of a large atom such as phosphorus are relatively constant among the analogous cations **4**–**6**. Since the anomalously high ^{31}P NMR shielding value in **5** (−42.9 ppm) compared with **6** (−11.0 ppm) and **4** (−10.1 ppm) obviously cannot be rationalized upon inductive grounds, the only major factors remaining in the model are the orbital charge imbalance terms in the paramagnetic shielding equation which then must be small for **5** compared with **4** and **6**, thus leading to pronounced ^{31}P shielding associated with greater orbital charge balance[11] in **5**. Decreased orbital charge imbalance signaling a greater basicity of **2** can also account for the upfield shift of **2** (89.3 ppm) relative to the shifts of **1** and **3** (120.8[1] and 128.3 ppm, respectively).

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for a grant supporting this work. We also thank Dr. Lee Daniels of the Iowa State Molecular Structure Laboratory for the crystal and molecular structure of **5**(Cl), Dr. W. Menge for his synthetic route to $(HBzNCH_2CH_2)_3N$, and the W. R. Grace Company for a research sample of tren.

Supplementary Material Available: ^1H, ^{13}C, and ^{31}P NMR and high-resolution mass spectral data and tables of X-ray crystallographic data, positional parameters, bond distances and angles, and general displacement parameters for **5**(Cl) (7 pages); listing of observed and calculated structure factors for **5**(Cl) (4 pages). Ordering information is given on any current masthead page.

(11) Wrackmeyer, B. *Annu. Rep. NMR Spectrosc.* **1985**, *16*, 73.

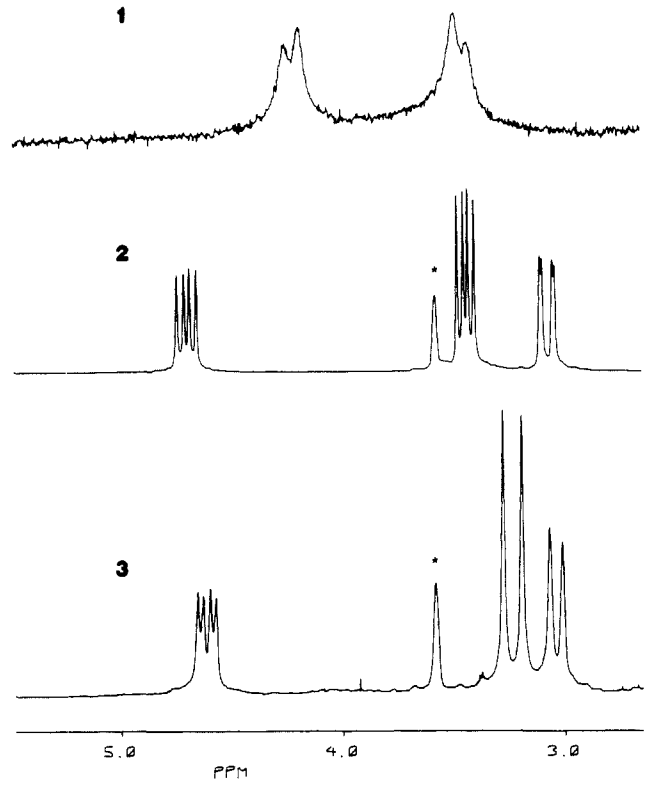


Figure 1. Portion of the ^1H NMR spectra of **1** in $CDCl_3$, **2** in THF-d_8, and **3** in THF-d_8. Peaks marked with an asterisk are due to THF-d_8. Coupling constant data for **2**: δ 3.07 ($^5J_{PH}$ = 2.0 Hz), 4.69 ($^5J_{PH}$ = 6.4 Hz, $^2J_{HH}$ = 11.2 Hz), 3.44 ($^3J_{PH}$ = 9.7 Hz, $^3J_{HH}$ = 5.6 Hz). For **3**: δ 3.04 ($^5J_{PH}$ not observed), 4.61 ($^5J_{PH}$ = 4.9 Hz, $^2J_{HH}$ = 11.3 Hz), 3.44 ($^3J_{PH}$ = 16.9 Hz).

Putting "Bottoms on Baskets". The First Main-Group-Element Single-Atom Bridge of a Calixarene

Dilip V. Khasnis and Michael Lattman*

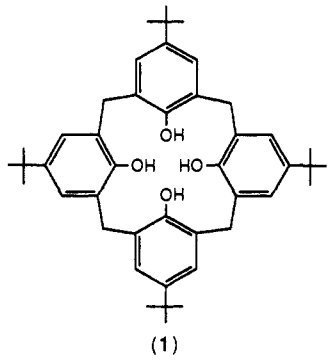
Department of Chemistry
Southern Methodist University, Dallas, Texas 75275

C. David Gutsche*

Department of Chemistry, Box 32908
Texas Christian University, Fort Worth, Texas 76129

Received July 30, 1990

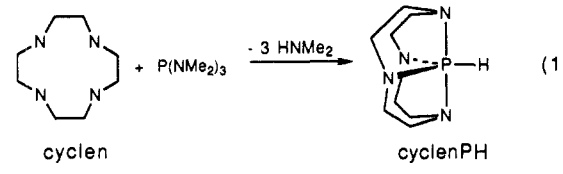
Calixarenes are unique macromolecules that have been shown to be important as complexing agents, biomimics, physiological compounds, and catalysts.[1] We have been interested in putting a "bottom on the basket" of *p-tert*-butylcalix[4]arene (**1**) by



(1)

connecting the oxygens with a single "hypervalent" main-group atom. A recent report in which a metal atom is used to tie the oxygens together[2] prompts us to communicate our efforts. We herein report the reaction of **1** with tris(dimethylamino)phosphine, which links all four oxygens to the phosphorus in an unexpected coordination mode.

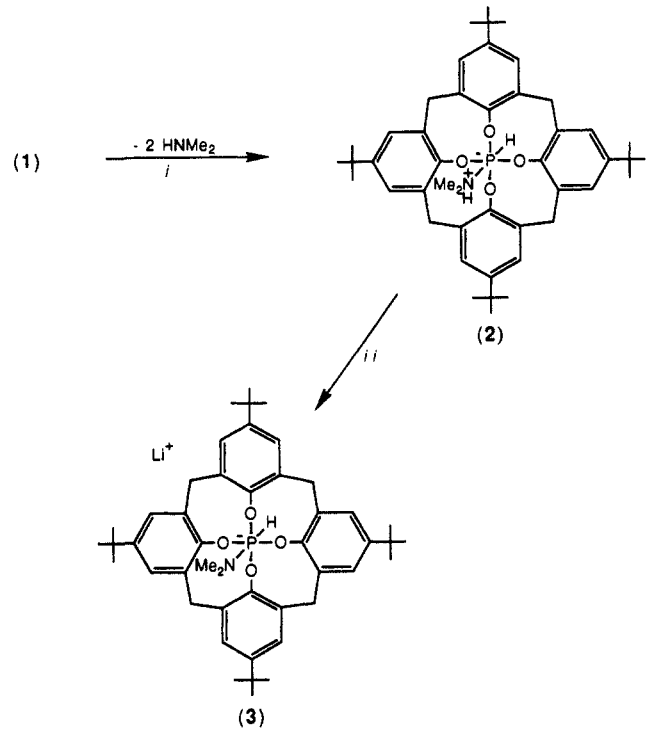
Treatment of **1**[3] with $P(NMe_2)_3$ in benzene yields a precipitate (**2**) which, when dissolved in THF-d_8, shows a peak in the ^{31}P NMR spectrum at δ −120 with a large phosphorus–proton coupling constant of 733 Hz. The upfield position of the ^{31}P chemical shift indicates a high coordinate phosphorus, and the large coupling constant suggests a direct P–H bond. The OH resonance at δ 10.33 in the ^1H NMR spectrum of **1** is absent in **2**. The *tert*-butyl and aromatic protons appear as singlets at δ 1.20 and 7.01, respectively, while the P–H resonance is centered at δ 4.45. The methylene resonances at δ 3.07 and 4.69 are doublets of doublets and are shown in Figure 1 (the second doublet at δ 3.07 is barely discernible). One doublet of each resonance is due to phosphorus coupling (confirmed by $^1H\{^{31}P\}$ NMR spectroscopy) while the other is due to geminal proton coupling. These peaks can be compared to the starting material in Figure 1 (the broadness of the peaks in **1** and their assignments have been discussed elsewhere).[1,4] Doublets for these methylene resonances (in systems with no phosphorus coupling) have been taken to indicate the cone conformation for calix[4]arenes.[1] If these were the only peaks present, it would suggest that the reaction proceeded analogously to that for the synthesis of cyclenphosphorane (cyclenPH),[5] where



(1) (a) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. (b) Gutsche, C. D. In *Synthesis of Macrocycles*; Izatt, R. M., Christensen, J. J., Eds.; Wiley: New York, 1987; pp 93–165.
(2) Corazza, F.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *J. Chem. Soc., Chem. Commun.* **1990**, 640.
(3) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1989**, *68*, 234.
(4) (a) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052. (b) Kämmerer, H.; Happel, G.; Caesar, F. *Makromol. Chem.* **1972**, *162*, 179. (c) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1984**, 981.

0002-7863/90/1512-9422$02.50/0

Scheme I[a]



[a] Reagents and solvents: (i) $P(NMe_2)_3$, benzene; (ii) butyllithium, THF.

3 mol of dimethylamine are eliminated and one proton is transferred from nitrogen to phosphorus, as was originally anticipated. However, an additional four-line resonance is seen in the ^1H NMR spectrum of **2** at δ 3.44, as well as a broad peak at δ 7.8. The former integrates for six protons while the latter for one. The multiplicity of the δ 3.44 signal is puzzling since, if it is due to a dimethylamino group bonded to phosphorus, a doublet would be expected. In fact, ^{31}P decoupling and homonuclear ^1H decoupling show that one doublet of this resonance is due to phosphorus coupling while the other is due to coupling from the proton at δ 7.8.

Deprotonation of **2** with butyllithium was attempted, a method that successfully cleaves the P-H bond in cyclenPH to yield a phosphoranide ion.[6] In the present case, the P-H bond is not cleaved: the product **3** has a ^{31}P resonance at δ -113 with an even larger P-H coupling of 836 Hz. The ^1H NMR spectrum of **3** still shows singlets for the *tert*-butyl (δ 1.19) and aromatic (δ 6.97) protons but no longer has the broad peak at δ 7.8; the "dimethylamino" resonance, now at δ 4.61, is a doublet. (In addition, the small phosphorus coupling in the upfield methylene resonance is no longer observed.)

Taken together, the above data indicate that the initial product **2** has a phosphorus connected not only to the four oxygens, but also to hydrogen and dimethylamine, to yield a zwitterionic species. In the initial reaction, the calix[4]arene transfers one proton to the phosphorus and three to the dimethylamino groups; however, only two dimethylamines are given off. Deprotonation of **2** cleaves the N-H rather than the P-H bond to give **3**. These reactions are summarized in Scheme I.

Further support for these formulations comes from a molecular weight determination (vapor pressure osmometry) of **2**, which yielded a value of 701 (calculated 722) indicating that the compound is monomeric.[7] In fact, the ^{31}P NMR chemical shifts of these species are more in the hexacoordinate than pentacoordinate region.[8] Low-temperature ^1H and ^{31}P NMR spectra of **2** to -70 °C are identical with the ambient-temperature spectra, except for some broadening in the ^1H peaks; this suggests that the observed spectra are in fact due to all four oxygens being bound to phosphorus rather than a fast exchange process equilibrating the rings (in which, for example, only three P-O bonds are present at any one time). All attempts at growing X-ray quality crystals of **2** have, so far, been unsuccessful.

As mentioned above, the methylene resonances suggest a cone conformation for **2**, however, at this time, we do not know the orientations of the hydrogen and amine with respect to the cone, although steric factors would argue that the amine is outside and the hydrogen inside.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society (M.L.), the Robert A. Welch Foundation (M.L. and C.D.G.), and National Institutes of Health Grant GM-23534 (C.D.G.) for generous financial support. We thank Dr. Mark O'Neil-Johnson of Bruker Instruments for obtaining the $^1H\{^{31}P\}$ NMR spectra.

(5) Richman, J. E.; Atkins, T. J. *Tetrahedron Lett.* **1978**, 4333.

(6) Lattman, M.; Olmstead, M. M.; Power, P. P.; Rankin, D. W. H.; Robertson, H. E. *Inorg. Chem.* **1988**, *27*, 3012.

(7) Synthesis of **2**: In an inert atmosphere, a stirred slurry of **1** (130 mg, 0.20 mmol) in benzene (10 mL) was treated dropwise with $P(NMe_2)_3$ (65 μL, 0.36 mmol). After stirring for 24 h, the resulting precipitate was filtered, washed with benzene, and pumped dry, yielding **2** as a white, air-stable solid (115 mg, 80%): mp (nitrogen-filled tube) 385-387 °C; satisfactory elemental analyses (CHN) for **2** were obtained; $^{13}C\{^1H\}$ NMR (THF-d_8), δ 31.8 [C-$(CH_3)_3$, s], 34.6 [$C(CH_3)_3$, s], 36.3 (CH_2, s), 44.6 [$N(CH_3)_2$, d, $^2J_{PC}$ = 4 Hz], 124.7 (CH, s), 138.6 [$C(CH_2)$, d, $^3J_{PC}$ = 9 Hz], 145.7 [$CC(CH_3)_3$, d, $^5J_{PC}$ = 5 Hz], 149.0 (CO, d, $^2J_{PC}$ = 7 Hz).

(8) Tebby, J. C. In *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; Verkade, J. G., Quin, L. D., Eds.; VCH: Deerfield Beach, FL, 1987; Chapter 1.

Reaction of the Quinone Methide from Reductive Glycosidic Cleavage of Daunomycin with Molecular Oxygen. Evidence for Semiquinone Methide Formation[1]

Giorgio Gaudiano and Tad H. Koch*

Department of Chemistry and Biochemistry
University of Colorado, Boulder, Colorado 80309-0215

Received April 25, 1990

Anthracycline antitumor drugs, especially adriamycin and daunomycin (**1**),[2] are proposed to be bioreductively activated to semiquinone, hydroquinone, and quinone methide states through sequential one-electron reductions.[3,4] All of these states are of biological interest with regard to mechanisms of cytotoxicity. Semiquinone and hydroquinone states react rapidly with molecular oxygen to produce reactive oxygen species that inflict oxidative stress.[5] In the absence of molecular oxygen, the hydroquinone state of daunomycin (**1**) undergoes elimination of daunosamine to give the quinone methide **2**.[4,6-8] Quinone methides are of

(1) Financial assistance is gratefully acknowledged from U.S. PHS (Grant CA-24665) and the University of Colorado CRCW (faculty fellowship to T.H.K.). We thank Dr. Sergio Penco of Farmitalia Carlo-Erba for samples of **1** and **6** and an NMR spectrum of **3**, Mr. Ronald Sadecky and Dr. Robert Barkley for the MS measurements, and Dr. Ned Porter for helpful suggestions.

(2) Arcamone, F. *Doxorubicin Anticancer Antibiotics*; Academic Press: New York, 1981.

(3) Moore, H. W. *Science (Washington, D.C.)* **1977**, *197*, 527. Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249. Abdella, B. R. J.; Fisher, J. *Environ. Health Perspect.* **1985**, *64*, 3. Powis, G. *Pharmacol. Ther.* **1987**, *35*, 57.

(4) Kleyer, D. L.; Koch, T. H. *J. Am. Chem. Soc.* **1984**, *106*, 2380.

(5) Bachur, N. R.; Gordon, S. L.; Gee, M. V. *Mol. Pharmacol.* **1977**, *13*, 901. Lown, J. W.; Sim., S.-K.; Majumdar, K. C.; Change, R. Y. *Biochem. Biophys. Res. Commun.* **1977**, *76*, 705. Lown, J. W.; Chen, H.-H.; Plambeck, J. A.; Acton, E. M. *Biochem. Pharmacol.* **1982**, *31*, 575. Davies, K. J. A.; Doroshow, J. *J. Biol. Chem.* **1986**, *261*, 3060. Doroshow, J.; Davies, K. J. A. *J. Biol. Chem.* **1986**, *261*, 3068. Doroshow, J. H. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4514. Powis, G. *Free Radicals Biol. Med.* **1989**, *6*, 63.

0002-7863/90/1512-9423$02.50/0