2318 *J. Am. Chem. Soc.* **1989**, *111*, 2318-2319

Chiral Recognition in the Synthesis of Dimetalla-4-*tert*-butylcalix[8]arene Complexes. The Incorporation of a Metal Alkoxide Ligand into a Molecular Cavity

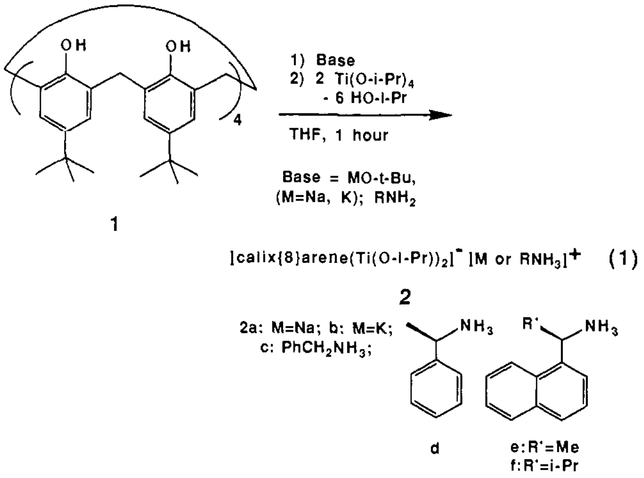
Gretchen E. Hofmeister, F. Ekkehardt Hahn, and
Steven F. Pedersen*

Department of Chemistry, University of California
Berkeley, California 94720

Received November 3, 1988

The ease with which the calixarenes[1] are made, and the large number of potential binding sites they offer, make them especially attractive ligands for the incorporation of transition-metal ions.[2] We have focused on preparing metallacalixarenes that contain a metal ligand directed into a cavity defined by the calixarene aryl groups. The confines of the cavity could then lead to shape selective reactions involving the encapsulated ligand and a substrate. Herein we describe the synthesis and characterization of a variety of chiral dimetalla-4-*tert*-butylcalix[8]arenes (dimetallacalixarenes).

The reaction between 4-*tert*-butylcalix[8]arene[3] (**1**) and 1 equiv of a base (eq 1) in tetrahydrofuran followed by the addition of 2 equiv of titanium(IV) isopropoxide provides yellow crystalline complexes of the general molecular formula [4-*tert*-butylcalix[8]arene $(\mathrm{Ti^{IV}(O\text{-}\mathit{i}\text{-}Pr)})_2]^-[\mathrm{M}$ or $\mathrm{RNH_3}]^+$ (**2**) (established by FAB-MS[4]). The ^{1}H NMR spectra of all of these complexes are similar and indicate the presence of some unique structural features. Each isopropoxide ligand has diastereotopic methyl group resonances located at approximately 0.5 and −1.0 ppm. The methine proton is observed at approximately 2.0 ppm (compare with 1.2 ppm ($\mathrm{CH_3}$) and 4.4 ppm (CH) for $\mathrm{Ti(O\text{-}\mathit{i}\text{-}Pr)_4}$). These upfield shifts indicate that the isopropoxide ligands experience the shielding of nearby aryl rings. The other unique resonance observed in these complexes arises from the remaining phenolic hydrogen; it is located between 15.0 and 17.0 ppm. This shift suggests that the proton is strongly hydrogen bonded,[5] most likely to another calixarene oxygen.



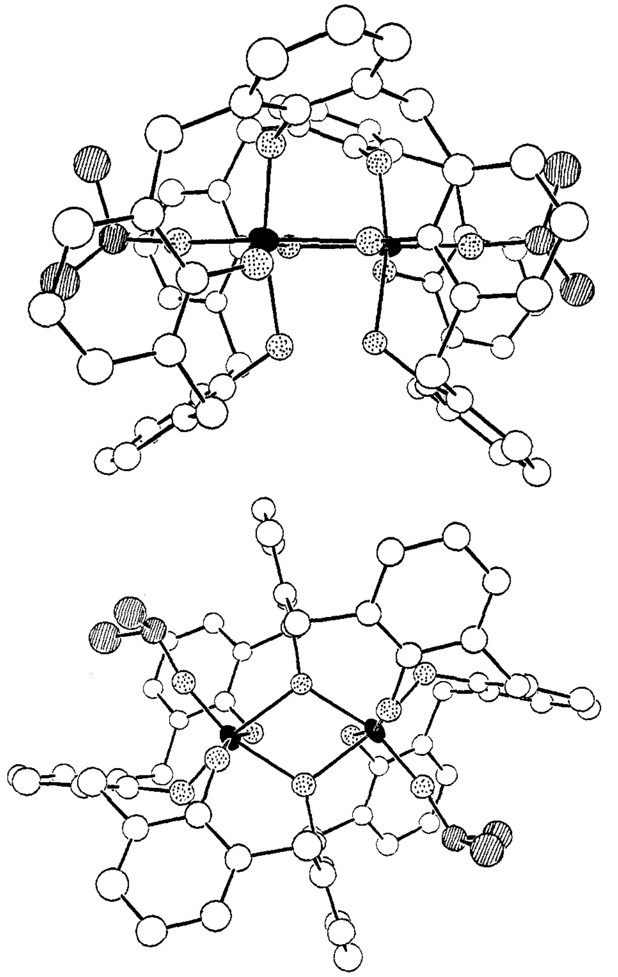


Figure 1. Two views of **2a**. Top: Side view. Bottom: A view from the bottom looking into the open side of the cavities. The *tert*-butyl groups have been omitted for viewing purposes. The isopropoxide carbons are striped; titanium atoms are solid; oxygen atoms are speckled; all other atoms belong to the calixarene ligand. The sodium ion is not interacting with the calixarene framework in the solid state and is therefore left out of the figure.

An X-ray crystal structure[6] of **2a** was obtained, and two views of this molecule are shown in Figure 1. The two titanium atoms are located in pseudooctahedral environments bonded to all eight of the calixarene oxygens, two of which are bridging.[7] The remaining coordination site on each titanium is filled by an isopropoxide ligand that is located inside a cavity defined by three aryl rings. This arrangement explains why the methyl groups in these complexes are experiencing such effective shielding in the ^{1}H NMR spectra (vide supra). The complex is chiral, a result of the conformation adopted by the macrocycle upon wrapping around the two titanium atoms.

The integrity of the conformation in solution was confirmed by using (*R*)-(+)-α-methylbenzylamine as the base in eq 1 and obtaining a 1:1 mixture of diastereomers (**2d**) (established by ^{1}H NMR spectra of the crude reaction mixture[8]). The use of

---

(1) Gutsche, C. D. In *Progress in Macrocyclic Chemistry*; Izatt, R. M., Christensen, J. J., Eds.; John Wiley and Sons, Inc.: New York, 1987; Vol. 3, Chapter 3.

(2) For complexes where the metal is bound directly to the calixarene oxygens, see: (a) Furphy, B. M.; Harrowfield, J. M.; Kepert, D. L.; Skelton, B. W.; White, A. H.; Wilner, F. R. *Inorg. Chem.* **1987**, *26*, 4231. (b) Andreetti, G. D.; Calestani, G.; Ugozzoli, F.; Arduini, A.; Ghidini, E.; Ungaro, R. *J. Incl. Phenom.* **1987**, *5*, 123. (c) Bott, S. G.; Coleman, A. W.; Atwood, J. L. *J. Chem. Soc., Chem. Commun.* **1986**, 610. (d) Olmstead, M. M.; Sigel, G.; Hope, H.; Xu, X.; Power, P. P. *J. Am. Chem. Soc.* **1985**, *107*, 8087.

(3) Gutsche, C. D.; Dhawan, B.; No, K.; Mathukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782.

(4) Compounds **2a–e** were all analyzed by positive ion FAB-MS in a 2-nitrophenyl octyl ether matrix (*m/e*): **2a**, 1551 ([M + Na]$^+$); **2b**, 1582 ([M − H + K]$^+$); **2c**, 1613 (M$^+$); **2d**, 1627 (M$^+$); **2e**, 1678 ([M + H]$^+$).

(5) Eyman, D. P.; Drago, R. S. *J. Am. Chem. Soc.* **1966**, *88*, 1617.

(6) Crystal data for **2a**: $\mathrm{C_{94}H_{119}O_{10}Ti_2Na}$ (formula does not include the five solvent molecules found in the crystal lattice), orthorhombic, *Pbca*, $T = -80$ °C, $a = 26.81$ (4) Å, $b = 29.37$ (3) Å, $c = 28.16$ (4) Å, $V = 22\,173.5$ Å^3, $Z = 8$, d(calcd) = 1.15 g cm^{-3}, $\mu = 2.047$ cm^{-1}. $R = 0.116$ and $R_w = 0.130$ (GOF = 4.47) for refinement on 6274 ($F^2 > 3\sigma(F^2)$) reflections, 548 variables. Due to unresolved disorder in the solvent molecules and high thermal motion (despite the low-temperature data collection), the structure could not be further refined. Details are found in the Supplementary Material.

(7) The mode of binding of the macrocycle in **2a** is similar to that recently described for a dieuropium(III)-4-*tert*-butylcalix[8]arene complex (ref 2a), suggesting that this may be a general structural type for dimetallacalix[8]arene complexes.

(8) The phenol hydroxyl region (15–17 ppm) is used to establish these ratios.

0002-7863/89/1511-2318$01.50/0 © 1989 American Chemical Society

(*R*)-(+)-1-(1-naphthyl)ethylamine enhances the diastereomeric ratio to 3:1 (**2e**). A 10:1 mixture of diastereomers is observed upon changing the α-methyl substituent in the latter amine to an isopropyl group (**2f**). Chiral recognition in these systems is proposed to result from the following interactions between the calixarene skeleton and the ammonium ion: (1) a hydrogen bond between an ammonium ion hydrogen and a phenolate oxygen and (2) the stacking[9] of one calixarene aryl ring with the naphthyl ring of the chiral amine. Evidence for the latter interaction is indicated by an upfield shift of one calixarene *tert*-butyl resonance per diastereomer (ca. 0.5 ppm for the minor and 1.0 ppm for the major diastereomer). This is not observed in the analogous sodium or potassium salts (**2a**,**b**). Furthermore, many of the resonances associated with these ammonium ions (e.g., methine, α-alkyl and naphthyl ring hydrogens) are shifted upfield (up to 1.3 ppm), relative to their analogous hydrochloride salts. Steric repulsion between the metallacalixarene frame and the α-alkyl substituent on the chiral amine would account for the third interaction necessary for chiral recognition.

The crystal structure together with space-filling models indicate that the shape and size of the cavities in **2** should prevent the synthesis of analogous dititanacalix[8]arene complexes containing sterically demanding alkoxide ligands. We have in fact observed that using Ti(O-*t*-Bu)$_4$ in place of Ti(O-*i*-Pr)$_4$ in eq 1 leads to a compound that is *not* structurally related to the isopropoxide complexes discussed above (deduced by ^{1}H NMR). However, reaction of this material with 2 equiv of isopropyl alcohol provides the isopropoxide complex in quantitative yield. This observation leads to a convenient and practical synthesis of a variety of dititana(alkoxy)calix[8]arene complexes as shown in eq 2.[14] The ^{1}H NMR spectra of the crude products from these reactions (after removal of the solvent in vacuo) indicate that these compounds may be used in further reactions without purification.

$$1 \xrightarrow[\text{2) 2 [Ti(O-t-Bu)}_4\text{/R'OH] (previously mixed in THF)}]{\text{1) Base}} [\text{calix(8)arene(Ti(OR'))}_2]^- [\text{M or RNH}_3]^+ \quad (2)$$
$$+\ 8\ \text{HO-t-Bu}$$

Finally, we have also prepared zirconium(isopropoxy)calix[8]arene and vanadium(oxo)calix[8]arene complexes[10] by substituting Zr(O-*i*-Pr)$_4$(HO-*i*-Pr) and V(O)(O-*i*-Pr)$_3$, respectively, as the metal reagents in eq 1.

A search employing other chiral amines (especially those derived from the chiral pool[11]) should lead to a synthesis of homochiral dimetallacalixarenes.[12] The reaction chemistry[13] of these complexes as well as their potential applications as resolving agents, protecting groups, and chiral auxiliaries in organic synthesis are also being explored.

Acknowledgment. S.F.P. is grateful to the National Science Foundation for a Presidential Young Investigator Award (Grant No. CHE-8552735) and to Eli Lilly and Company for financial support of this work. We also thank Dr. Julie Leary of the U.C.B. Department of Chemistry Mass Spectrometry Facility for obtaining the FAB-MS data and Professor Paul Bartlett for helpful discussions.

Supplementary Material Available: NMR, mass spectral data, and elemental analysis information for all dimetallacalixarenes and crystallographic details and tables of atomic positional and thermal parameters for **2a** (26 pages); tables of observed and calculated structure factors (74 pages). Ordering information is given on any current masthead page.

---

[9] (a) Rebek, J., Jr.; Askew, B.; Ballester, P.; Buhr, C.; Jones, S.; Nemeth, D.; Williams, K. *J. Am. Chem. Soc.* **1987**, *109*, 5033. (b) Hamilton, A. D.; Van Engen, D. *J. Am. Chem. Soc.* **1987**, *109*, 5035.

[10] On the basis of the similarities between the ^{1}H and ^{13}C NMR and IR spectra of these compounds and the dititanacalixarene complexes.

[11] Scott, J. W. In *Asymmetric Synthesis*; Morrison, J. S., Scott, J. W., Eds.; Academic Press: New York, NY, 1984; Vol. 4, p 1.

[12] We have already isolated some homochiral complexes by selective crystallization of one diastereomer from a mixture.

[13] Alcohol exchange with the alkoxy ligands in **2** has been observed. For example, 2 equiv of 4-nitrophenol react with **2a** to give the analogous 4-nitrophenolate complex in high yield.

[14] Representative alcohols are as follows: cyclopentanol, geraniol, 4-*tert*-butylcyclohexanol, 4-nitrophenol, ethanol, (±)-3-butyn-2-ol, (*R*)-*sec*-phenethyl alcohol, α-methyl-2-naphthalenemethanol.

Intramolecular Cyclization of an Allyl Cation. The Formation of 11-Membered Carbocyclic Rings *via* Cationic Processes

Paul G. Gassman* and Richard J. Riehle[1]

Department of Chemistry, University of Minnesota
Minneapolis, Minnesota 55455

Received December 2, 1988

Although cationic cyclization processes have been proposed as part of the biosynthetic pathway to a variety of large-ring terpenes, such as humulene and cembrene,[2] little experimental evidence exists in support of such entropically unfavorable cyclization processes.[3,4] As part of our continuing interests in both the intramolecular[5] and intermolecular[6] cyclization reactions of allyl cations, we have explored the intramolecular addition of an allyl cation to a vinylcyclopropane moiety. We now report that 11-membered rings, similar to that of humulene, can be formed in good yield through entropically unfavorable cationic cyclization reactions at low temperature.

In a typical procedure, a dry methylene chloride solution of **1a**[7,8] was treated with 2 mol % of triflic acid at 0 °C for 3 min. Quenching of the acid catalyst with excess triethylamine, followed

---

[1] National Science Foundation Fellow, 1984–1987.

[2] For general discussions, see: *Natural Products Chemistry*; Nakanishi, K., Goto, T., Ito, S., Natori, S., Nozoe, S., Eds.; University Science Books: Mill Valley, CA, 1974; 1983; Vol. 1 and 3. Cane, D. E. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W., Spurgeon, S. L., Eds.; John Wiley and Sons: New York. 1981; Vol. 1. West, C. A. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W., Spurgeon, S. L., Eds.; John Wiley and Sons: New York, 1981; Vol. 1.

[3] For an intramolecular acylation reaction to form a 14-membered ring, see: Kato, T.; Suzuki, M.; Kobayashi, T.; Moore, B. P. *J. Org. Chem.* **1980**, *45*, 1126. Kato, T.; Suzuki, M.; Nakazima, Y.; Shimizu, K.; Kitahara, Y. *Chem. Lett.* **1977**, 705. Kitahara, Y.; Kato, T.; Kobayashi, T.; Moore, B. P. *Chem. Lett.* **1976**, 219. Kato, T.; Kobayashi, T.; Kitahara, Y. *Tetrahedron Lett.* **1975**, 3299.

[4] See, also: Baker, P. M.; Bycroft, B. W.; Roberts, J. C. *J. Chem. Soc. C* **1967**, 1913. von Hans Gerlach, V. *Helv. Chim. Acta* **1977**, 3039. Huisgen, R.; Rietz, Y. *Tetrahedron* **1958**, *2*, 271. Smith, A. B., III; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 219. Nishimura, J.; Yamada, N.; Ueda, E.; Ohbayashi, A.; Oku, A. *Tetrahedron Lett.* **1986**, *27*, 4331. Nichimura, J.; Hashimoto, K.; Okuda, T.; Hayami, H.; Mukai, Y.; Oku, A. *J. Am. Chem. Soc.* **1983**, *105*, 4758. Overman, L. E.; Blumenkopf, T. A.; Castañeda, A.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516. Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248. Cockerill, G. S.; Kocienski, P.; Treadgold, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2093, 2101. Marshall, J. A.; DeHoff, B. S.; Crooks, S. L. *Tetrahedron Lett.* **1987**, *28*, 527.

[5] Gassman, P. G.; Singleton, D. A. *J. Am. Chem. Soc.* **1984**, *106*, 6085. Gassman, P. G.; Singleton, D. A. *J. Org. Chem.* **1986**, *51*, 3075.

[6] Gassman, P. G.; Singleton, D. A.; Wilwerding, J. J.; Chavan, S. P. *J. Am. Chem. Soc.* **1987**, *109*, 2182. Gassman, P. G.; Chavan, S. P. *J. Org. Chem.* **1988**, *53*, 2392.

[7] The synthesis of **1a** involved treatment of glutaraldehyde with 1,1-dimethylethyl triphenylphosphoranylideneacetate to give 1,1-dimethylethyl (2*E*)-7-oxoheptenoate in 78% yield. Treatment of this aldehyde with 1-triphenylphosphoranylidene-2-propanone gave 91% of 1,1-dimethylethyl (2*E*,7*E*)-9-oxodecadienoate. Reaction of this keto ester with dimethylsulfoxonium ylid yielded 32% of 1,1-dimethylethyl [2*E*(1*S**,2*S**)]-6-(2-acetylcyclopropyl)hexenoate. The acetyl group of this ester was treated with triphenylphosphoranylidenemethane to give 92% of 1,1-dimethylethyl [2*E*-(1*S**,2*S**)]-6-[2-(1-methylethenyl)cyclopropyl]hexenoate. Addition of methyllithium to this ester gave 70% of **1a**. Treatment of **1a** with potassium hydride followed by methyl iodide gave 93% of **1b**.

[8] Satisfactory elemental analyses and/or exact mass molecular weights were obtained on all new compounds. All compounds described had IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data which were consistent with the assigned structures.

0002-7863/89/1511-2319$01.50/0