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Synthesis of Cavity Extended Cyclotriveratrylenes

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Abstract: Aromatic nucleophilic substitution reaction of cyclotriguaiacylene **1** with fluorobenzene derivatives bearing electron-withdrawing groups X (CHO, $COCH_3$, CN, NO_2) in the *para* position gives a series of cyclotriveratrylene derivatives (**3a**−**d**), where the X substituents can be transformed to hydrogen-bond donor groups to afford new CTV-based heteroditopic receptors. The substituents of compounds **3a**−**d** favor the facile demethylation reaction of the CTV derivatives. Attempts to perform alkylation reactions on derivatives (**8c**,**d**) evidenced the formation of a stereoisomeric mixture of symmetrical and unsymmetrical compounds.

An attractive target of supramolecular chemistry[1] is the construction of devices working through molecular recognition processes. Therefore the synthesis of efficient and selective receptors having shape and size complementary with the target guest still represent a field of current interest. A very convenient strategy for the construction of efficient hosts is the synthesis of heteroditopic receptors starting from a preformed molecular platform on which to introduce and orient in space additional binding sites.

During this past decade, we focused our investigations on the recognition of neutral[2] and charged guests[2a,3] in apolar media, through the cavity of several derivatives of cone conformer calix[4]arene[4] having a 4-fold symmetry.[5] The synthetic approach we followed for the synthesis of these hosts consists of two main steps: functionalization of the lower rim to fix the platform in a rigid cone conformation and then introduction of suitable additional binding sites at the upper rim. Cyclotriveratrilenes[6] (CTVs) are intrinsically rigid macrocycles having a shallow cone 3-fold symmetry structure bearing all of the potentially useful anchoring groups at its upper rim.[7] Like the calixarenes, CTVs show very interesting supramolecular properties. However, differently from the former, their ability to act as cavitands and form endo-cavity inclusion complexes in solution has only occasionally been evidenced so far.[8] Nevertheless, examples exist where CTV derivatives have been used to bind fullerenes and *o*-carborane in solution,[9] although the role of the π-donor CTV cavity itself remains questionable.

It thus appeared us that, despite the very interesting structural and chemical features of CTVs, only a limited amount of research on their chemical modification has been reported so far. In this paper we present a synthetic study to extend the aromatic cavity of the CTV platform by using its phenol groups for anchoring three aromatic moieties and the other three oxygen atoms to increase the lipophilicity of the receptor.

The design of the new CTV-based hosts was inspired by our previous results obtained with the heteroditopic calix[4]arene host[3b] **I** that we previously used in the complexation of tetramethylammonium salts in apolar media. The four *p*-hydroxybenzyl substituents present on the wider rim of **I** were able to interact with both the cation and the anion of the tetramethylammonium salts, through a cooperative effect exerted by the host cavity and the hydrogen-bond donor ability of the phenol groups, thus favoring a positive allosteric effect on the ion-pair recognition (see Figure 1).

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(7) The shape of the host cavity can be defined through the angle δ between the aromatic rings and the plane defined by the bridging methylene carbons of the hosts. This δ angle is 132° in cyclotriveratrylene[6] and about 115° in the cone conformer of calix[4]arenes, see e.g. Arduini, A.; Nachtigall, F. F.; Pochini, A.; Secchi, A.; Ugozzoli, F. *Supramol. Chem.* **2000**, *12*, 273−291.

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(9) (a) Atwood, J. L.; Barnes, M. J.; Burkhalter, R. S.; Junk, P. C.; Steed, J. W.; Raston, C. L. *J. Am. Chem. Soc.* **1994**, *116*, 10346−10347. (b) Atwood, J. L.; Barnes, M. J.; Gardiner, M. G.; Raston, C. L. *Chem. Commun.* **1996**, 1449−1450. (c) Blanch, R. J.; Williams, M.; Fallon, G. D.; Gardiner, M. D.; Kaddour, R.; Raston, C. L. *Angew. Chem., Int. Ed. Engl.* **1997**, *37*, 5504−506. (d) Matsubara, H.; Hasegawa, A.; Shiwaku, K.; Asano, K.; Takahashi, S.; Yamamoto, K. *Chem. Lett.* **1998**, 923−924. (e) Matsubara, H.; Oguri, S.; Asano, K.; Yamamoto, K. *Chem. Lett.* **1999**, 431−434. (f) Hardie, M. J.; Godfrey, P. D.; Raston, C. L. *Chem. Eur. J.* **1999**, *5*, 1828−1833. (g) Hardie, M. J.; Raston, C. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 3835−3839. (h) Bond, A. M.; Miao, W.; Raston, C. L.; Ness, T. J.; Barnes, M. J.; Atwood, J. L. *J. Phys. Chem.* **2001**, 1687−1695. (i) Hardie, M. J.; Raston, C. L. *Cryst. Growth Des.* **2001**, *1*, 53−58.

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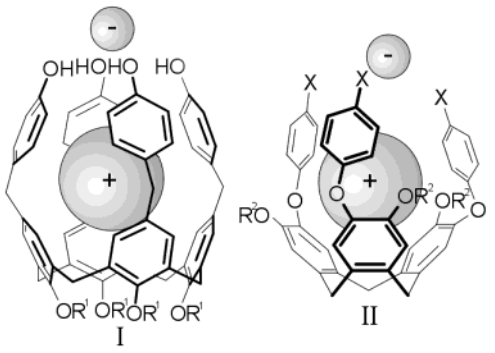
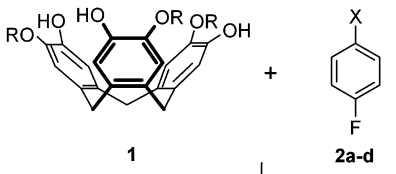


FIGURE 1. Schematic representation of heteroditopic hosts for ion-pair recognition.

SCHEME 1[a]



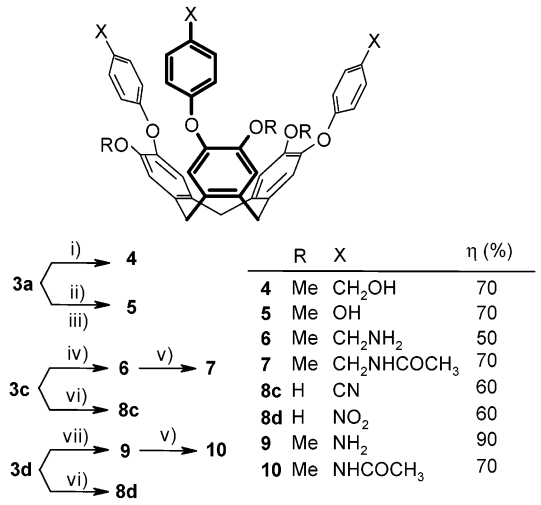
	R	X	η (%)
3a	Me	CHO	70
b	Me	$COCH_3$	55
c	Me	CN	70
d	Me	NO_2	70

[a] Reagents and conditions: (i) DMF, K_2CO_3, reflux.

Starting from this perspective, the employment of hosts having 3-fold symmetry such as **II** could result in an improvement of the recognition properties. The introduction of aryl moieties onto the CTV upper rim could be achieved by nucleophilic aromatic substitution (S_NAr) reaction onto the cyclotriguaiacylene (**1**),[10] which, because it has three hydroxy groups, could be a suitable platform for this type of reaction.[11,12]

To obtain good yields in the triple nucleophilic aromatic attack, *p*-fluorobenzene derivatives having electron-withdrawing substituents **X** in the *para* position (**X** = CHO, $COCH_3$, CN, NO_2) were chosen as electrophiles. These **X** groups can then be converted, through common functional group interconversion (FGI) methods, to groups such as NH_2 or OH, having an electron-donating character that could enhance the π-donor ability of the phenyl rings and thus the recognition ability of the host. In particular, reaction of triguaiacylene **1** with fluorobenzenes **2a**−**d** in DMF, in the presence of potassium carbonate, gave the triaryl-substituted CTV derivative (**3a**−**d**) in good yield (see Scheme 1).

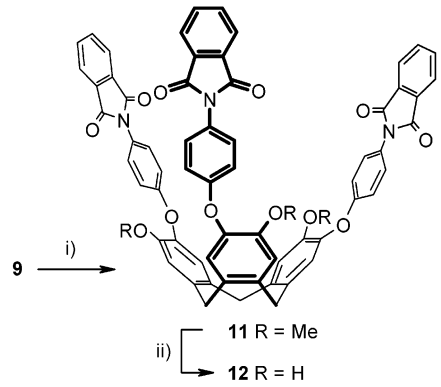
SCHEME 2[a]



	R	X	η (%)
4	Me	CH_2OH	70
5	Me	OH	70
6	Me	CH_2NH_2	50
7	Me	$CH_2NHCOCH_3$	70
8c	H	CN	60
8d	H	NO_2	60
9	Me	NH_2	90
10	Me	$NHCOCH_3$	70

[a] Reagents and conditions: (i) $NaBH_4$, EtOH; (ii) MCPBA, $C_2H_4Cl_2$; (iii) HCl 37%, EtOH; (iv) B_2H_6, THF, reflux; (v) $N(C_2H_5)_3$, Ac_2O; (vi) BBr_3, CH_2Cl_2 or toluene; (vii) $NH_2NH_2 \cdot H_2O$, Pd/C (cat.), EtOH, reflux.

SCHEME 3[a]



[a] Reagent and conditions: (i) phthalic anhydride, AcOH, toluene/CH_3CN, reflux; (ii) BBr_3, CH_2Cl_2.

The structure of compounds **3a**−**d** was confirmed by ^{1}H NMR spectroscopy. The main common feature of the ^{1}H NMR spectra of compounds **3a**−**d** in $CDCl_3$ is the upfield shift experienced by the methoxy protons. In fact, whereas those of **1** resonate at δ 3.85 ppm, those of compounds **3a**−**d** resonated in the 3.7−3.5 ppm interval, probably because of the shielding effect from the aryl ether groups that are in close proximity to these methyl groups.

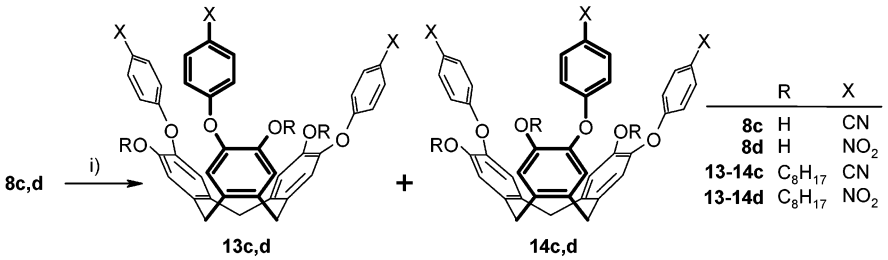
Common FGI reactions were then used to convert the nature of the **X** substituents to electron-donating ones. In particular, the formylated product **3a** was easily transformed by reduction into the corresponding hydroxymethyl derivative **4**. Baeyer−Villiger oxidation of **3a** gave the phenol derivative **5** in very good yield (see

(10) Canceill, J.; Collet, A.; Gottarelli, G. *J. Am. Chem. Soc.* **1984**, *106*, 5997−6003.

(11) Atwood and co-workers reported the synthesis of new CTV-based hosts characterized by the presence of metal arene moieties, which were introduced on a cyclotriguaiacylene by S_NAr substitution; see: Holman, K. T.; Orr, G. W.; Steed, J. W.; Atwood, J. L. *Chem. Commun.* **1998**, 2109−2110.

(12) S_NAr reactions have been employed for the synthesis of lower rim aryl substituted calix[4]arenes (see Chowdhury, S.; Georghiou, P. E. *J. Org. Chem.* **2001**, *66*, 6257−6262) and for both the upper and lower rim functionalization of resorcinarenes (see, e.g., Rudkevich, D. M.; Rebek, J., Jr *Eur. J. Org. Chem.* **1999**, 1991−2005. Saito, S.; Rudkevich, D. M.; Rebek, J., Jr *Org. Lett.* **1999**, *1*, 1241−1244).

SCHEME 4[a]



[a] Reagents and conditions: (i) *n*-$C_8H_{17}I$, K_2CO_3, CH_3CN, reflux.

Scheme 2). The cyano and the nitro groups of **3c** and **3d**, respectively, were reduced to yield the corresponding methylamino **6** or amino **9** derivatives, which were then transformed into their *N*-acetyl derivatives **7** and **10**, by reaction with acetic anhydride. Compounds **4**, **5**, **7**, and **10** are heteroditopic hosts having the aromatic cavity of the CTV skeleton extended with electron-rich aryl substituents bearing H-bond donor groups.

Finally, reaction of compound **9** with phthalic anhydride in acetic acid afforded the CTV derivative **11** in 70% yield (see Scheme 3), whose resulting walls are further extended by the three phthalimido groups.

The removal of the three methoxy groups present on derivatives **3c**,**d** and **11** are facilitated by the presence of their aryloxy substituents and thus avoids the employment of the regioselective demethylating reagents commonly used in CTV chemistry.[13] In particular, treatment of compounds **3c**,**d** and **11** with boron tribromide in dichloromethane or toluene solution (see Schemes 2 and 3) afforded derivatives **8c**,**d** and **12** in satisfactory yields.

Although these phenolic derivatives can be considered as potential heteroditopic hosts for the recognition of ion pairs, they were used to verify the possibility of being able to increase their lipophilicity, since the low solubility in apolar media of CTVs still represents a drawback for their utilization as molecular receptors.

Quite unexpectedly, attempts to introduce long alkyl chains onto the three OH of compounds **8c**,**d** with *n*-octyl iodide in the presence of potassium carbonate yielded a mixture of two fully alkylated compounds, as shown by MS analysis. ^{1}H NMR analysis of the separated components of the mixture revealed the presence of two isomeric compounds whose identities were assigned to the alkylated symmetrical compound **13c** and to the nonsymmetrical **14c**. Similar results were also obtained starting from **8d** that gave the two isomeric trioctyloxy-tri-*p*-cyanophenyloxy derivatives **13d** and **14d** (see Scheme 4).

These results could be explained by hypothesizing the formation of a spiro-Meisenheimer intermediate (see Figure 2) from the deprotonated starting materials **8c**,**d**, probably favored by the presence of electron-withdrawing groups present in the *para* position of the aryl groups.[14] To the best of our knowledge no reports of this last reaction are present in the literature, and probably only the specific stereoisomerism of these starting materials

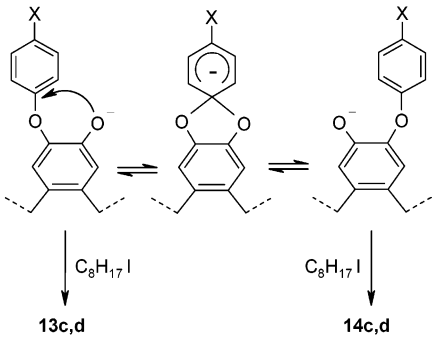


FIGURE 2. Schematic representation of the formation of a spiro-intermediate during the alkylation reaction of derivatives **8c**,**d**.

allowed the detection of this rearrangement. Although this interesting reaction is a drawback for the synthesis of these symmetrical more lipophilic receptors, it nevertheless could disclose the possibility to design new geometries for complexation.

These results indicate that S_NAr is a very useful reaction to extend the cavity of CTVs and obtain new heteroditopic receptors. The evaluation of the binding ability of these new hosts toward tetramethylammonium salts is in progress. Preliminary results showed that derivatives **6** and **11** are not able to recognize tetramethylammonium salts in apolar solvents, whereas the heteroditopic **12** shows promising binding efficiency toward these salts.[15] This indicate that, in contrast to calixarenes, for CTV-based hosts, despite their intrinsic rigidity, the extension of the cavity alone is not sufficient to enhance binding efficiency and that both extension of the cavity and the presence of hydrogen-bond donor groups should be present on their skeleton as additional chemical and structural information.

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Supporting Information Available: Full spectral characterization and experimental procedures of new compounds **3a**−**d** and **4**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Canceill, J.; Collet, A.; Gabard, J.; Gottarelli, G.; Spada, G. P. *J. Am. Chem. Soc.* **1985**, *107*, 1299−1308.

(14) See for example: (a) Artamkina, G. A.; Egorov, M. P.; Beletskaya, I. P. *Chem. Rev* **1982**, *82*, 427−459. (b) Bernasconi, C. F.; Howard, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 7248−7257.

(15) A stability constant, *K*, of 620 ± 180 M^{-1} was determined for the complexation of **12** with tetramethylammonium tosylate in $CDCl_3$, using methods reported elsewhere (see ref 3).