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Communications

Calix[4]arenes with Pyridine Pendant Groups. Regioselective Proximal Alkylation at the "Lower Rim"

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Summary: Treatment of calix[4]arenes **1** with a large excess of 2-(chloromethyl)pyridine hydrochloride in *N,N*-dimethylformamide produced tetrakis[(2-pyridylmethyl)oxy]calix[4]arenes (**2**) in a fixed cone conformation. When lower calix[4]arene:2-(chloromethyl)pyridine molar ratios (1:4) were used, regioselective *proximal* disubstitution at the phenolic oxygens (lower rim) was realized in good yield.

Sir: Readily available calix[4]arenes present attractive possibilities as molecular frameworks for the preparation of relatively rigid polyfunctional compounds whose convergent ligating groups can act cooperatively to bind and catalyze.[1] The parent calix[4]arenes **1** are conformationally flexible at room temperature and exist preferentially in the cone conformation,[2] as shown in Figure 1. This particular conformation can be fixed by suitable derivatization at the phenolic OH groups.[3] The attachment of ester,[4] keto,[5] and amide[6] groups to the lower rim of calix[4]arenes produced a series of new lipophilic cation receptors in a fixed cone conformation with remarkable complexing properties toward alkali metal cations. X-ray structural studies have shown that the free tetraester, tetraketo, and tetramide calix[4]arenes exist in a slightly distorted cone conformation,[4-6] with all the pendant functionalities in a convergent arrangement defining a hydrophilic cavity which binds the metal ion to give capsular complexes.[6a] Therefore, the preorganization of the binding sites prior to complexation[7] appears to be of paramount importance in determining the ligating ability of these calix[4]arenes.

In order to extend the coordination chemistry of calix[4]arenes to transition metals,[8] we have designed and synthesized calix[4]arene-based receptors that are conformationally fixed in the cone conformation and which carry pendant pyridine groups at the lower rim as potential binding sites. The regioselective *proximal* disubstitution at the lower rim of calix[4]arenes were also realized in good yield.

Treatment of *p-tert*-butylcalix[4]arene (**1a**) with NaH and 2-(chloromethyl)pyridine hydrochloride (20 equiv) in anhydrous *N,N*-dimethylformamide (DMF) at 60 °C for 24 h afforded tetrakis[(2-pyridylmethyl)oxy] derivative **2a**, mp 231–233 °C (MeOH), in 80% yield.[9] Similarly, exhaustive alkylation of the parent calix[4]arene (**1b**) with 2-(chloromethyl)pyridine hydrochloride produced **2b**, mp 186–188 °C (AcOEt–*n*-hexane), in 72% yield. Sulfonation of **2b** with concentrated H_2SO_4 at 100 °C for 24 h, followed

(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) Gutsche, C. D.; Bauer, L. J. *Tetrahedron Lett.* **1981**, *22*, 4763.
(3) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409.
(4) (a) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1984**, 981. (b) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R.; Andreetti, G. D.; Uguzzoli, F. *Tetrahedron* **1986**, *42*, 2089. (c) McKervey, M. A.; Seward, E. M.; Ferguson, G.; Ruhl, B.; Harris, S. J. *J. Chem. Soc., Chem. Commun.* **1985**, 388. (d) Chang, S.-K.; Cho, I. *J. Chem. Soc., Perkin Trans. 1* **1986**, 211.
(5) Ferguson, G.; Kaitner, B.; McKervey, M. A.; Seward, E. M. *J. Chem. Soc., Chem. Commun.* **1987**, 584.
(6) (a) Calestani, G.; Uguzzoli, F.; Arduini, A.; Ghidini, E.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1987**, 344. (b) Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R.; Andreetti, G. D.; Calestani, G.; Uguzzoli, F. *J. Incl. Phenom.* **1988**, *6*, 119.
(7) Cram, D. J.; Kaneda, T.; Helgeson, R. C.; Brown, S. B.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 3645.
(8) (a) Olmstead, M. M.; Sigel, G.; Hope, H.; Xu, X.; Power, P. *J. Am. Chem. Soc.* **1985**, *107*, 8087. (b) Gutsche, C. D.; Nam, K. C. *J. Am. Chem. Soc.* **1988**, *110*, 6153.
(9) Satisfactory analytical and spectral data were obtained for all new compounds. The molecular weights were deduced by positive ion FAB-MS in a 3-nitrobenzyl alcohol matrix.

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Table I. Selected ^{1}H NMR Spectral Data of *Proximal* and *Distal* Isomers 3a and 5a[a,b]

compd	chemical shift, δ			
	$ArCH_2Ar$	OCH_2Py	ArH	OH
3a	3.26, 4.37 (AB q, J = 13.1 Hz, 4 H) 3.34, 4.27 (AB q, J = 13.7 Hz, 2 H) 3.43, 4.61 (AB q, J = 12.8 Hz, 2 H)	4.88, 5.33 (AB q, J = 13.0 Hz, 4 H)	6.91 (d, 2 H)[c] 6.94 (d, 2 H)[c] 6.99 (d, 2 H)[c] 7.01 (d, 2 H)[c]	9.42 (b s, 2 H)
5a	3.35, 4.31 (AB q, J = 13.1 Hz, 8 H)	5.19 (s, 4 H)	6.80 (s, 4 H) 7.08 (s, 4 H)	7.21 (s, 2 H)

[a] For $CDCl_3$ solutions, Me_4Si as internal standard. [b] Multiplicities, coupling constants, and proton intensity ratios in parentheses. [c] J = 2.3 Hz.

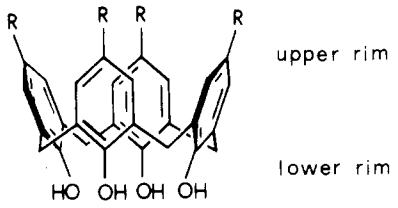

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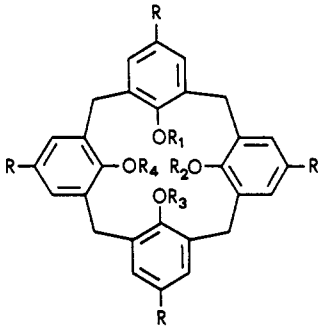
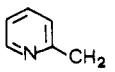
Figure 1. The cone conformation of parent calix[4]arenes 1.

by neutralization, furnished the water-soluble[4a,10] sodium salt of tetrasulfonate **2c**.



	R	R_1	R_2	R_3	R_4
1a	$C(Me)_3$	H	H	H	H
1b	H	H	H	H	H
2a	$C(Me)_3$	2-Pic	2-Pic	2-Pic	2-Pic
2b	H	2-Pic	2-Pic	2-Pic	2-Pic
2c	SO_3Na	2-Pic	2-Pic	2-Pic	2-Pic
3a	$C(Me)_3$	2-Pic	2-Pic	H	H
3b	H	2-Pic	2-Pic	H	H
4	$C(Me)_3$	2-Pic	H	H	H
5a	$C(Me)_3$	2-Pic	H	2-Pic	H
5b	H	2-Pic	H	2-Pic	H
6a	$C(Me)_3$	2-Pic	2-Pic	2-Pic	H
6b	H	2-Pic	2-Pic	2-Pic	H

2-Pic = 

Compounds **2a–c** adopt a fixed cone conformation in solution, with the pyridine pendant groups on the same side with respect to an ideal plane containing the bridging methylene groups of the macrocycle. This conclusion is consistent with their proton and carbon NMR spectra, which display simple but distinctive patterns [e.g., an AB system for the methylene protons (J = 12.6–13.7 Hz), and a pattern of four lines for the phenyl carbon atoms of the calix[4]arene skeleton].[3]

Preliminary extraction data of alkali metal picrates show less efficiency for **2a** compared to analogous tetraester and tetramide calix[4]arenes, although the selectivity follows the expected order $Na^+ > K^+ > Rb^+ > Cs^+$.[4b,6]

Diminished calix[4]arene:2-(chloromethyl)pyridine hydrochloride molar ratios and reaction times gave mixtures of products representing various stages of alkylation. When **1a** was reacted with 4 equiv of 2-(chloromethyl)-pyridine hydrochloride for 3 h at 60 °C in the presence of NaH, *proximal* bis[(2-pyridylmethyl)oxy]calix[4]arene (**3a**), mp 204–206 °C, was produced as the major component (65–70% yield), along with very small amounts of mono[(2-pyridylmethyl)oxy]calix[4]arene (**4**), mp 275–277 °C, *distal* bis[(2-pyridylmethyl)oxy]calix[4]arene (**5a**), mp 250–252 °C, and tris[(2-pyridylmethyl)oxy]calix[4]arene (**6a**), mp 219–222 °C.[11]

The ^{1}H NMR spectrum of *proximal* bis[(2-pyridylmethyl)oxy]calix[4]arene (**3a**) is characterized by a pattern of three well-resolved AB systems for the bridging methylene groups, an AB system for the diastereotopic OCH_2Py groups, and a set of four doublets for the aromatic protons of the calix[4]arene framework. On the other hand, *distal* isomer **5a** exhibits, as expected,[3] a single AB system for the bridging methylene groups, a singlet for the OCH_2Py groups, and two singlets for the phenyl protons. The critical ^{1}H NMR data of isomers **3a** and **5a** are shown in Table I.

Distal and *proximal* isomers **5a** and **3a** also display distinctively different ^{13}C NMR patterns.[12] In particular the two signals for the bridgehead carbon atoms (δ 127.61 and 132.32) and one signal for the bridging methylenes (δ 31.50) in **5a** are split into four lines of equal intensity (δ 127.41, 128.17, 133.18, and 133.54) and two lines of roughly 1:3 intensity ratio (δ 32.40 and 32.57), respectively, in **3a**.

In a similar manner, calix[4]arene **1b** was partially alkylated with 2-(chloromethyl)pyridine hydrochloride under standard reaction conditions to afford *proximal* bis[(2-pyridylmethyl)oxy]calix[4]arene (**3b**), mp 193–195 °C, in 55–60% yield, along with minor amounts of tri- and tetrasubstituted calix[4]arenes **6b** and **2b**. *Proximal* dialkylated derivative **3b** exhibits NMR spectral features similar to those of **3a**.[13]

(10) (a) Shinkai, S.; Mori, S.; Koreishi, H.; Tsubaki, T.; Menabe, O. *J. Am. Chem. Soc.* **1986**, *108*, 2409. (b) Shinkai, S.; Araki, K.; Tsubaki, T.; Arimura, T.; Manabe, O. *J. Chem. Soc., Perkin Trans. 2* **1987**, 2297. (c) Gutsche, C. D.; Alam, I. *Tetrahedron* **1988**, *44*, 4689. (d) Almi, M.; Arduini, A.; Casnati, A.; Pochini, A.; Ungaro, R. *Ibid.* **1989**, *45*, 2177.

(11) Separation of the reaction mixture into the pure components was achieved by chromatography (SiO_2, column), using a gradient of AcOEt in cyclohexane as the eluent. **4**: R_f 0.32 (cyclohexane–AcOEt, 4:1). **5a**: R_f 0.25 (cyclohexane–AcOEt, 2:1). **3a**: R_f 0.14 (cyclohexane–AcOEt, 2:1). **6a**: R_f 0.47 (Al_2O_3, cyclohexane–AcOEt, 2:1). The NMR spectral features of partially alkylated calix[4]arenes **3–6** are commensurate with a fixed cone conformation at room temperature.

(12) **3a**: ^{13}C NMR ($CDCl_3$, 250 MHz) δ 31.21, 31.47, 32.40, 32.57, 33.74, 33.96, 77.88, 122.24, 122.59, 125.21, 125.93, 127.41, 128.17, 133.18, 133.54, 136.80, 141.87, 146.39, 148.67, 149.16, 152.00, and 157.37. **5a**: ^{13}C NMR ($CDCl_3$, 250 MHz) δ 30.95, 31.50, 31.69, 33.84, 33.93, 78.15, 121.26, 122.48, 125.07, 125.64, 127.61, 132.32, 137.22, 141.68, 147.30, 148.95, 149.45, 150.60, and 157.67.

Proximal functionalization at the lower rim of calix[4]arenes is unprecedented in the literature. Several authors[3,14-16] have observed regioselective *distal* alkylation by using a variety of electrophiles, such as diazomethane, methyl tosylate, allyl bromide, benzyl bromide, α-bromoacetates, α-halo ketones, and chloroacetonitrile. Steric factors and stabilizing hydrogen bond effects of the deprotonated monoalkylated species have been proposed to play an important role in determining the regioisomeric outcome.[16] In our case, the reversed regioselectivity may be ascribed to the tendency of the pyridine pendant group in the monoalkylated intermediate to establish favorable hydrogen bonding with the nearest hydroxy group, which results in a remarkable enhancement of its acidity and reactivity. The above effects are also believe to exert an important role in keeping and stabilizing calix[4]arenes **3–6** in the cone conformation.

The synthetic approach leading to *proximal* disubstituted calix[4]arenes in the cone conformation opens up new perspectives for the construction of calix[4]arenes with mixed ligating groups, for the synthesis of chiral trisubstituted calix[4]arenes, and for the selective *proximal* difunctionalization at the "upper rim".

Acknowledgment. We wish to thank the Italian Ministry of Education for partial financial support of this work and Professor Rocco Ungaro for helpful discussions.

Supplementary Material Available: Experimental procedures and characterization data for **2a–c**, **4**, **5a**, and **6a,b** (4 pages). Ordering information is given on any current masthead page.

(13) **3b**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.28 and 4.41 (AB q, J = 13.0 Hz, $ArCH_2Ar$, 4 H), 3.37 and 4.36 (AB q, J = 13.7 Hz, $ArCH_2Ar$, 2 H), 3.48 and 4.65 (AB q, J = 12.7 Hz, $ArCH_2Ar$, 2 H), 4.88 and 5.34 (AB q, J = 13.0 Hz, OCH_2Py, 4 H), 6.58 (t, J = 7.5 Hz, ArH, 2 H), 6.78 (t, J = 7.5 Hz, ArH, 2 H), 6.9–7.0 (m, ArH, 6 H), 7.05 (dd, J = 7.5, 1.6 Hz, ArH, 2 H), 7.14 (ddd, J = 7.3, 4.9, 1.1 Hz, 5-PyH, 2 H), 7.46 (ddd, J = 7.7, 7.3, 1.7 Hz, 4-PyH, 2 H), 7.56 (d, J = 7.8 Hz, 3-PyH, 2 H), 8.58 (d, J = 4.9 Hz, 6-PyH, 2 H), and 9.72 (b s, OH, 2 H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 30.92, 31.78, 31.90, 77.84, 120.00, 122.17, 122.80, 124.69, 128.18, 128.32, 128.66, 128.76, 128.87, 129.16, 134.46, 134.51, 136.95, 148.78, 151.47, 154.31, and 157.20.

(14) Ungaro, R.; Pochini, A.; Andreetti, G. D. *J. Incl. Phenom.* **1984**, *2*, 199.
(15) Collins, E. M.; McKervey, M. A.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 372.
(16) van Loon, J.-D.; Arduini, A.; Verboom, W.; Ungaro, R.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron Lett.* **1989**, *30*, 2681.

Dramatic Changes in Diastereoselectivity with the Quantity of Titanium Tetrachloride Used in Lewis Acid Mediated Reactions of Allylsilane with α-Amino Aldehydes[1]

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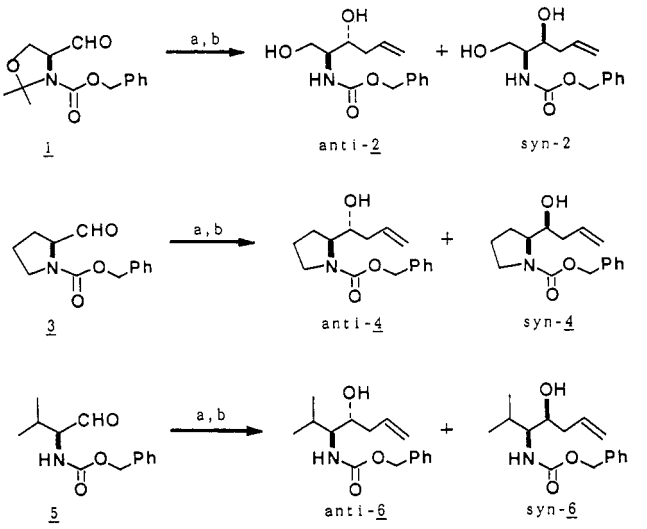
Summary: Dramatic changes in diastereoselectivity, depending upon the quantity of titanium tetrachloride used in the Lewis acid mediated reactions of allylsilane with chiral α-*N*-(carbobenzyloxy)amino aldehydes (**1**, **3**, and **5**), have been observed. These results are discussed, and the possibility that a 2:1 complex of aldehyde and $TiCl_4$ is being generated and its role are proposed.

Sir: Over the past 10 years, the Lewis acid mediated reactions of silyl nucleophiles with aldehydes and several other electrophiles have attracted the interest of synthetic organic chemists, especially from the standpoint of stereoselectivity.[2] While the development of this methodology has been impressive, a variety of reaction conditions have been adopted in order to make the reaction more selective. It has been become customary for synthetic organic chemists to weigh a slightly excessive amount of $TiCl_4$ and transfer it into the reaction flask via a syringe in lab-scale (millimole) experiments, but the molar ratios of $TiCl_4$ to aldehyde are not necessarily accurate in this procedure. Furthermore, it has not been possible to determine the minimum quantity of $TiCl_4$ required in order to provide satisfactory yields in the so-called stoichiometric $TiCl_4$-mediated reactions of allylsilane with aldehyde.[3]

Scheme I[a]



[a] (a) $TiCl_4$–CH_2Cl_2, allylsilane, −78 °C; (b) H_3O^+.

We disclose herein that the quantity of Lewis acid ($TiCl_4$) added significantly affects the stereoselectivity in the Lewis acid mediated reactions[4] with three structurally

(1) Presented in part at the 58th Annual Meeting of the Chemical Society of Japan, Kyoto, April 1–4, 1989 (Abstracts of Papers, p 1624).

(2) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295. Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. Weidmann, B.; Seebach, D. *Ibid.* **1983**, *22*, 31. Reetz, M. T. *Ibid.* **1984**, *23*, 556. Heathcock, C. H.; Kiyooka, S.-I.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214. Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *Ibid.* **1986** *51*, 3027. Keck, G. E.; Castellino, S.; Wiley, M. R. *Ibid.* **1986**, *51*, 5478. Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986. Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. Reetz, M. T.; Jung A.; Bolm, C. *Tetrahedron* **1988**, *44*, 3889. Fujisawa, T.; Ukaji, Y. *Yuki Gosei Kagaku Kyokaishi* **1989**, *47*, 186.

(3) Kiyooka, S.; Nakano, M., unpublished results. The $TiCl_4$-mediated reaction of allylsilane with 2-phenylpropanal gave the product in ca. 80% yield by using 0.5 molar equiv of $TiCl_4$, but the reaction with less than 0.4 molar equiv of $TiCl_4$ failed.

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