Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 8, pp. 1169–1173, 1997

Printed in Great Britain
PII: S0957-4166(97)00115-8
0957-4166/97 $17.00 + 0.00

Resolution of inherently chiral 1,4-2,5-calix[8]bis-crown-4 derivatives by enantioselective HPLC †

Salvatore Caccamese*,[a] Grazia Principato,[a] Corrada Geraci[b] and Placido Neri*[b,*]

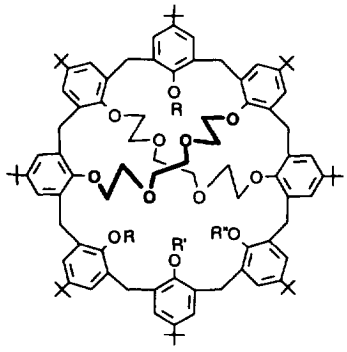
[a] Dipartimento di Scienze Chimiche, Università di Catania, Viale A. Doria 6, I-95125 Catania, Italy

[b] Istituto per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico-Farmaceutico, C.N.R., Via del Santuario 110, I-95028 Valverde (CT), Italy

Abstract: The first example of the resolution of inherently chiral calix[8]arenes, 1,4-2,5-calix[8]bis-crown-4 **1** and its methyl derivatives **2–4**, has been achieved using enantioselective HPLC methods. The enantiomeric nature of isolated (+)-**1** and (−)-**1** was confirmed by CD spectra, specific optical rotation and ^{1}H NMR in the presence of Pirkle's reagent. A rationale is given for the observed HPLC enantioselectivity among compounds **2–4**. © 1997 Elsevier Science Ltd

Inherent chirality in calixarene macrocycles[1] is an intellectually appealing subject which has attracted the attention of several research groups over the past decade.[2] As a result of these efforts several examples of asymmetric or dissymmetric inherently chiral calix[n]arenes have been obtained with n up to 6 exploiting the tridimensionality of their structure.[2,3] In some of these instances racemate resolution has also been achieved mainly by enantioselective HPLC.[4]

In the case of the larger calix[8]arenes, their high conformational mobility imposes a preliminary intramolecular bridging step in order to obtain tridimensionally defined derivatives[5] to be successively elaborated to give inherent chirality. Following these lines, an inherently chiral calix[8]arene **1** has recently been obtained by one of us exploiting the steric constraint of two intercrossing polyether chains.[6] Here we wish to report the first examples of enantiomeric resolution and isolation of inherently chiral calix[8]arenes, namely **1** and its methylated derivatives **2–4**.



1 R = R' = R" = H
2 R = R' = R" = Me
3 R' = Me; R = R" = H
4 R" = Me; R = R' = H

Dissymmetric 1,4-2,5-calix[8]bis-crown-4 **1**[6] was prepared by Cs_2CO_3-promoted direct alkylation of *p-tert*-butylcalix[8]arene and was fully methylated using a large excess MeI in the presence of

† Dedicated to Professor Mario Piattelli on the occasion of his 70th birthday.

* Corresponding author. Email: neri@issn.ct.cnr.it

Table 1. HPLC behaviour of inherently chiral calix[8]bis-crowns-4 **1–4** on Chiralpak AD and Chiralcel OD

Compd	CSP	A (%)[a]	FR[b]	K'$_1$[c]	α	R_s
1	AD	10	0.7	0.10	1.34	< 0.5
1	AD	5	0.7	0.21	1.42	0.7
1	OD	5	0.7	0.42	1.34	0.7
1	AD	3	0.7	0.29	1.54	1.0
1	AD	3[d]	0.4	0.27	1.58	1.1
1	OD	3	0.4	0.74	1.35	0.9
2	AD	3	0.4	0.07	1.77[e]	0.6
2	OD	3	0.4	0.14	NS[f]	—
3	AD	5	0.7	0.50	1.19	0.6
3	AD	3	0.4	0.63	1.25	0.9
4	AD	5	0.7	0.43	NS	—
4	AD	3	0.4	0.53	NS[g]	—

[a] Percentage of 2-propanol in *n*-hexane. [b] Flow rate (mL/min), FR = 0.7, t_0 = 4.80 min and 4.75 min; FR = 0.4, t_0 = 8.19 min and 8.01 min for Chiralpak AD and Chiralcel OD, respectively. [c] Capacity factor of the first-eluted enantiomer. [d] Experimental conditions used for semipreparative isolation, t_1 = 10.47 min, t_2 = 11.74 min. [e] Indicative value (see text). [f] Not separated. [g] Shoulder in the rising edge of the peak.

NaH in THF/DMF to give **2** in 60% yield.[7] Monomethylation of **1** was achieved using CsF as base in acetone and affording 7-methoxy-1,4-2,5-calix[8]bis-crown-4 **3** and its isomer 6-methoxy-1,4-2,5-bis-crown-4 **4** in 80% and 12% yield, respectively.[7] In this instance, the preferential methylation at position 7 can be explained in terms of formation of an intermediate monoanion stabilized by two flanking hydrogen bonds.[5]

The presence of four methoxyls in **2** was confirmed by three singlets at δ 3.38, 3.54 and 3.63 in a 1:1:2 ratio in its ^{1}H NMR spectrum which also evidences five resonances for *tert*-butyl groups.[7] This proves that the C_2 symmetry axis bisecting opposite aromatic rings (Ar–Ar symmetry) of parent bis-crown **1** is still present in tetramethyl derivative **2** and indicates that the passage of the OMe groups through the annulus is fast on the NMR time scale. On the basis of this conclusion structure assignment of monomethyl derivative **4** relays on the asymmetry evidenced by its NMR spectra.[7] In the case of **3** an Ar–Ar symmetry was observed which points to a methoxyl at position 3 or 7. This latter can be chosen on the basis of the chemical shift of OH groups[7] and mechanistic considerations, however a definitive proof was obtained by a 2D HETCOR NMR study.

Evidence for inherent chirality of **1** has previously been reported,[6] which, of course, holds true for methyl derivatives **2–4**. The HPLC enantiomeric resolution of these compounds was accomplished using chiral stationary phases (CSPs) Chiralpak AD (amylose tris-3,5-dimethylphenylcarbamate) and Chiralcel OD (cellulose tris-3,5-dimethylphenylcarbamate) coated on a 10 μm silica gel. The chromatographic results are presented in Table 1 and typical HPLC chromatograms (resolution of racemic **1** and **2**) are shown in Figure 1. Chiralpak AD CSP was superior in the enantiomeric resolution with respect to Chiralcel OD phase, as shown by comparison of experiments performed under the same conditions (polarity of mobile phase and flow rate). The difference in chiral recognition of cellulose and amylose derivatives is probably due to a different chiral environment around the carbamate residue and to the wider and more compact helix of the amylose derivative.[8–10]

Regarding the results obtained with Chiralpak AD it is evident from Table 1 that separation factor (α) and resolution factor (R_S) are much better for tetrahydroxy-bis-crown **1** with respect to monomethylated derivatives **3** and **4** and tetramethylated bis-crown **2**. This behaviour can be attributed to the presence of four hydroxyls in **1** that can interact via hydrogen bond with the carbamate moiety

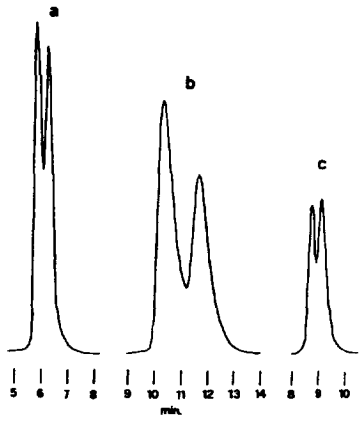


Figure 1. Chiralpak AD HPLC enantioresolution of compounds **1** (a, b) and **2** (c). Mobile phase *n*-hexane/2-propanol 95:5 at flow 0.7 mL/min (a), 97:3 at flow 0.4 mL/min (b, c).

of CSP. In accordance, tetramethylated bis-crown **2**, unable to form H-bonds with CSP, is very weakly adsorbed on the stationary phase thus eluting too near to column void time (t_0) ($K'=0.07$) and giving a modest R_S and an α value very sensitive to small changes of a few seconds in the elution time. The presence of intramolecular hydrogen bonding in asymmetric monomethyl derivative **4**, that is formally excluded in **3**, can be used to explain the better interaction with CSP and enantiodifferentiation of **3** with respect to **4** which remain unresolved.[11] Other features for compound **1** that can be extracted from the results in Table 1 are: i) an increase in the polarity of mobile phase has a detrimental effect on enantioselectivity α and resolution factor R_S; ii) a decrease in the flow rate of mobile phase has a beneficial effect on these parameters (Figure 1).

After several trials an acceptable resolution factor of 1.1 was found for **1** (Table 1) and these conditions were used for a quantitative separation of enantiomers. Repeated 100 µl injections of racemic **1** (0.2÷0.3 mg) and collection of the eluates corresponding to the two chromatographic peaks afforded two samples whose CD spectra are mirror images of each other (Figure 2) indicating their enantiomeric nature. Analytical HPLC reruns of the two eluates indicates an enantiomeric excess (ee) of 100% for the first peak and 89% for the second one. The almost equal negative and positive band area in the CD spectra indicates exciton coupled chromophores. In fact, the CD split shows a positive Cotton effect (CE) ($\Delta\epsilon=+15$ at 281 nm, $\Delta\epsilon=-34$ at 214 nm) for the less retained enantiomer, while a negative CE is observed for the other one. The distance (nm) between the two components CD curves of opposite sign is very high and has never been observed in calix[4]arenes showing CE. As expected, the UV spectra of the enantiomeric pair are identical and exhibit $\lambda_{shoulder}$ at 228 nm ($\epsilon=280{,}000$) and λ_{max} at 280 and 288 nm ($\epsilon=13{,}500$ and 12,500, respectively). In accordance, a specific rotation $[\alpha]_D^{25}$ of -30.5 (*c* 0.2, $CHCl_3$) was measured for the first-eluted sample, while the second one afforded an experimental $[\alpha]_D^{25}$ of +27.0 (*c* 0.1, $CHCl_3$), that after correction for 89% ee gives the expected $[\alpha]_D^{25}$ within experimental errors. Comparable results were also obtained upon addition of excess Pirkle's reagent [(*S*)-(+)-(9-anthryl)-2,2,2-trifluoroethanol] to $CDCl_3$ solutions of both enantiomers. Under conditions where racemic **1** gives splitting of the five *tert*-butyl signals,[6] only a single set of them was observed for (+)-**1** and (−)-**1** (Figure 3).[12]

In conclusion, we have accomplished the first example of a resolution of inherently chiral calix[8]arenes by enantioselective HPLC methods. Thus, we have experimentally demonstrated that the steric constraint of two intercrossing polyether chains suffices for chirality generation in 1,4-2,5-calix[8]bis-crowns notwithstanding the residual freedom of conformational interconversion of the four remaining *tert*-butylphenyl groups. The extension of this approach to other calixarene systems is currently under investigation in our laboratory.

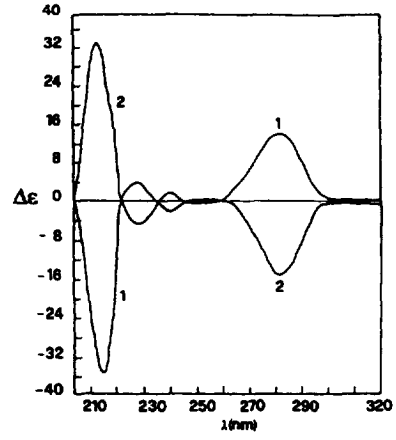


Figure 2. CD spectra (ethanol 95%) of the enantiomers of compound **1** obtained for the first (1) and the second (2) HPLC eluted peaks.

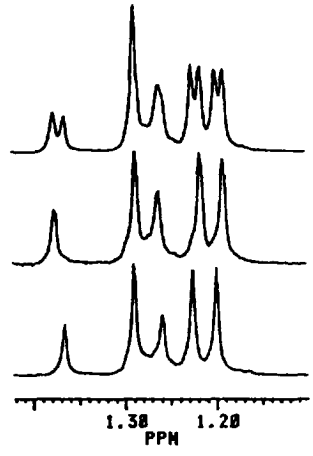


Figure 3. *tert*-Butyl region of the ^{1}H NMR spectra ($CDCl_3$, 295 K) of (±)-**1** (top), (+)-**1** (middle), and (−)-**1** (bottom) in the presence of Pirkle's reagent.[12]

Acknowledgements

Thanks are due to Mrs Concetta Rocco (ISSN-CNR, Valverde) for the acquisition of NMR spectra.

References

1. Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J.; Böhmer, V., Eds.; Kluwer: Dordrecht, 1991. For an update to 1994 see: Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713.
2. Böhmer, V.; Kraft, D.; Tabatabai, M. *J. Incl. Phenom.* **1994**, *19*, 17 and references therein.
3. For more recent examples see: Gonzalez, J. J.; Nieto, P. M.; Prados, P.; Echavarren, A. M.; de Mendoza, J. *J. Org. Chem.* **1995**, *60*, 7419. Verboom, W.; Bodewes, P. J.; van Essen, G.; Timmerman, P.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron* **1995**, *51*, 499. Pappalardo, S.; Parisi, M. F. *Tetrahedron Lett.* **1996**, *37*, 1493. Arnecke, R.; Böhmer, V.; Ferguson, G.; Pappalardo, S. *Tetrahedron Lett.* **1996**, *37*, 1497. Fu, D.-K; Xu, B.; Swager, T. M. *J. Org. Chem.* **1996**, *61*, 802.

4. (a) Pappalardo, S.; Caccamese, S.; Giunta, L. *Tetrahedron Lett.* **1991**, *32*, 7747. (b) Caccamese, S.; Pappalardo, S. *Chirality* **1993**, *5*, 159. (c) Pickard, S. T.; Pirkle, W. H.; Tabatabai, M.; Vogt, W.; Böhmer, V. *Chirality* **1993**, *5*, 310. (d) Iwamoto, K.; Shimizu, H.; Araki, K.; Shinkai, S. *J. Am. Chem. Soc.* **1993**, *115*, 3997 (*Corrigendum* **1993**, *115*, 12228). (e) Otsuka, H.; Shinkai, S. *J. Am. Chem. Soc.* **1996**, *118*, 4271.
5. Neri, P.; Consoli, G. M. L.; Cunsolo, F.; Geraci, C.; Piattelli, M. *New J. Chem.* **1996**, *20*, 433 and references therein.
6. Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1996**, *37*, 7627.
7. Satisfactory microanalytical and spectral data were obtained for compounds **2–4**. Compound **2**: ^{1}H NMR ($CDCl_3$, 295 K) δ 1.10, 1.15, 1.21, 1.22, 1.25 [s, $(CH_3)_3$, 18H, 9H, 18H, 9H, 18H], 2.90–3.36 (m, OCH_2, 24H), 3.38, 3,54, 3.63 (s, OCH_3, 3H, 3H, 6H), 3.64 (d, J=15.3 Hz, 2H), 3.70 (d, $ArCH_2Ar$, J=14.9 Hz, 2H), 3.93 (d, $ArCH_2Ar$, J=15.2 Hz, 4H), 4.08 (d, $ArCH_2Ar$, J=12.4 Hz, 2H), 4.14 (d, $ArCH_2Ar$, J=11.2 Hz, 2H), 4.23 (d, $ArCH_2Ar$, J=14.8 Hz, 2H), 4.37 (d, $ArCH_2Ar$, J=15.3 Hz, 2H), 6.87 (d, ArH, J=2.3 Hz, 2H), 6.88 (bs, ArH, 4H), 6.91 (s, ArH, 2H), 6.99 (d, J=2.2 Hz, ArH, 2H), 7.12 (s, ArH, 2H), 7.14 (d, J=2.3 Hz, ArH, 2H),7.18 (d, J=2.3 Hz, ArH, 2H). Compound **3**: ^{1}H NMR ($CDCl_3$, 295 K) δ 1.16, 1.17, 1.21, 1.27, 1.35 s, $(CH_3)_3$, 9H, 18H, 18H, 18H, 9H], 3.37 and 4.38 (AX, J=14.2 Hz, $ArCH_2Ar$, 4H), 3.64 and 4.27 (AX, J=14.4 Hz, $ArCH_2Ar$, 4H), 3.42–3.89 (m, OCH_2, 24H), 3.94 (s, OCH_3, 3H), 3.96 and 4.05 (AB, J=15.6 Hz, $ArCH_2Ar$, 4H), 4.00 and 4.16 (AB, J=15.4 Hz, $ArCH_2Ar$, 4H), 6.95 (d, J=2.1 Hz, ArH, 2H), 6.99–7.04 (m, ArH, 6H), 7.03 (s, ArH, 2H), 7.12 and 7.24 (AB, J=2.3 Hz, ArH, 4H), 7.14 (s, ArH, 2H), 7.68, 7.82 (s, OH, 1H, 2H). Compound **4**: ^{1}H NMR ($CDCl_3$, 295 K) δ 1.11, 1.14, 1.19, 1.21, 1.22, 1.27, 1.31, 1.33 [s, $(CH_3)_3$, 9H each], 3.45–3.90 (m, OCH_2, 24H), 3.32 and 4.44 (AX, J=15.0 Hz, $ArCH_2Ar$, 2H), 3.38 and 4.30 (AX, J=14.8 Hz, $ArCH_2Ar$, 2H), 3.40–4.21 (m, $ArCH_2Ar$, 10H), 3.53 and 4.22 (AX, J=15.0 Hz, $ArCH_2Ar$, 2H), 3.95 (s, OCH_3, 3H), 6.79 and 7.11 (AB, J=2.0 Hz, ArH, 2H), 6.88 (d, J=2.0 Hz, ArH, 1H), 6.90 and 7.09 (AB, J=2.0 Hz, ArH, 2H), 7.10 and 7.21 (AB, J=2.1 Hz, ArH, 2H), 6.91–7.26 (m, ArH, 9H), 7.57, 8.01 (s, OH, 1H, 2H).
8. In fact, Zugenmaier et al. proposed left-handed 3/2 and 4/1 helical structure for cellulose tris(phenylcarbamate)[9a] and amylose tris(phenylcarbamate),[9b] respectively. Complete surveys on chiral discriminations by using polysaccharide derivatives have recently appeared.[10]
9. (a) Vogt, U.; Zugenmaier, P. *Ber. Bunsenges. Phys. Chem.* **1985**, *89*, 1217. (b) Vogt, U.; Zugenmaier, P. presented at the *European Science Foundation Workshop on Specific Interactions in Polysaccharide Systems*, Uppsala, 1983.
10. Yashima, E.; Okamoto, Y. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3289. Okamoto, Y.; Kaido, Y. *J. Chromatogr.* **1994**, *666*, 403.
11. Similar results showing how hydrogen bonding with CSP plays a major role in the chiral recognition process were previously reported for tri-*O*-alkylated calix[4]arenes (ref 4b).
12. This splitting is observed only at low temperatures (260–250 K) immediately after the addition of Pirkle's reagent (see Figure 2 in ref 6), but can also be obtained at rt after standing at +4°C for 72 h.

(Received in UK 27 February 1997)