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Novel Ligands Deriving from *p-tert*-Butylcalix[4]arene O-Substituted by Diethyl Malonate Functions.

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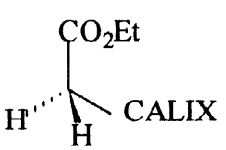
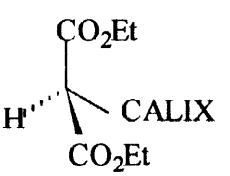
Abstract: The synthesis of calixarenes **1-6** combining a *p-tert*-butyl calix[4]arene unit and diethyl malonate functions is described. Preliminary complexing properties are given.

One of the first examples of calixarene-based cation receptors is probably the family of O-substituted *p-tert*-butyl calix[4]arene podands containing *ethyl ester* binding functions attached at the lower rim. This family of tetra ester derivatives has been observed by several groups to be selective for sodium cation when the calix[4]arene unit is in cone conformation.[1] The strong preference of the tetra ethyl ester derivatives towards the sodium cation has been attributed to the cone conformation steering the four donating binding groups to converge and encapsulate the cation in a preorganised oxygen-donor cavity.[1] The only known crystal structure of such a complex is that of the related potassium-tetra amide complex.[1] The crystal structure indicates the complex to have a fourfold symmetry involving the carbonyl oxygen atoms and the phenolic ones to maintain the whole structure of the 1:1 complex.[1]

In the present Note we report on the synthesis and complexing properties of ligands **1-6** made of a *p-tert*-butylcalix[4]arene in cone conformation and O-substituted by *diethyl malonate* groups. Due to the presence of two ethyl ester functions in each malonate unit, as to compare with the single ethyl ester one (see below), they are *poly ethyl ester* derivatives of *p-tert*-butyl calix[4]arene in which the complexing cavity is delineated by *four* (compounds **3** and **4**) or *six* (compounds **5** and **6**) ethyl ester binding groups.



ethyl ester function



diethyl malonate function

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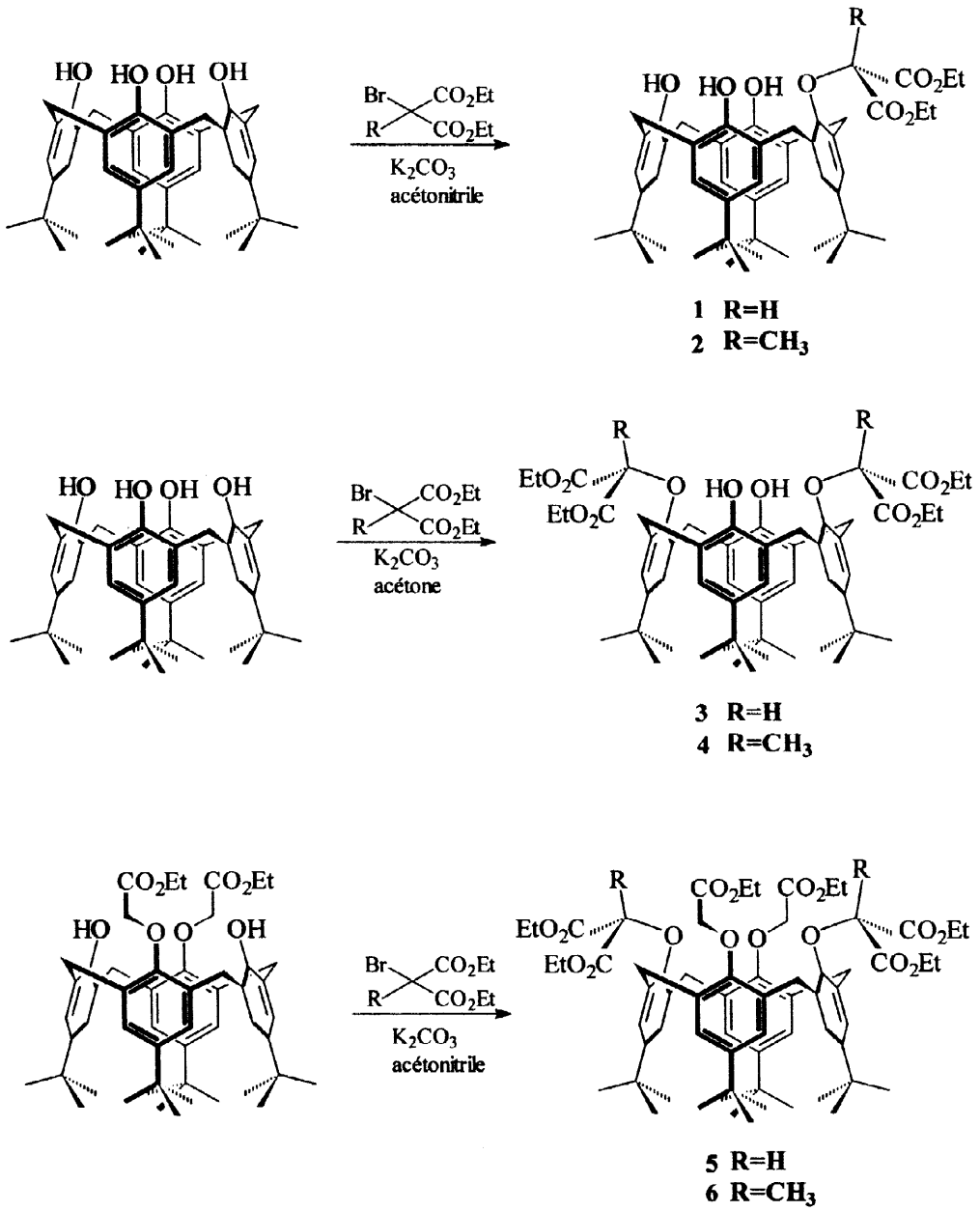
The synthetic procedure for the preparation of ligands **1-6** is illustrated in Scheme 1.



Scheme 1. Synthetic pathways to ligands **1-6**

According to similar procedures described by us,[2] *p-tert*-butyl calix[4]arene was first treated with 1 equiv. of potassium carbonate in acetonitrile for 1h at r. t. for preliminary deprotonation. Then, 1 equiv of diethyl bromo malonate or diethyl 2-bromo-2-methylmalonate were added and the reacting mixtures were

refluxed for additional 24 h. After removal of the solvent and extraction with CH_2Cl_2-1N HCl-H_2O (pH ~ 2), **1** and **2** were obtained pure in 7% and 16% respective yields by chromatography of the crude residue on SiO_2 with a 3:2 mixture of dichloromethane-hexane as eluent. Similarly, **3-6** were obtained by reacting *p-tert*-butylcalix[4]arene or its 1,3-O-diethyl ester derivative with 4 equivs of diethyl bromomalonate or diethyl 2-bromo-2-methylmalonate with a deprotonation time of 3h in the presence of 4 equivs of potassium carbonate in acetone or acetonitrile. Reflux was 24 h. The residues were precipitated with CH_3OH to afford **3-6** as white solids in 76 %, 57 %, 80 %, and 40 % respectively.

That **1-6** adopted the cone conformation was deduced from their ^{1}H-NMR spectra.[3] We observed 3 doublets at 3.46 ppm, 4.34 ppm, and 4.69 ppm (J = 13.5 Hz, integration ratio 1:2:1) in the spectrum of **1** and 4 doublets at 3.25 ppm, 3.40 ppm, 4.26 ppm, and 4.46 ppm (J = 13.0 Hz, integration ratio 1:1:1:1) in the one of **2** for the Ar-CH_2-Ar methylene protons of the calixarene moiety. The ^{1}H-NMR spectra of **3-6** showed one pair of doublets at 3.23 ppm and 4.38 ppm (J = 13.5 Hz) for **3**, at 3.16 ppm and 4.40 ppm (J = 13.0 Hz) for **4**, at 3.13 ppm and 4.79 ppm (J = 13.0 Hz) for **5**, and at 3.05 ppm and 4.62 ppm (J = 13.0 Hz) for **6**.

The suitability of **1-6** as ligands for hard cations such as those of alkali metals was demonstrated by the use of ^{1}H-NMR. By a method already described by us,[6] solid alkali picrates were added to deuteriated chloroform solutions of **1-6**. After a period of 2 days reaction at r. t. we estimated the ratio of metal to ligand ($R_{Me/L}$) in solution by integration of the picrate proton resonance *vs* those of the aromatics. **1-4** poorly extracted alkali metal picrates. Interestingly, ligands **3** and **4** were poorer complexants than the isofunctional tetra ethyl ester *p-tert*-butylcalix[4]arene.[7] We concluded that the binding ester functions of **3** and **4** cannot adopt the required fourfold symmetry and are less predisposed for complexation. Ligands **5** and **6** only extracted lithium and sodium picrates with $R_{Li/5}$ = 1.0:1, $R_{Na/5}$ = 1.0:1, $R_{Li/6}$ = 1.0:1 and $R_{Na/6}$ = 0.5:1. The value $R_{Na/6}$ = 0.5:1 was assumed to be due to the presence of the methyl group on the malonate function. $R_{Na/6}$ = 1.0:1 could be reached by refluxing ligand **6** with sodium picrate in chloroform for 2 days. The ^{1}H-NMR spectra of the solutions were interpreted as 1:1 complexes for **5:Li, 5:Na, 6:Li,** and **6:Na**.[3] The largest signal shifts were observed for the ArOC***H***$_2$$CO_2$Et and ArOC***H***($CO_2$Et)$_2$ of **5** and ArOC***H***$_2$$CO_2$Et and ArOCC***H***$_3$($CO_2$Et)$_2$ of **6** for the 1:1 complexes with Na. This was in agreement of a location of the sodium cation nearby the phenolic oxygen atoms of the calix unit in a very similar topology as observed for the 1:1 sodium complex of tetra ethyl *p-tert*-butyl calix[4]arene.[1] This was not observed in the case of lithium complexes probably because the cation is located at the level of the carbonyl ester functions.

Evidence that in the gas phase the stability of the complexes was similar to that in solution was the fact that in the mass spectra peaks could be detected in all cases (**5:Li** m/z = 1143.2; **5:Na** m/z = 1159.3; **6:Li** m/z =1171.9; **6:Na** m/z =1187.8).[3]

Preliminary complexation studies were carried out with UV-visible spectrometry in acetonitrile and confirmed that the 1:1 stoichiometry is maintained in this solvent. Further studies of the complexation properties of **3-6** are currently under investigation and will be presented in due course. Our objectives include : a.) showing evidence of carriers properties of this novel series of calixarenes; b.) studying the complexation of alkaline-earth metal cations; c.) preparing homologues of ligands **5** and **6**, bearing *five* ethyl ester binding groups instead of *six*, by fully O-alkylating the OH groups in **1** and **2** by ethyl ester functions.

References and notes

1. Ungaro, R. and Pochini, A. in *Calixarenes: a Versatile Class of Macrocyclic Compounds*, Vicens J. and Böhmer V. Eds, Kluwer Academic Publishers, Dordrecht, 1991.
2. Abidi, R.; Harrowfield, J.; Skelton, B. W. White, A.; Asfari, Z. Vicens, J. *J. Incl. Phenom. Mol. Recogn. Chem.* **1997**, *27*, 291-302.
3. *Chemicals.* Diethyl bromomalonate, diethyl 2-bromo-2-methylmalonate, potassium carbonate and the solvents were commercial reagents and used without further purification. *p-tert*-Butylcalix[4]arene[4] and 1,3-diethylester *p-tert*-butylcalix[4]arene[5] were prepared according to the literature.
   General. Mps, capillaries under N_2, Büchi 500. Chromatography SiO_2,columns with Kieselgel Merck (Art. 11567). ^{1}H-NMR Bruker AC 200 spectrometer (δ in ppm, J in Hz). FAB (+) MS, VG-Analytical ZAB HF. Elemental analyses performed at the Service de Microanalyse of the Institut de Chimie de Strasbourg.

Analytical data of compound **1**: (Mp 271-272° C) *^{1}H-NMR* (200 MHz, $CDCl_3$): 1.22 (s, Ar-C(CH_3)$_3$), 1.25 (s, 2 Ar-C(CH_3)$_3$), 1.27 (s, Ar-C(CH_3)$_3$), 1.36 (t, *J* = 7.0, 2 $CO_2CH_2CH_3$), 3.46 (d, *J* = 13.5, Ar-CH_2-Ar), 4.34 (d, *J* = 13.5, 2 Ar-CH_2-Ar), 4.40 (q, *J* = 7.0, 2 $CO_2CH_2CH_3$), 4.69 (d, *J* = 13.5, Ar-CH_2-Ar), 5.66 (s, ArO$CH(CO_2Et)_2$), 7.01-7.10 (m, 8 Ar-*H*), 9.13 (s, 2 Ar-O*H*), 9.21 (s, Ar-O*H*) FAB (+) MS *m/z* 806.7 *Anal. Found* C, 76.17; H, 8.28 *Calcd For* $C_{51}H_{66}O_8$ C, 75.93; H 8.18.

Analytical data of compound **2**: (Mp 273-274° C) *^{1}H-NMR* (200 MHz, $CDCl_3$): 1.11 (s, Ar-C(CH_3)$_3$), 1.18 (s, 2 Ar-C(CH_3)$_3$), 1.20 (s, Ar-C(CH_3)$_3$), 1.33 (t, *J* = 7.0, 2 $CO_2CH_2CH_3$), 1.51 (s, ArOCC$H_3(CO_2Et)_2$), 3.25 (d, *J* = 13.0, Ar-CH_2-Ar), 3.40 (d, *J* = 13.0, Ar-CH_2-Ar), 4.26 (d, *J* = 13.0, Ar-CH_2-Ar), 4.34 (q, *J* = 7.0, 2 $CO_2CH_2CH_3$), 4.46 (d, *J* = 13.0, Ar-CH_2-Ar), 6.93-7.03 (m, 8 Ar-*H*), 9.11 (s, 2 Ar-O*H*), 10.22 (s, Ar-O*H*) FAB (+) MS *m/z* 820.6. *Anal. Found* C, 76.26; H, 8.63 *Calcd For* $C_{52}H_{68}O_8$ C, 76.04; H 8.28.

Analytical data of compound **3**: (Mp 133-134° C) *^{1}H-NMR* (200 MHz, $CDCl_3$): 0.76 (s, 2 Ar-C(CH_3)$_3$), 1.27 (s, 2 Ar-C(CH_3)$_3$), 1.27 (t, *J* = 7.0, 4 $CO_2CH_2CH_3$), 3.23 (d, *J* = 13.5, 2 Ar-CH_2-Ar), 4.27 (q, *J* = 7.0, 4 $CO_2CH_2CH_3$), 4.38 (d, *J* = 13.5, 2 Ar-CH_2-Ar), 5.04 (s, 2 ArO$CH(CO_2Et)_2$), 6.26 (s, 2 Ar-O*H*), 6.49 (s, 4 Ar-*H*), 7.02 (s, 4 Ar-*H*) FAB (+) MS *m/z* 964.4 *Anal. Found* C, 72.38 H, 7.94 *Calcd For* $C_{58}H_{76}O_{12}$ C, 72.05; H 7.55.

Analytical data of compound **4**: (Mp 160-161° C) *^{1}H-NMR* (200 MHz, $CDCl_3$): 0.84 (s, 2 Ar-C(CH_3)$_3$), 1.32 (s, 2 Ar-C(CH_3)$_3$), 1.33 (t, *J* = 7.0, 4 $CO_2CH_2CH_3$), 1.53 (s, 2 ArOCC$H_3(CO_2Et)_2$), 3. 16 (d, *J* = 13.0, 2 Ar-CH_2-Ar), 4.32 (q, *J* = 7.0, 4 $CO_2CH_2CH_3$), 4.40 (d, *J* = 13.0, 2 Ar-CH_2-Ar), 6.44 (s, 2 Ar-O*H*), 6.62 (s, 4 Ar-*H*), 7.04 (s, 4 Ar-*H*) FAB (+) MS *m/z* 993.8 *Anal. Found* C, 72.89; H, 8.32 *Calcd For* $C_{60}H_{80}O_{12}$ C, 72.45; H 8.05.

Analytical data of compound **5**: (Mp 151-156° C) *^{1}H-NMR* (200 MHz, $CDCl_3$): 0.74 (s, 2 Ar-C(CH_3)$_3$), 1.14-1.20 (m, 6 $CO_2CH_2CH_3$), 1.26 (s, 2 Ar-C(CH_3)$_3$), 3.13 (d, *J* = 13.0, 2 Ar-CH_2-Ar), 4.14 (q, *J* = 6.0, 2 $ArOCH_2CO_2CH_2CH_3$), 4.16 (q, *J* = 6.0, 2 $ArOCH(CO_2CH_2CH_3)_2$), 4.79 (d, *J* = 13.0, 2 Ar-CH_2-Ar), 5.04 (s, 2 ArO$CH(CO_2CH_2CH_3)_2$), 5.16 (s, 2 $ArOCH_2CO_2CH_2CH_3$), 6.36 (s, 4 Ar-*H*), 7.21 (s, 4 Ar-*H*) FAB (+) MS *m/z* 1159.3 ($M+Na^+$, 100%) ; 1136.3 (M^+, 45%). *Anal. Found* C, 70.10; H, 8.01 *Calcd For* $C_{66}H_{88}O_{16}$ C, 69.70; H 7.80.

Analytical data of compound **6**: (Mp 168-169° C) *^{1}H-NMR* (200 MHz, $CDCl_3$): 0.77 (s, 2 Ar-C(CH_3)$_3$), 1.12-1.22 (m, 6 $CO_2CH_2CH_3$), 1.29 (s, 2 Ar-C(CH_3)$_3$), 1.45 (s, 2 ArOCC$H_3(CO_2Et)_2$), 3.05 (d, *J* = 13.0, 2 Ar-CH_2-Ar), 4.03-4.36 (m, 2 $ArOCH_2CO_2CH_2CH_3$ and 4 $ArOCH(CO_2CH_2CH_3)_2$), 4.62 (d, *J* = 13.0, 2 Ar-CH_2-Ar), 5.31 (s, 2 $ArOCH_2CO_2CH_2CH_3$), 6.36 (s, 4 Ar-*H*), 7.03 (s, 4 Ar-*H*) FAB (+) MS *m/z* 1164.6 *Anal. Found* C, 70.62; H, 8.24 *Calcd For* $C_{68}H_{92}O_{16}$ C, 70.08; H 7.96.

Spectral data of 1:1 complex **5:Li**: *^{1}H-NMR* (200 MHz, $CDCl_3$): 0.98 (broad s, 2 Ar-C(CH_3)$_3$), 1.18 (t, 2 $ArOCH(CO_2CH_2CH_3)_2$), 1.18 (s, 2 Ar-C(CH_3)$_3$), 1.31 (t, *J* = 6.5, 2 $ArOCH_2CO_2CH_2CH_3$), 3.28 (d, *J* = 13.0, 2 Ar-CH_2-Ar), 4.18 (q, *J* = 7.5, 6 $CO_2CH_2CH_3$), 4.51 (broad d, *J* = 13.0, 2 Ar-CH_2-Ar), 5.08 (s, 2 ArO$CH(CO_2CH_2CH_3)_2$), 5.25 (s, 2 $ArOCH_2CO_2CH_2CH_3$), 6.96 (s, 4 Ar-*H*), 7.10 (s, 4 Ar-*H*) FAB (+) MS ***m/z* = 1143.2**.

Spectral data of 1:1 complex **5:Na**: *^{1}H-NMR* (200 MHz, $CDCl_3$): 1.02 (s, 2 Ar-C(CH_3)$_3$), 1.18 (t, 2 $ArOCH(CO_2CH_2CH_3)_2$), 1.18 (s, 2 Ar-C(CH_3)$_3$),), 1.37 (t, *J* = 7.0, 2 $ArOCH_2CO_2CH_2CH_3$), 3.32 (d, *J* = 13.0, 2 Ar-CH_2-Ar), 4.20 (q, *J* = 7.0, 2 $ArOCH(CO_2CH_2CH_3)_2$), 4.26 (q, *J* = 7.0, 2 $ArOCH_2CO_2CH_2CH_3$), 4.43 (broad d, *J* = 13.0, 2 Ar-CH_2-Ar), 4.53 (broad s, 2 ArO$CH(CO_2CH_2CH_3)_2$), 5.10 (s, 2 $ArOCH_2CO_2CH_2CH_3$), 6.99 (s, 4 Ar-*H*), 7.13 (s, 4 Ar-*H*) FAB (+) MS ***m/z* = 1159.3**.

Spectral data of 1:1 complex **6:Li**: *^{1}H-NMR* (200 MHz, $CDCl_3$): 0.77 (s, 2 Ar-C(CH_3)$_3$), 1.20-1.27 (m, 6 $CO_2CH_2CH_3$), 1.27 (s, 2 Ar-C(CH_3)$_3$), 1.43 (s, 2 ArOCC$H_3(CO_2Et)_2$), 3.13 (d, *J* = 13.0, 2 Ar-CH_2-Ar), 4.13-4.33 (m, 6 $CO_2CH_2CH_3$), 4.31 (d, *J* = 13.0, 2 Ar-CH_2-Ar), 4.99 (s, 2 $ArOCH_2CO_2CH_2CH_3$), 6.50 (s, 4 Ar-*H*), 7.21 (s, 4 Ar-*H*) FAB (+) MS *m/z* **1171.9**.

Spectral data of 1:1 complex **6:Na**: *^{1}H-NMR* (200 MHz, $CDCl_3$): 0.77 (broad s, 2 Ar-C(CH_3)$_3$), 1.21 (s, 2 Ar-C(CH_3)$_3$), 1.21-1.27 (m, 6 $CO_2CH_2CH_3$ and 2 $ArOCC H_3(CO_2Et)_2$), 3.19 (d, *J* = 13.0, 2 Ar-CH_2-Ar), 4.16-4.24 (m, 6 $CO_2CH_2CH_3$ and 2 $ArOCH_2CO_2CH_2CH_3$), 4.45 (d, *J* = 13.0, 2 Ar-CH_2-Ar), 6.87 (broad s, 4 Ar-*H*), 7.12 (s, 4 Ar-*H*) FAB (+) MS *m/z* **1187.8**.

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5. Soedarsono, J.; Burgard, M.; Asfari, Z.; Vicens, J. *New J. Chem.* **1993**, *17*, 601-611.
6. Saadioui M.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1997**, *38*, 1187-1190.

7. Tetra ethyl ester *p-tert*-butylcalix[4]arene[1] was reacted with alkali picrates in our conditions and we found $R_{Li/ligand}$ = 0.7:1, $R_{Na/ligand}$ = 1.0:1, $R_{K/ligand}$ = 0.8:1.