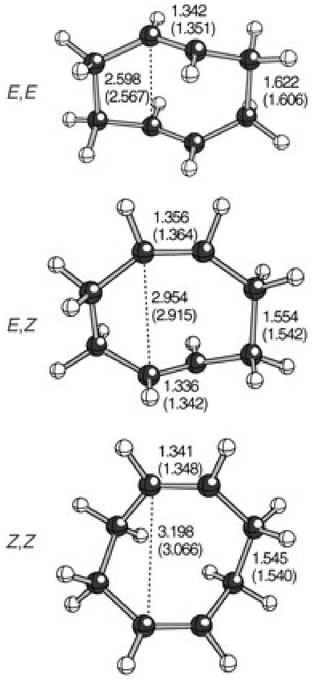


Figure 7. Computed geometries of cyclooctadienes. Selected bond lengths and distances (Å; B3LYP/6-31 + G(d,p) (MP2/6-31 + G(d,p) in parentheses)) are shown.

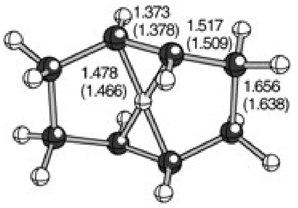


Figure 8. Geometry of cation **5**. Selected bond lengths (Å; B3LYP/6-31 + G(d,p) (MP2/6-31 + G(d,p) in parentheses)) are shown.

ized cations could not, however, be located for *E*,*Z* and *Z*,*Z* isomers of **2** (Figure 7).[22] This finding is consistent with the fact that the *E*,*E* isomers seem to be better preorganized to share a proton; that is, they have shorter distances between their double bonds.

In summary, we have described a new type of nonclassical carbocation with a tetracoordinate proton. While exotic in their appearance, such species might be formed from suitable cyclooctadienes or by rearrangements of other cations and may even play a role in some biosynthetic terpenoid cyclizations. We are exploring both of these possibilities.[3] The prospect that such intermediates can lead to many different species through simple addition, rearrangement, or deprotonation reactions is particularly attractive from the perspective of reaction design.

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[1] For leading references, see: a) D. E. Cane, *Chem. Rev.* **1990**, *90*, 1089–1103; b) K. U. Wendt, G. E. Schulz, E. J. Corey, D. R. Liu, *Angew. Chem.* **2000**, *112*, 2930–2952; *Angew. Chem. Int. Ed.* **2000**, *39*, 2812–2833; c) I. Abe, M. Rohmer, G. D. Prestwich, *Chem. Rev.* **1993**, *93*, 2189–2206; d) T. Hoshimo, T. Sato, *Chem. Commun.* **2002**, 291–301; e) D. E. Cane, *Acc. Chem. Res.* **1985**, *18*, 220–226.

[2] For leading references on proposed nonclassical intermediates in terpenoid biosynthesis, see: a) L. A. Wessjohann, W. Brandt, *Chem. Rev.* **2003**, *103*, 1625–1647; b) J.-L. Giner, P. Buzek, P. v. R. Schleyer, *J. Am. Chem. Soc.* **1995**, *117*, 12871–12872; c) H. K. Erickson, C. D. Poulter, *J. Am. Chem. Soc.* **2003**, *125*, 6886–6888; d) X. He, D. E. Cane, *J. Am. Chem. Soc.* **2004**, *126*, 2678–2679; e) M. J. S. Dewar, J. M. Ruiz, *Tetrahedron* **1987**, *43*, 2661–2674; f) G. A. Olah, *Angew. Chem.* **1995**, *107*, 1519–1532; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1393–1405; g) For leading references to older proposals by Djerassi, Arigoni, and Eschenmoser, see: J.-L. Giner, *Chem. Rev.* **1993**, *93*, 1735–1752.

[3] P. Gutta, D. J. Tantillo, unpublished results. Preliminary calculations indicate that **1** lies on the pathway between the farnesyl cation and pentalenene, a polycyclic terpenoid natural product, at least in the absence of a surrounding enzyme (see Ref. [1] for background on this and related terpenoid cyclizations).

[4] a) All calculations were performed with Gaussian03 (Revision B.04), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **2003**; b) Geometries were optimized without symmetry constraints using B3LYP/6-31+G(d,p) (A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372–1377; C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789; P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623–11627) and MP2/6-31+G(d,p) (C. Møller, M. S. Plesset, *Phys. Rev.* **1934**, *46*, 618–622). All structures were characterized by frequency calculations, and reported energies include zero-point energy corrections (unscaled). Intrinsic reaction coordinate (IRC) calculations (C. Gonzalez, H. B. Schlegel, *J. Phys. Chem.* **1990**, *94*, 5523–5527 and K. Fukui, *Acc. Chem. Res.* **1981**, *14*, 363–368) were also used to verify the identity of the transition structure associated with the interconversion of **3** and **4**; c) Extremely similar results (for both geometries and relative energies) were obtained by using the 6-311+G(d,p) basis set. For example, for cation **3**, the biggest change in bond lengths on going from the double-zeta to triple-zeta basis set was 0.004 Å with both B3LYP and MP2, and predicted barriers for the **3**-to-**4** rearrangement changed by less than 0.5 $\mathrm{kcal\,mol^{-1}}$ for each. See Supporting Information for additional details; d) For recent reports that compare the B3LYP and MP2 methods for computing geometries and relative energies of small three-center, two-electron cations, see: I. V. Vrcek, V. Vrcek, H.-U. Siehl, *J. Phys. Chem. A* **2002**, *106*, 1604–1611 and D. Farcasiu, P. Lukinskas, S. V. Pamidighantam, *J. Phys. Chem. A* **2002**, *106*, 11672–11675; e) Structural drawings were produced by using Ball & Stick (N. Müller, A. Falk, Ball & Stick V.3.7.6—Molecular Graphics Application for MacOS Computers, Johannes Kepler University, Linz, **2000**).

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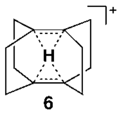
[10] Note that the doubly allylic bonds in **2** are already rather long, presumably as a result of through-bond coupling between the two alkenes. For leading references on through-bond coupling in

related systems, see: a) H. Gan, M. G. Horner, B. J. Hrnjez, T. A. McCormack, J. L. King, Z. Gasyna, G. Chen, R. Gleiter, N. C. Yang, *J. Am. Chem. Soc.* **2000**, *122*, 12098–12111; b) R. Gleiter, W. Schäfer, *Acc. Chem. Res.* **1990**, *23*, 369–375.

[11] a) This species can also be thought of as a σ-polyacene with a proton sandwiched between its two polyene chains. For details on σ-polyacenes, see: D. J. Tantillo, R. Hoffmann, K. N. Houk, P. W. Warner, E. C. Brown, D. K. Henze, *J. Am. Chem. Soc.* **2004**, *126*, 4256–4263; b) In addition, **3** can be thought of as a protonated version of a suprafacial–suprafacial transition state for [4+4] dimerization of butadiene. For a recent discussion on the protonation of pericyclic transition structures, see: R. Hoffmann, D. J. Tantillo, *Angew. Chem.* **2003**, *115*, 6057–6062; *Angew. Chem. Int. Ed.* **2003**, *42*, 5877–5882.



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[12] a) Addition of methoxy groups to all four carbon atoms of the doubly allylic bonds results in a structure which is similar to that of **3**, but with slightly lengthened (1.652 Å) doubly allylic bonds; b) The following structure, **6**, has also been shown to contain a tetracoordinate proton; P. von R. Schleyer, personal communication after this manuscript was submitted.

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[16] The computed chemical shifts for all of the other protons in **3** ranged between $\delta = +3.08$ and $+6.16$ ppm at the B3LYP/6-31+G(d,p) level ($+2.99$ and $+5.93$ ppm at the MP2/6-31+G(d,p) level). All values are referenced to that for the protons in tetramethylsilane ($\delta = 0.00$ ppm).

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[18] R. Stowasser, R. Hoffmann, *J. Am. Chem. Soc.* **1999**, *121*, 3414–3420.

[19] a) For an excellent review on "in–out" isomerism see: R. W. Alder, S. P. East, *Chem. Rev.* **1996**, *96*, 2097–2111; b) The possibility that tunneling may contribute to rearrangements of **3** was suggested by a referee. However, additional calculations will be required to test this proposition.

[20] Note that the computed proton affinity of **2** (to form **3**) is 182.8 kcal mol^{-1} at the B3LYP/6-31+G(d,p) level, considerably larger than values for normal alkenes, which are typically around 165 kcal mol^{-1}. See Ref. [11b] as well as F. A. Carroll, *Perspectives on Structure and Mechanism in Organic Chemistry*, Brooks/Cole, Pacific Grove, **1998**, and references therein.

[21] There is also an analogy between **3** and the well-known bis-amine "proton sponges" in that they both chelate protons. For reviews on "proton sponges", see: a) H. A. Staab, T. Saupe, *Angew. Chem.* **1988**, *100*, 895–909; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 885–887; b) A. L. Llamas-Saiz, C. Foces-Foces, J. Elguero, *J. Mol. Struct.* **1994**, *328*, 297–323; See also Ref. [6].

[22] The energies of the *E*,*Z* and *Z*,*Z* isomers, relative to that of **2**, are −3.1 and −22.9 kcal mol^{-1} at the B3LYP/6-31+G(d,p) level and +1.1 and −18.9 kcal mol^{-1} at the MP2/6-31+G(d,p) level, respectively.