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Synthesis of multivalent oxamate ligands based on calix[4]arene and thiacalix[4]arene backbones in *1,3*-Alternate conformation

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ABSTRACT

Five new multivalent ligands based on either *p-tert-butyl*thiacalix[4]arene (TCA) 1 or *p-tert-butyl*calix[4]arene (CA) 2 backbones in *1,3*-Alternate conformation bearing four oxamate coordinating groups at their lower rim were designed and synthesized by a multistep strategy. These ligands differ either by the nature of the calix[4]arene backbone (CA or TCA) or by the nature of the spacer ($(CH_2)_n$) connecting the oxamate binding units to the backbone.

1. Introduction

For the design of multivalent ligands, calixarenes,[1] macrocyclic organic entities based on interconnection of phenolic moieties by CH_2 groups, are of particular interest. Indeed, this class of preorganized backbone offers unlimited design possibilities through functionalization of the lower and/or upper rims. Furthermore, the CH_2 moiety connecting the phenolic units may be replaced by other groups or atoms. Calixarene derivatives have been widely used in the field of supramolecular chemistry[2] for substrate binding, recognition and transport of neutral molecules or ions.[3]

Among the calix[n]arene derivatives, differing by the number of phenolic units (n = 4–12), thiacalix[4]arene (TCA, **1**, Fig. 1),[4] for which the four aryl rings are connected by thioether junctions and calix[4]arene (CA, **2**, Fig. 1)[1] are of interest owing to their conformational flexibility leading to four limit conformers called cone, partial cone, *1,2*-Alternate and *1,3*-Alternate. This aspect may be exploited for the design of multivalent ligands for which the interaction sites are positioned either on the same face of the backbone (cone conformer) or distributed on both sides of the mean plane of the macrocyclic framework (partial cone, *1,2*-Alternate and *1,3*-Alternate conformers). As stated above, both compounds **1** and **2** may be readily modified allowing thus the design of a large variety of receptors and ligands. Indeed, both backbones may be equipped with interaction sites both at the lower rim though functionalization of the OH groups or at upper rim by introduction of almost any group in the *para* position. For the thiacalix[4]arene backbone, the thioether junctions may be oxidized to sulfonyl (X = SO)[5] or sulfinyl ($X = SO_2$).[6] Among the four limit conformations adopted by CA and TCA, the *1,3*-Alternate conformation is of interest for the design of multivalent entities since it allows to position four interactions below and above the macrocyclic backbone in an alternate fashion. We shall focus here on calix based coordinating derivatives. Both calix[4]arene and thiacalix[4]arene have been decorated both at the upper and/or lower rims with a variety of monodentate donor sites (cyano,[7] pyridine,[8] pyrazole,[9] etc..) as well as bidendate (bipyridine,[10] carboxylate,[11] ethylene diamine,[12] etc..) units. These polydentate ligands have been used for the formation of discrete coordination complexes[13] or infinite coordination polymers. Among bis-bidentate N and/or O donor units such as bis-pyrimidine, chloranilate, oxalate and oxamate ligand, the latter has been widely used for the synthesis of a variety of coordination complexes used in catalysis,[14] molecular magnetism[15] and in medicinal chemistry.[16]

To the best of our knowledge, no example of calix[4]arene bearing oxamate coordinating groups has been reported to date.

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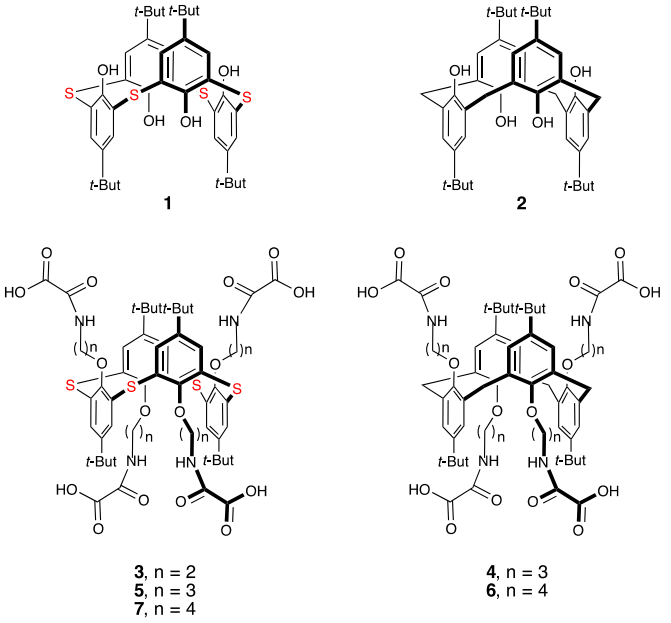

Fig. 1. p-*tert*-butylthiacalix[4]arene TCA **1** and *p*-*tert*-butylcalix[4]arene CA **2** in 1,3-Alternate conformation and their derivatives bearing four oxamate units 3–7.

Furthermore, no examples of ligands based on tetrasubstituted CA or TCA *1,3*-Alternate conformation bearing bis-bidentate ligands has been published.

Here, we report on the design, synthesis and characterization of a series of multivalent ligands based on CA or TCA, in *1,3*-Alternate conformation, bearing four oxamate units (compounds **3**–**7**, Fig. 1).

2. Results and discussion

The design of the five unprecedented ligands **3**–**7** (Fig. 1) is based on either *p*-*tert*-butylthiacalix[4]arene TCA (**3**, **5**, **7**) and *p*-*tert*-butylcalix[4]arene CA (**4**, **6**) backbones in *1,3*-Alternate conformation equipped with four oxamate units. The latter coordinating groups are connected to the macrocyclic backbone by $(CH_2)_n$ spacers (n = 2, 3 or 4).

The synthesis of ligands **3**–**7** was achieved following a stepwise strategy. The main intermediate for the synthesis of all five ligands were the phthalimido derivatives **9**–**13** in *1,3*-Alternate conformation (Fig. 2).

The synthesis of phthalimido derivatives **10**[17] and **11**[18] (n = 3, TCA and CA respectively) has been previously described. Following the reported procedure, condensation of *N*-(3-bromopropyl) phthalimide with the parent TCA **1** or CA **2** compounds in the presence of Cs_2CO_3 in DMF or Acetone respectively afforded compounds **10** and **11** in 68 and 55% yields respectively. By applying the same procedure, compounds **12** and **13** (n = 4, TCA and CA respectively) were obtained in 50% and 29% yields respectively (see experimental section).

Using the same procedure, the condensation of either compound **1** or **2** with (2-bromoethyl)phthalimide in the presence of base, failed to produce intermediates in *1,3*-Alternate conformation, with a shorter spacer (n = 2). It has been previously reported that, the condensation between TCA **1** and (2-bromoethyl)phthalimide in the presence of M_2CO_3 (M = Na, K or Cs) leads to the formation of the mono-substituted derivative in cone conformation.[17a] The same was observed upon increasing the amount of (2-bromoethyl)phthalimide up to 8 equivalents. In order to prepare the tetrasubstituted phthalimido compounds derived from compounds **1** and **2**, another previously reported procedure based on the Mitsunobu reaction was applied. This strategy requires the coupling of an hydroxy derivative **8** with phthalimide **25** in the presence of PPh_3 and DIAD as coupling agent.

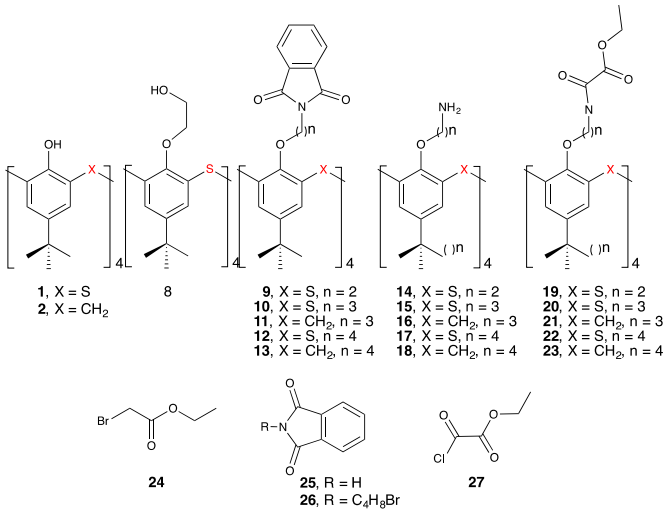

Fig. 2. Starting compounds **1** and **2**, precursors **8**–**27** used for the synthesis of ligands **3**–**7**.

Using K_2CO_3 as base, the synthesis of the tetraethylester derivative of CA in cone conformation was reported.[19] We found that the replacement of K_2CO_3 by Cs_2CO_3 upon the condensation of **1** with **24** leads to the formation of the tetraethylester derivative in *1,3*-Alternate conformation. The required compound **8** was then obtained upon reduction of the tetraethyl ester by $LiALH_4$ in THF.[20] Unfortunately, this synthetic approach was only successful with thiacalix[4]arene derivative **8**.

Compound **9**, in *1,3*-Alternate conformation, was prepared in 78% yield upon condensation of **8** with the phthalimide derivative **25** (see experimental section).

The phthalimido derivatives **9**–**13** were converted into their amino derivatives **14**–**18** by hydrazinolysis.[21] The amino compounds **15** and **16** have been already reported[18] and were obtained in 97% and 98% yield respectively. The other three amino derivatives **14**, **17** and **18** were prepared in 98%, 97% and 92% yields respectively (see experimental section).

The ethyloxamate derivatives **19**–**23**, in *1,3*-Alternate conformation, were obtained upon condensation of the amino derivatives **14**–**18** with ethylchloro(oxo)acetate **27** with yields in the 63–96% range (see Table 1 and experimental section). Finally, the targeted ligands **3**–**7** were obtained upon saponification of the ester derivatives **19**–**23**, with yields in the 85–94% range (see Table 1 and experimental section).

All intermediates and final compounds **3**–**7**, were fully characterized in solution by ^1H and ^{13}C NMR spectroscopy, in addition to other usual technics such as elemental analysis, melting point and mass spectrometry.

Table 1
Yields for the condensation of the amino derivatives **14**–**18** with ethyl chloro(oxo) acetate leading to compounds **19**–**23** and their saponification affording the targeted compounds **3**–**7**.

Compound	**19**	**20**	**21**	**22**	**23**
Yield (%)	76	68	67	63	96
Compound	**3**	**4**	**5**	**6**	**7**
Yield (%)	94	92	85	87	83