Pergamon

Tetrahedron Letters 40 (1999) 2113–2116

TETRAHEDRON
LETTERS

Synthesis and Solid State Structural Analysis of Conformers of Tetrakis((ethoxycarbonyl)methoxy)tetrathiacalix[4]arene

Huriye Akdas[a], Gilles Mislin[a], Ernest Graf[a], Mir Wais Hosseini*[a], André De Cian[b], Jean Fischer[b]

[a]Laboratoire de Chimie de Coordination Organique, [b]Laboratoire de Cristallochimie et Chimie Structurale, associé au CNRS,
Université Louis Pasteur, Institut Le Bel, 4, rue Blaise Pascal, F-67000 Strasbourg, France

Received 26 December 1998; accepted 12 January 1999

Abstract: The role of alkaline metal cations in the synthesis and in determining the conformer distribution of tetrakis((ethoxycarbonyl)methoxy)tetrathiacalix[4]arene obtained by treatment of tetrathiacalix[4]arene **1** in acetone by ethyl bromoacetate in the presence of M_2CO_3 was systematically investigated. Among the four possible conformers, the cone, partial cone and 1,3-alternate conformers were obtained, purified and structurally characterised by X-ray analysis in the solid state. Although for Li^+ no tetra substituted derivative was observed, for Na^+ the cone conformer was exclusively formed while for both K^+ and Cs^+ a mixture of partial cone and 1,3-alternate conformers was obtained.

Calixarenes are among the most used macrocyclic frameworks.[1] The increasing interest over the last two decades in this class of molecules results on one hand from the ease and reproducibility of the synthetic procedures reported by Gutsche *et al* [2]and on the other hand from the wide range of their synthetically achievable structural as well as functional modifications. In particular, for the calix[4]arene derivatives, in addition to the more classical functionalisation of the lower and/or upper rims, both the aromatic moieties as well as the methylene junctions between them may be modified.[1] Regarding the latter modification, only recently an efficient procedure leading to the substitution of the methylene junctions between the phenolic moieties by sulfur atoms leading thus to thiacalixarenes was reported (scheme).[3,4] The remarkable binding ability of the thiacalix[4]arene **1** towards transition metals was recently investigated.[5] Furthermore, partial oxidation of the thio junctions affording the tetrasulfoxide derivatives[6,7] or complete oxidation of the sulfur atoms leading to the tetrasulfone derivatives[8] have been recently achieved. The O-alkylation of **1** has been also recently reported.[9] Dealing with other sulfur containing calixarenes, one may mention the synthesis of di[10]- and tetra[11,12] mercaptocalix[4]arenes in which two or four OH groups were replaced by SH groups.

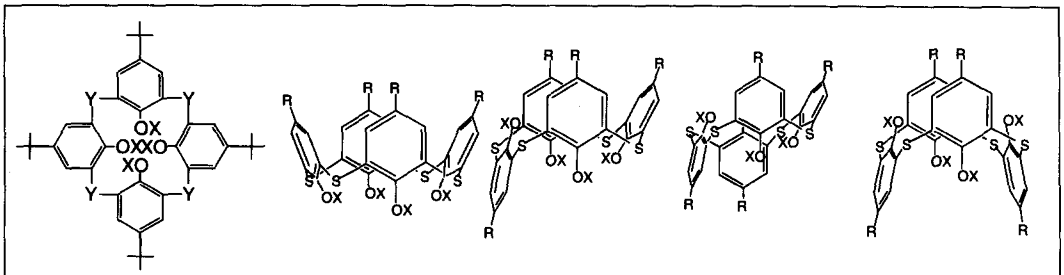
The ionophoric properties of calix[4]arene derivatives bearing four ester groups such as compound **4** have been established.[13] Furthermore, for the reaction of **3** with ethyl bromoacetate leading to the compound **4**, the role on the isomer distribution of alkaline metal cations, introduced as the counter cation of carbonate used as the base, has been studied (see table).[14]

In the present communication, we report the first systematic synthetic as well as structural study dealing with the conformer distribution of tetrakis((ethoxycarbonyl)methoxy)tetrathiacalix[4]arene **2** (scheme).

Fax: 33 388 41 62 66, E-mail: hosseini@chimie.u-strasbg.fr

PII: S0040-4039(99)00143-4

For calix[4]arene derivatives, the relative orientation of the aromatic moieties leads to four limit conformers named Cone (C), Partial cone (PC), 1,2-alternate (1,2-A) and 1,3- alternate (1,3-A). Although in the solid state, for both unsubstituted **1**[4] and **3**[1] the cone conformation was observed, in solution the interconversion between the four conformers takes place rather rapidly above r.t. However, for the substituted derivative **2**, as in the case of compound **4**, due to the bulkiness of the substituents all four conformers may be separately obtained (Scheme).



1 X = H, Y = S
2 X = CH_2CO_2Et, Y = S
3 X = H, Y = CH_2
4 X = CH_2CO_2Et, Y = CH_2

Cone ($\mathbf{2}_C$) Partial Cone ($\mathbf{2}_{PC}$) 1,2-alternate ($\mathbf{2}_{1,2\text{-}A}$) 1,3-alternate ($\mathbf{2}_{1,3\text{-}A}$)

Scheme

The role played by alkaline metal cations in the synthesis as well as in the distribution of conformers of **2** was studied by treatment of tetrathiacalix[4]arene **1**[3] in refluxing acetone by 8 eq. of ethylbromoacetate in the presence of 6 eq. of M_2CO_3.[15] The highest overall yield of *ca* 76-80 % for the tetra substituted derivatives **2** was obtained after 7 days (Table). Except for the $\mathbf{2}_{1,2\text{-}A}$ isomer which was not obtained, all other three isomers were isolated and structurally studied both in solution and in the solid state.

It has been reported that in the case of **3** in the presence of alkaline metal carbonate no trace of $\mathbf{4}_{1,2\text{-}A}$ nor of $\mathbf{4}_{1,3\text{-}A}$ conformers could be detected.[14] The results obtained with thiacalix **1** were rather different. Indeed, although no ($\mathbf{2}_{1,2\text{-}A}$) isomer could be observed, in marked contrast with **3**, up to 85 % of the ($\mathbf{2}_{1,3\text{-}A}$) isomer was obtained. When using Li_2CO_3, as previously observed for **3**[14], no trace of the tetra substituted **2** was detected. Again, as observed for **3**[14], in the presence of Na_2CO_3 the $\mathbf{2}_C$ conformer was exclusively formed although with higher overall yield of 80 %. In the case of K_2CO_3, in marked contrast with the reported results for **3** (96 and 3 % of $\mathbf{4}_C$ and $\mathbf{4}_{PC}$, respectively)[14], for **1**, although no $\mathbf{2}_C$ conformer was detected, in addition to 70 % of $\mathbf{2}_{PC}$, 30 % of $\mathbf{2}_{1,3\text{-}A}$ were formed. Finally, in the presence of Cs_2CO_3, again in marked contrast with **3** for which the $\mathbf{4}_{PC}$ conformer was found to be exclusively formed, in the case of **1**, although the $\mathbf{2}_{PC}$ conformer was obtained in 15 % yield, the major isomer obtained was the $\mathbf{2}_{1,3\text{-}A}$ (85 % yield).

***Table**: Reaction (56 °C, 7 days) of ethylbromoacetate (22.16 mmol) with 1 (2.77 mmol) in acetone in the presence of 16.6 mmol M_2CO_3 (M= Li^+, Na^+, K^+, Cs^+) leading to compound 2[15] All yields reported are based on isolated conformers.*

	Li_2CO_3	Na_2CO_3	K_2CO_3	Cs_2CO_3	r_f[a]	m.p. (°C)	Elemental Analysis[b]
% $\mathbf{2}_C$ ($\mathbf{4}_C$)	0 (0)[c]	100 (100)[c]	0 (96)[c]	0 (0)[c]	0.6	165-167	C 63.07, H 6.72
% $\mathbf{2}_{PC}$ ($\mathbf{4}_{PC}$)	0 (0)[c]	0 (0)[c]	70 (3)[c]	15 (100)[c]	0.9	202-204	C 63.20, H 6.79
% $\mathbf{2}_{1,2\text{-}A}$ ($\mathbf{4}_{1,2\text{-}A}$)	0 (0)[c]	0 (0)[c]	0 (0)[c]	0 (0)[c]	-	-	-
% $\mathbf{2}_{1,3\text{-}A}$ ($\mathbf{4}_{1,3\text{-}A}$)	0 (0)[c]	0 (0)[c]	30 (0)[c]	85 (0)[c]	0.4	>260	C 63.27, H 6.72
Total yield (%)	0 (0)[c]	80 (59)[c]	80 (99)[c]	76 (100)[c]			

a) SiO_2, CH_2Cl_2/MeOH : 99/1; b) Calc. for $C_{56}H_{72}O_{12}S_4$, C 63.13, H 6.81, c) for **4**, literature results (in parenthesis) obtained under the same conditions for treatment of **3**.[14]

In solution, all three conformers isolated (2_C, 2_{PC} and $2_{1,3\text{-}A}$) were studied by both ^1H and ^{13}C NMR spectroscopy which showed sharp signals indicating the presence of conformationally blocked isomers. As expected for symmetry reasons, for both 2_C and $2_{1,3\text{-}A}$ conformers, the same number of signals as well as the same pattern were observed precluding thus precise assignments.[15] On the other hand, for the 2_{PC} isomer possessing a lower symmetry, both the proton as well as the carbon signals could be assigned.[15] In order to precisely assign all three isomers a structural analysis in the solid state based on X-ray diffraction on single crystals was achieved.

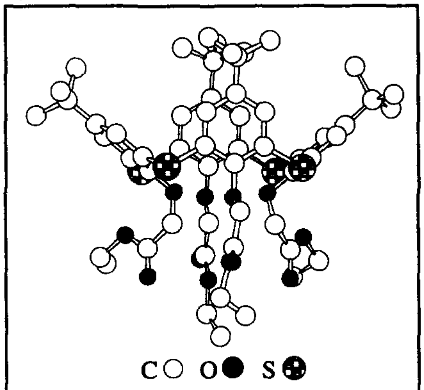


Figure 1 : X-ray structure of the cone conformer 2_C. H atoms are not presented for sake of clarity

Suitable single crystals for the cone conformer 2_C could be obtained from a Et_2O/MeOH mixture.[16] 2_C crystallised in a monoclinic form, space group P 1 2_1/n 1 (Figure 1). No solvent molecules were present in the lattice. The average CS distance and CSC angle were 1.785 Å and 100.1°, respectively. The average C=O distance was 1.190 Å whereas the average C-O(arom) and C-O (ethyl) distances were found to be 1.376 and 1.326 Å, respectively.

Single crystals for the partial cone conformer 2_{PC} could be obtained from a CH_2Cl_2/MeOH mixture.[16] 2_{PC} crystallised in monoclinic system with P1 2_1/n as the space group. In the unit cell two crystallographically slightly different molecules of 2_{PC} as well as a CH_2Cl_2 molecule (not included in the cavity of the calix) were present. Only one of the two molecules are shown in figure 2. The average CS distance and CSC angle were 1.784 Å and 100.5°, respectively. The average C=O distance was 1.191 Å whereas the average C-O(arom) and C-O (ethyl) distances were found to be 1.377 and 1.333 Å, respectively.

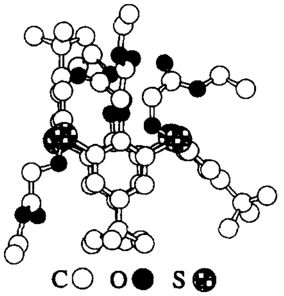


Figure 2 : X-ray structure of the partial cone conformer 2_{PC}. Only one of the two molecules present in the unit cell is presented. H atoms and CH_2Cl_2 molecule are not presented for sake of clarity

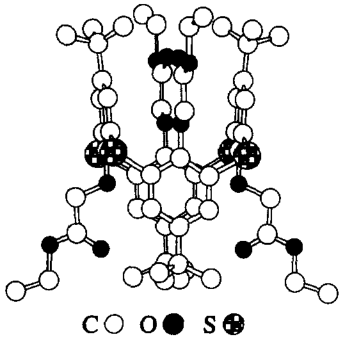


Figure 3 : X-ray structure of the 1,3-alternate conformer $2_{1,3\text{-}A}$. H atoms are not presented for sake of clarity

Suitable single crystals for the 1,3-alternate conformer $2_{1,3\text{-}A}$ could be obtained from a $CHCl_3$/MeOH mixture.[16] $2_{1,3\text{-}A}$ crystallised in monoclinic form, space group I 1 2/a 1 (Figure 3). No solvent molecules were present in the lattice. The average CS distance and CSC angle were 1.777 Å and 102.25°, respectively. The average C=O distance was 1.169 Å whereas the average C-O(arom) and C-O (ethyl) distances were found to be 1.377 and 1.268 Å, respectively.

In conclusion, using M_2CO_3, the effect of alkaline metal cations on the distribution of conformers of 2 bearing four ester groups was studied. Among the four possible conformers, the cone, partial cone and 1,3-alternate conformers were isolated and structurally characterised. Whereas for Li^+, no tetra substituted derivative was obtained, for Na^+ the cone conformer was exclusively formed, while for both K^+ and Cs^+ a mixture of partial cone and 1,3-alternate conformers was obtained. The ionophoric property as well coordination ability of the three isolated isomers is under current investigation.

Acknowledgement: We thank the CNRS and the Institut Universitaire de France.

References

1. C. D. Gutsche, *"Calixarenes"Revisited,* Monographs in Supramolecular Chemistry, Ed. J. F. Stoddart, R.S.C., London, **1998**.
2. Gutsche, C. D., Iqbal, M. *Organic Synthesis*, **1989**, *68*, 234.
3. H. Kumagai, M. Hasegawa, S. Miyanari, Y. Sugawa, Y. Sato, T. Hori, S. Ueda, H. Kamiyama, S. Miyano, *Tetrahedron Lett.*, **1997**, *38*, 3971-3972; T. Sone, Y. Ohba, K. Moriya, H. Kumada, K. Ito, *Tetrahedron Lett*, **1997**, *38*, 10689-10698.
4. H. Akdas, L. Bringel, E. Graf, M. W. Hosseini, G. Mislin, J. Pansanel, A. De Cian, J. Fischer, *Tetrahedron Lett.*, **1998**, *39*, 2311-2314.
5. G. Mislin, E. Graf, M. W. Hosseini, A. Bilyk, A. K. Hall, J. McB. Harrowfield, B. W. Skelton, A. H. White, *J. Chem. Soc., Chem. Commun.*, **1999**, in press.
6. N. Iki, H. Kumagai, N. Morohashi, K. Ajima, M. Hasegawa, S. Miyano, *Tetrahedron Lett*, **1998**, *39*, 7559-7562.
7. G. Mislin, E. Graf, M. W. Hosseini, A. De Cian, J. Fischer, *Tetrahedron Lett.*, **1999**, 40, in press.
8. G. Mislin, E. Graf, M. W. Hosseini, A. De Cian, J. Fischer, *J. Chem. Soc., Chem. Commun.*, **1998**, 1345-1346.
9. P. Lhotak, M. Himl, S. Pakhomova, I. Stibor *Tetrahedron Lett.*, **1998**, *39*, 8915-8918.
10. X. Delaigue, M. W. Hosseini, N. Kyritsakas, A. De Cian, J. Fischer, *J. Chem. Soc., Chem. Commun.*, **1995**, 609-610.
11. C. G. Gibbs, C. D. Gutsche, *J. Amer. Chem. Soc.*, **1993**, *115*, 5338-5339.
12. X. Delaigue, J. McB. Harrowfield, M. W. Hosseini, A. De Cian, J. Fischer, N. Kyritsakas, *J. Chem. Soc., Chem. Commun.*, **1994**, 1579-1580.
13. M. A. McKervey, E. M. Seward, G. Ferguson, BV. Ruhl, S. Harris, *J. Chem. Soc., Chem. Commun.***1985**, 388-390; A. Arduini, A. Pochini, S. Reverberi, R. Ungaro, G. D. Andreetti, F. Ugozzoli, *Tetrahedron*, **1986**, *42*, 2089-2100; S.-K. Chang, I. Cho, *J. Chem. Soc., Perkin Trans. 1*, **1986**, 211-214.
14. K. Iwamoto, S. Shinkai, *J. Org. Chem.*, **1992**, *57*, 7066-7073.
15. To a suspension of compound **1** (2 g, 2.77 mmol) in dry acetone (50 ml), alkaline metal carbonate (16.6 mmol) (M_2CO_3, M = Li^+ (1.23 g) Na^+ (1.76 g), K^+ (2.29 g) Cs^+ (5.4 g) and ethylbromoacetate (2.45 ml, 22.16 mmol) were added and the mixture refluxed for 7 days. After allowing the reaction mixture to cool to r. t., the insoluble material was filtered and the solid thus obtained was washed with CH_2Cl_2 (3x10 ml). The filtrate and washes were combined and evaporated to dryness leaving thus a solid residue. The desired conformers of **2** ($\mathbf{2}_{C}$, $\mathbf{2}_{PC}$ and $\mathbf{2}_{1,3\text{-}A}$) were obtained in different yields depending on the nature of the cation used upon fractional crystallisation from CH_2Cl_2/MeOH mixture. $\mathbf{2}_{C}$: ^1H (300 MHz, $CDCl_3$, 25 °C): δ (ppm) : 1.08 (s, 36H, CH_3); 1.27 (t, 12H, J = 7.0 Hz, C_2H_5); 4.21 (q, 8H, J = 7.0 Hz, C_2H_5); 5.16 (s, 8H, OCH_2O); 7.28 (s, 8H, Ph); ^{13}C (75.48 MHz, $CDCl_3$, 25 °C): δ(ppm): 14.02 (CH_2CH_3); 31.03 (CH_3); 34.01 ($C(CH_3)_3$); 60.52 (OCH_2CO), 70.60 (CH_2OPh), 129.22, 134.07, 146.38 (*C* arom.), 157.27 (*C*O), 169.39 (*C*=O); $\mathbf{2}_{PC}$: ^1H (300 MHz, $CDCl_3$, 25 °C): δ (ppm) : 1.04 (s, 18H, CH_3); 1.31 (s, 9H, CH_3), 1.42 (s, 9H, CH_3), 1.13 (t, 3H, J = 7.0 Hz, C_2H_5); 1.27 (t, 6H, J = 7.0 Hz, C_2H_5); 1.32 (t, 3H, J = 7.0 Hz, C_2H_5); 3.97 (q, 2H, J = 7.0 Hz, C_2H_5); 4.20 (m, 6H, C_2H_5); 4.64 (s, 2H, OCH_2O); 4.73 (s, 2H, OCH_2O); 4.74 (s, 4H, OCH_2O); 7.00 (d, 2H, J = 2.5 Hz, Ph); 7.51 (d, 2H, J = 2.5 Hz, Ph);7.53 (s, 2H, Ph);7.85 (s, 2H, Ph); ^{13}C (75.48 MHz, $CDCl_3$, 25 °C): δ(ppm): 13.84, 14.11, 14.18 (CH_2CH_3); 30.98, 31.12, 31.29 (CH_3); 33.93, 34.11, 34.34 ($C(CH_3)_3$); 59.60, 60.54, 65.93, 69.26, 70.61 (OCH_2), 126.59, 127.92, 128.46, 129.25, 133.00, 133.87, 134.57, 135.48, 144.93, 146.60 (*C* arom.), 156.64, 157.62, 158.57 (*C*O), 167.78, 168.43, 170.05 (*C*=O); $\mathbf{2}_{1,3\text{-}A}$: ^1H (300 MHz, $CDCl_3$, 25 °C): δ (ppm) : 1.25 (s, 36H, CH_3); 1.28 (t, 12H, J = 7.0 Hz, C_2H_5); 4.22 (q, 8H, J = 7.0 Hz, C_2H_5); 4.60 (s, 8H, OCH_2O); 7.50 (s, 8H, Ph); ^{13}C (75.48 MHz, $CDCl_3$, 25 °C): δ(ppm): 14.11 (CH_2CH_3); 30.96 (CH_3); 34.06 ($C(CH_3)_3$); 60.40 (OCH_2CO), 68.13 (CH_2OPh), 127.57, 133.34, 146.10 (*C* arom.), 157.12 (*C*O), 167.82 (*C*=O).
16. *X-ray data for* $\mathbf{2}_{C}$: $C_{56}H_{72}O_{12}S_4$, M = 1065.45, monoclinic, a = 16.3740 (4), b = 21.3540 (6), c = 16.5740 (3) Å, β = 93.522(1), U = 5784.2 (4) Å^3, space group P 1 2_1/n 1, Z = 4, Dc = 1.22 gcm^{-3}, μ(Mo-$K\alpha$) = 0.222 mm^{-1}. Crystal dimensions 0.20x0.20x0.20 mm. Data were measured at 173 K on a kapa CCD diffractometer with graphite monochromated Mo-Kα radiation. The structure was solved by direct methods using OpenMoleN 2.2 and refined anisotropically using absorption corrected data to give R = 0.055, Rw = 0.083 for 10668 independent observed reflections [$|F_o| > 3\sigma(|F_o|$]; *X-ray data for* $\mathbf{2}_{PC}$: $2(C_{56}H_{72}O_{12}S_4).CH_2Cl_2$, M = 2215.83, monoclinic, a = 21.3672 (4), b = 20.8343 (5), c = 28.5577 (5) Å, β = 111.632 (1), U = 11817.7 (8) Å^3, space group P1 2_1/n, Z = 4, Dc = 1.25 gcm^{-3}, μ(Mo-$K\alpha$) = 0.291 mm^{-1}. Crystal dimensions 0.20x0.20x0.10 mm. Data were measured at 294 K on a kapa CCD diffractometer with graphite monochromated Mo-Kα radiation. The structure was solved by direct methods using OpenMoleN 2.2 and refined anisotropically using absorption corrected data to give R = 0.080, Rw = 0.095 for 16199 independent observed reflections [$|F_o| > 3\sigma(|F_o|$]; *X-ray data for* $\mathbf{2}_{1,3\text{-}A}$: $C_{56}H_{72}O_{12}S_4$, M = 1065.45, monoclinic, a = 20.972 (5), b = 13.832 (2), c = 21.076 (4) Å, β = 107.15 (2), U = 5841 (4) Å^3, space group I 1 2/a 1, Z = 4, Dc = 1.21 gcm^{-3}, μ(Mo-$K\alpha$) = 0.209 cm^{-1}. Crystal dimensions 0.38x0.31x0.20 mm. Data were measured at 294K on a Anraf-Nonius CAD4 diffractometer with graphite monochromated Mo-Kα radiation. The structure was solved by direct methods using OpenMoleN 2.2 and refined anisotropically using absorption corrected data to give R = 0.059, Rw = 0.080 for 1681 independent observed reflections [$|F_o| > 3\sigma(|F_o|$]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.