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PAPER

Inherently chiral phosphonatocavitands as artificial chemo- and enantio-selective receptors of natural ammoniums†

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Inherently chiral phosphonatocavitands with various bridging moieties at their wide rim were synthesized. Optical resolution by chiral HPLC was performed with cavitand **8** to afford enantiopure compounds (+)-**8** and (–)-**8**. The molecular structures of hosts **8** and **12** were determined by X-ray diffraction. The host properties were investigated by ^{1}H and ^{31}P NMR spectroscopy. The phosphonatocavitands form inclusion complexes with chiral ammonium neurotransmitters, some presenting enantioselectivity towards the right or left-handed host enantiomers.

Introduction

Enantioselective recognition processes are part of various fascinating but complexes biological mechanisms and hence play a key role in living systems *via* hormones and neurotransmitters. A better understanding of these phenomena can be obtained from the study of artificial supramolecular systems as illustrated by several examples reported in the literature during the last two decades.[1] Following this pioneering work, an increasing interest in the design of various chiral systems with different sizes and binding properties has emerged with, as its target, potential applications as biosensors,[2] therapeutic vectors and also use in asymmetric synthesis and chiral separation.[3] Among these examples, calixarene type molecules have been shown to be some of the most promising candidates due to the possibility of functionalizing the narrow and/or the wide rim of this rigid scaffold.[4] These macrocycles being made from the repetition of achiral units, a simple way to introduce dissymmetry can be achieved by adding moieties bearing stereogenic centers usually located remotely from the cavity.[5] More recently, a growing interest in the development of inherently chiral macrocycles has emerged.[6] In this specific case, dissymmetry is the consequence of a difference between the binding sites or the bridging units and the presence of a curvature.[7] Atropoisomerism between the aromatic moieties is of importance to preserve this curvature leading to molecules belonging to the C_1 group, and several examples of inherently chiral cyclodextrins,[8] and calixarenes[9] were thus reported.

Previously, the groups of Cram, Rebek and Dalcanale successfully applied such a strategy to design inherently chiral cavitands.[10] However, in all these cases, the lack of strong binding groups and the rather achiral character of the inner cavity precluded their use as efficient enantioselective receptors in solution.[11] Interestingly, cavitands based on the phosphorylated resorcin[4]arenes, such as the tetraphosphonatocavitands,[12] show remarkable binding properties towards alcohols,[13] metal ions,[14] and ammonium cations.[15] Recently, our group described the synthesis of diphosphonate cavitands of the AB*ii* type, AB defining the vicinal positions of the two phosphorus groups, and *ii* corresponding to the inward orientations of the two P═O groups (Fig. 1).[16]

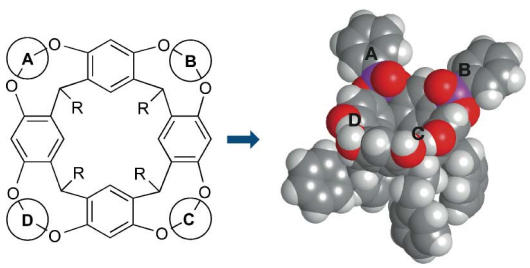

Fig. 1 The resorcin[4]arene structure with its four possible bridging sites A, B, C and D (left), and the AB*ii*(PO) X-ray molecular structure with its un-bridged C and D sites (right; R = C_2H_4Ph; from ref. 16a).

The AB*ii* structure possesses two P═O bonds oriented towards the cavity which favor the complexation of guest molecules. This compound is an ideal precursor for inherently chiral cavitands since bridging by at least one different group on a third site (C or D sites, Fig. 1) leads directly to chiral species. Following this idea, we recently reported the synthesis, the optical resolution and the

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† Electronic supplementary information (ESI) available: Synthetic procedures and characterizations including ^{1}H, ^{31}P and ^{13}C spectra, NMR complexation experiments, CD spectra and HPLC chromatograms, X-ray data. CCDC reference numbers 783436 and 783437. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05194f

determination of the absolute configuration of the first inherently chiral phosphonatocavitand (compound **1**, Fig. 2).[16b]

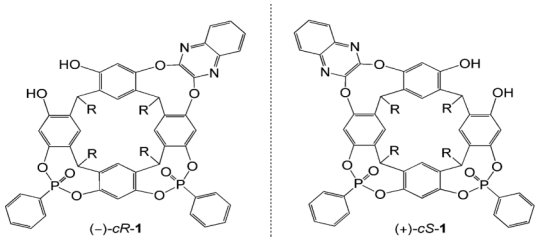


Fig. 2 Enantiomers of the inherently chiral phosphonatocavitand **1**: (−)-*cR*-**1** and (+)-*cS*-**1**.

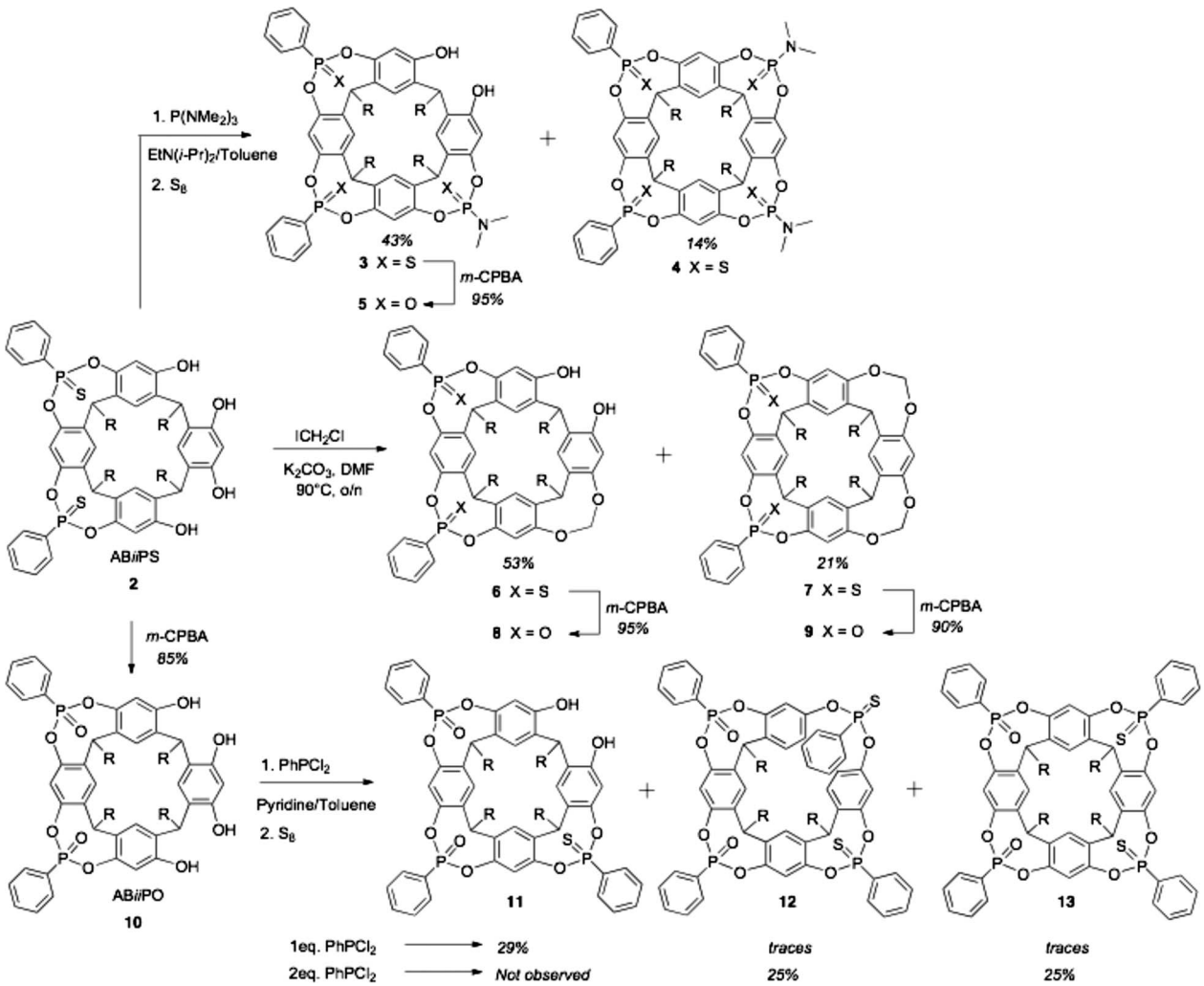
This compound showed interesting enantioselective binding properties towards L-adrenaline picrate, the complex L-adrenaline@(+)-**1** being favored in a 2 : 1 ratio compared to the complex L-adrenaline@(−)-**1**. In order to better understand the interactions involved in this type of cavitand, we wished to extend this study to other chiral host molecules as well as other chiral ammonium guests of biological interest such as nicotine and ephedrine derivatives and to compare the new cavitands towards the enantioselective complexation of such guest molecules. These species are known to take part in biological processes such as information transfers in the neuronal system.[17]

Starting from the precursor AB*ii*PS **2**, we synthesized the four new inherently chiral cavitands **5**, **8**, **11** and **12**, which differ in their extra bridging groups, which should afford different binding properties (Scheme 1). Another chiral cavitand was prepared from the tri-thiophosphonate cavitand **14**,[16b,18] incorporating a binaphthyl bridge (compound **16**) synthesized as a racemate and in one enantiopure form (Scheme 2). In this case, the molecule is not inherently chiral, with asymmetry resulting from the stereogenic binaphthyl group.

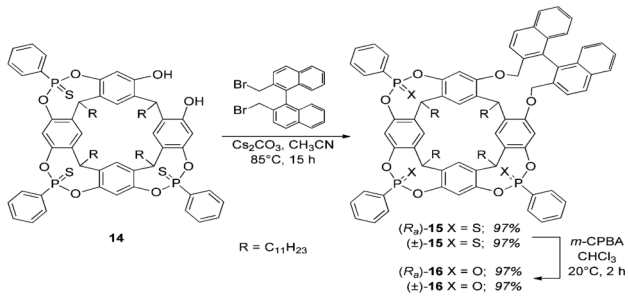
Results and discussion

Synthesis

We have considered four different bridges that were introduced in the AB*ii* type molecule bearing two inward oriented Ph–P═O moieties: (i) one inward Me_2N–P═O (C site; compound **5**), (ii) one methylene bridge (C site; compound **8**), (iii) one inward



Scheme 1 Synthesis of the inherently chiral cavitands **5**, **8**, **11** and **12** from the precursor AB*ii*PS **2** (R = $C_{11}H_{23}$).



Scheme 2 Synthesis of racemic cavitand (±)-**16** and enantiopure (R_a)-**16**.

Ph–P═S (C site; compound **11**) and (iv) one inward Ph–P═S bridge and one outward Ph–P═S bridge (C and D sites; compound **12**).

Concerning compound **5**, a survey of the literature showed that amidophosphite cavitands can be synthesized efficiently using tris(dimethylamino)-phosphine as reactant,[19] leading after sulfurization to the inward orientation of the thiophosphoryl moiety. The addition of one equivalent of tris(dimethylamino)-phosphine to a toluene solution of compound AB*ii*PS **2** in the presence of Hünig's base (*N*,*N*-diisopropylethylamine) followed by the addition of sulfur, led to a mixture of compound (±)-**3** and tetra-bridged derivative **4** that both have the desired inward orientation of the P═S groups. These compounds were separated by column chromatography in 43% and 14% yields respectively (Scheme 1). The three P═S moieties of compound (±)-**3** were further transformed into P═O groups by reaction with *m*-chloroperoxybenzoic acid (*m*-CPBA) to give cavitand (±)-**5**, the inward orientation of the three chelating groups being preserved.

Tetraresorcinarene type molecules bearing methylene bridges are well described in the literature.[10a,20] Following the reported procedures, the addition of one equivalent of iodochloromethane onto cavitand AB*ii*PS **2** in the presence of potassium carbonate, in DMF at 90 °C, led to the desired chiral cavitand (±)-**6** together with the tetra-bridged parent molecule **7**. Similarly to compounds (±)-**3** and **4**, compounds (±)-**6** and **7** were separated by column chromatography in 53% and 21% yield respectively (Scheme 1). As described above, the thiophosphonate groups in (±)-**6** and **7** were further transformed into phosphonate groups by reaction with *m*-CPBA to give cavitands (±)-**8** and **9**, respectively, in high yields. Compound **9** has been already reported and was obtained in 33% yield by addition of iodochloromethane to compound **10**,[16a] or by addition of phenyldichlorophosphine oxide to the bis-methylene-bridged precursor (10% yield).[21] Chiral compound **8** crystallizes in the triclinic crystal system ($P\bar{1}$) to give the racemate (±)-**8**.‡ The molecular structure depicted in Fig. 3 shows one encapsulated CH_3OH molecule with the CH_3 group located inside

‡ *Crystal data* **8**·$CHCl_3$·CH_3OH: $C_{87}H_{123}Cl_3O_{11}P_2$, M = 1513.23, triclinic, $P\bar{1}$, a = 11.9557(4), b = 15.3805(4), c = 22.8398(6) Å, α = 95.810(2)°, β = 95.876(2)°, γ = 90.902(2)°, V = 4155.9(2) Å^3, Z = 2, D_c = 1.209 g mL^{-1}, μ(Cu-Kα) = 1.816 mm^{-1}, $2\theta_{max}$ = 124.3°, T = 100 K, 60303 reflections collected, 13020 unique reflections with $I > 2\sigma(I)$, R_{int} = 0.050 (928 parameters) and R_1 = 0.092, wR_2 = 0.200, GooF = 1.042, CCDC 783437. **12**: $C_{96}H_{124}O_{10}P_4S_2$, M = 1626.06, monoclinic, $P2_1/c$, a = 14.338(1), b = 34.567(3), c = 18.529(2) Å, α = 90.00°, β = 106.02(1)°, γ = 90.00°, V = 8827(1) Å^3, Z = 4, D_c = 1.224 g mL^{-1}, μ(Cu-Kα) = 1.686 mm^{-1}, $2\theta_{max}$ = 134.7°, T = 100 K, 64964 reflections collected, 15406 unique reflections with $I > 2\sigma(I)$, R_{int} = 0.063 (1009 parameters) and R_1 = 0.130, wR_2 = 0.295, GooF = 1.07, CCDC 783436.

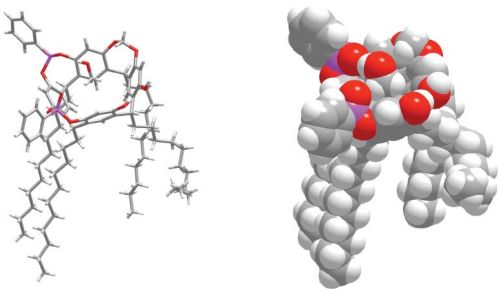


Fig. 3 Sticks and CPK views of the X-ray molecular structure of CH_3OH@(±)-**8**.

the molecular cavity (mean distance to the phenyl centroids = 3.74 Å), the OH group forming a strong H-bond with one PO group (d(P═O···OH) = 2.763 Å). A chloroform molecule occupies interstitial positions in the lattice.

The mixed cavitand with P═O and P═S groups, was synthesized from the AB*ii*PO derivative **10**. Addition of one equivalent of dichlorophenylphosphine, followed by *in situ* addition of sulfur, led predominantly to the tri-bridged chiral compound (±)-**11** with the P═S bond pointing inward, isolated in 29% yield. Interestingly, when adding two equivalents of dichlorophenylphosphine under the same reaction conditions, a 1 : 1 mixture of the chiral AB*ii*(PO)CD*io*(PS) (±)-**12** and the achiral AB*ii*(PO)CD*ii*(PS) (±)-**13** was exclusively obtained. These compounds were separated by column chromatography and both obtained with 25% yields. It seems unlikely that the chiral compound **12** will possess any binding affinity for a guest molecule as one of the P-phenyl groups is shielding the accessibility to the cavity. This is shown by the X-ray molecular structure depicted in Fig. 4.‡ Single crystals were grown from hexane solution to give racemate (±)-**12**. The *ii* and *io* orientation of the phosphonate and thiophosphonate groups, respectively, are confirmed in the solid, and one phenyl group is oriented towards the molecular cavity. The molecules are tightly packed in the crystal with efficient Van der Waals interactions between the long chain substituents of the narrow rim.

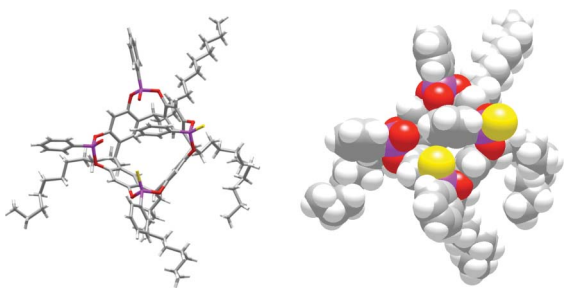


Fig. 4 Sticks and CPK views of the X-ray molecular structure of (±)-**12** showing the occupancy of the molecular cavity by a P-phenyl group.

Finally, as a matter of comparison, chiral cavitand **16**, bearing a binaphthyl stereogenic group was synthesized in two steps from the *3i*PS cavitand **14** (Scheme 2).[18] Combination of **14** and 2,2′-bis(bromomethyl)-1,1′-binaphthyl, which was prepared from 1,1′-bi(2-naphthol) (BINOL) following a reported procedure,[22] in the presence of Cs_2CO_3 in acetonitrile at reflux temperature led to compound **15**. The reaction of this latter compound with *m*-CPBA gave cavitand **16** quantitatively. While starting from

(±)-BINOL, (±)-**16** was obtained, whereas enantiopure (R_a)-BINOL gave enantiopure (R_a)-**16** (Scheme 2).

Chiroptical properties

The optical resolution of compound **8** was performed by semi-preparative HPLC using a Chiralpack IA column and a hexane/isopropanol/$CHCl_3$ 92/4/4 mixture as eluant. This afforded up to 19 mg of each enantiopure (+)-**8** (Rt = 9.03 min) and (−)-**8** (Rt = 12.39 min) with *ee* >99.5%. Interestingly, these compounds display no optical rotation at wavelengths λ = 589, 578, 546, 436 and 365 nm in $CHCl_3$ or ethanol solution. Thus, the dextrogyre and levogyre species were attributed from the sign observed with the ECD detector of the HPLC at 295 nm. The ECD spectra of (+)-**8** and (−)-**8** ($c \sim 4 \times 10^{-5}$ M, CH_2Cl_2) showed identical mirror-image signals confirming their enantiomeric relationship, and were compared to the previously reported ECD spectra of (+)-**1** and (−)-**1** (Fig. 5).[16b] A similar pattern was observed with two consecutive strong positive Cotton effects (around 240 nm and 280 nm) and a strong negative Cotton effect (around 295 nm) for the levogyre compounds (same but opposite observation for the dextrogyre compounds). Considering the high resemblance between the structures of cavitands **1** and **8**, it is likely that both levogyre compounds are of *cR* configuration and the dextrogyre compounds have the *cS* configuration. However, this hypothesis needs to be confirmed without ambiguity by other means. All attempts to perform the optical resolution, by semi-preparative HPLC, of the other inherently chiral cavitands **4**, **11** and **12**, failed. As mentioned above, compound **16** was obtained enantiopure ($[\alpha]_D^{25}$ = 158, c ~ 0.1, acetone) when using (R_a)-BINOL as the starting material. The ECD spectra of (R_a)-**16** ($c \sim 10^{-5}$ M, CH_2Cl_2) displayed a characteristic excitonic coupling around 230 nm corresponding to the $^1B_b(1)$ et $^1B_b(2)$ transitions from the two naphthyl moieties: a positive followed by a negative Cotton effect corresponding to the (R_a) configuration as depicted in Fig. 6.[23]

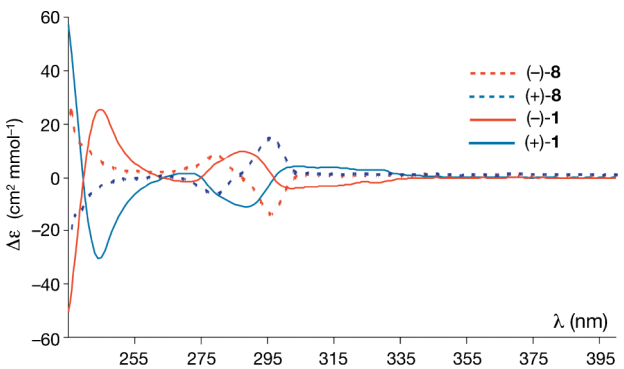


Fig. 5 ECD spectra of (−)-**1** (red solid line), (+)-**1** (blue solid line), (−)-**8** (red dotted line) and (+)-**8** (blue dotted line) ($c \sim 4 \times 10^{-5}$ M, CH_2Cl_2).

Enantioselective complexation

The enantioselective complexation experiments consist in adding a solution of the racemic cavitand (in $CDCl_3$ or CD_2Cl_2) to a solution of the enantiopure ammonium picrate salts in a 1 : 0.4 equiv host : guest ratio. This resulted in the formation of two diastereomeric host–guest complexes. The complexation can be observed either by ^{31}P NMR spectroscopy (downfield shift of the ^{31}P signals) or by ^1H NMR spectroscopy by following the highfield shift of the NCH_3 protons (for adrenaline, ephedrine and pseudoephedrine), of the terminal CH_3 protons (for norephedrine, ephedrine and pseudoephedrine), or by the split of the CH bridging protons of the cavitands (for nicotine) (Fig. 7).

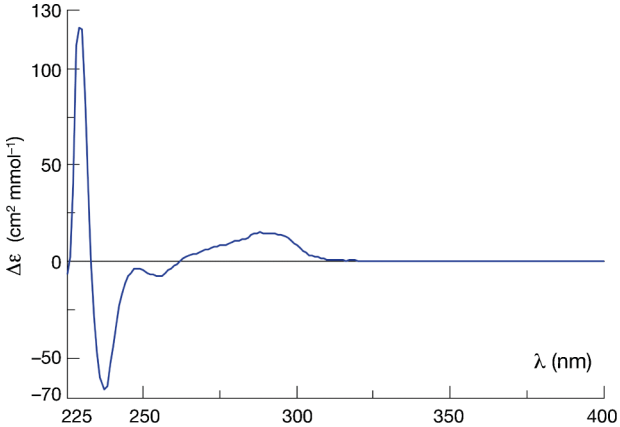


Fig. 6 ECD spectra of cavitand (R_a)-**16** ($c \sim 10^{-5}$ M, CH_2Cl_2).

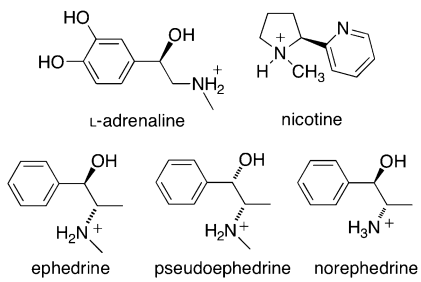


Fig. 7 Structures of the ammonium guests investigated.

The temperature was carefully controlled to run the experiment under slow exchange conditions on the NMR time scale, so that a good separation of the signals of the two diastereomeric host–guest complexes could be observed in the ^1H or ^{31}P NMR spectra. NMR experiments were performed at room temperature for nicotine, but as a general trend, it appeared necessary for the other ammonium guests to perform the experiments at lower temperatures (253 K for adrenaline and 233 K for ephedrine and its derivatives). In the cases where the cavitands were available in their enantiopure form (*i.e.* for compounds **1** and **8**) it has been possible to assign each diastereomeric host–guest complex.

The results are gathered in Table 1. As expected, compound **12** with an inward oriented phenyl group displayed no complexation towards ammonium salts. The other chiral cavitands tested formed host–guest complexes. Among the inherently chiral cavitands, only cavitands **1** and **8** showed noticeable diastereoselectivities except for nicotine (d.r. ~ 1 : 1). As mentioned above, the complex L-adrenaline@(+)-**1** was favored in a 2 : 1 ratio over complex L-adrenaline@(−)-**1**. A similar behavior was observed with pseudoephedrine with a 2.2 : 1 ratio in favor of pseudoephedrine@(+)-**1**. Interestingly, no diastereoselectivity was observed with ephedrine and a reversed selectivity was obtained with norephedrine (1 : 2.5 ratio in favor of norephedrine@(−)-**1**) (Fig. 8). Concerning cavitand **8**, a good selectivity was only observed with pseudoephedrine (2.5 : 1 ratio in favor of cavitand

Table 1 Diastereomeric ratios *d.r.* (guest@(+)-host/guest@(−)-host) for the complexes of the racemic cavitands **1**, **5**, **8**, **11**, **12** and **16** with enantiopure ammoniums (picrate salts; 1 : 0.4 host/guest ratio) measured by ^{1}H and/or ^{31}P NMR

	Host					
Guest	**1**	**5**	**8**	**11**	**12**	**16**
Nicotine	~1 : 1[a]	—[e]	~1 : 1[a]	—[e]	No Complex.	—[d]
Adrenaline	~2 : 1[b]	~1 : 1[a]	~1 : 1[c]	—[e]	No Complex.	~1 : 1[b]
Ephedrine	~1 : 1[c]	—[e]	~1 : 1.3[c]	~1 : 1[a]	—[e]	—[e]
Pseudoephedrine	~2.2 : 1[c]	—[e]	~2.5 : 1[c]	—[e]	—[e]	~1 : 1.5[b]
Norephedrine	~1 : 2.5[c]	—[e]	—[d]	—[e]	—[e]	—[d]

[a] At 298 K in $CDCl_3$. [b] At 253 K in $CDCl_3$. [c] At 233 K in CD_2Cl_2. [d] No split visible by ^{1}H and ^{31}P NMR between the two diastereomeric host–guest complexes. [e] Not done.

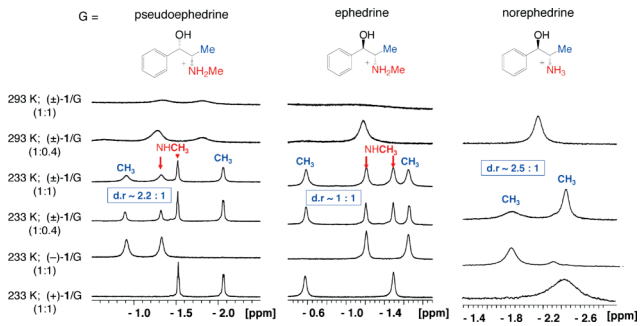


Fig. 8 Diastereomeric ratios (d.r) obtained from ^{1}H NMR spectra (CD_2Cl_2) during complexation experiments with cavitands (±)-**1**, (−)-**1** and (+)-**1** and with guests (G) pseudoephedrine, ephedrine and norephedrine (host : guest ratios are in parentheses).

(+)-**8**), the other ammoniums leading to either poor (1 : 1.3 ratio with ephedrine) or no selectivity at all (with adrenaline). Finally, compounds with *3i* stereochemistry **5**, **16** (three inward orientated P═O groups) and **11** (two inward P═O and one inward P═S), display either low selectivity (1.5 : 1 ratio with pseudoephedrine@(±)-**16** in favor of (−)-**16**) or no selectivity (1 : 1 ratio with adrenaline and ephedrine for **5** and **11**, respectively). The rather achiral character of the inner cavity is probably the reason for such behavior.

Chemoselective complexation

Considering the high similarity between the three ephedrine derivatives, we wondered if the chiral cavitands **1** and **8** could discriminate one of the three ammoniums in a competitive complexation experiment. To do so, we mixed the three CD_2Cl_2 solutions containing each host–guest complex in a 1 : 1 ratio, the guests being ephedrine, pseudoephedrine and norephedrine picrate salts. This led to a 1 : 1 host–guests ratio (*i.e.* 3 equiv. of host and 1 equiv. of each of the three guests). Two sets of experiments for each cavitand **1** and **8** were performed, one with the dextrogyre cavitands and one with the levogyre cavitands. In all cases, when lowering the temperature to 233 K, the three complexed ammonium guests were easily distinguishable in the ^{1}H and ^{31}P NMR spectra. Due to the slight precipitation of the ammonium salts in the NMR tube at this temperature, the integration of the signals for each ammonium led to a small deviation from the expected 1 : 1 : 1 stoichiometry. To this solution was added 2 more equivalents of a 1 : 1 : 1 ratio of the three ammoniums, resulting in a 1 : 3 host–guests ratio (*i.e.* 3 equiv. of cavitand host, 3. equiv of ephedrine, 3 equiv. of pseudoephedrine, and 3 equiv. of norephedrine). Interestingly, norephedrine is no longer complexed by the cavitands (+)-**1**, (−)-**1**, (+)-**8** and (−)-**8**. Concerning the dextrogyre cavitands (+)-**1** and (+)-**8**, a selectivity towards pseudoephedrine compared to ephedrine was observed with ~1.7 : 1 and 1.6 : 1 ratios, respectively (Fig. S69 and S71, respectively, in the ESI†). Furthermore, the levogyre cavitands (−)-**1** and (−)-**8** are selective for ephedrine, with a 1.8 : 1 ratio for (−)-**1** (Fig. S68 in the ESI†), and complete selectivity (>98 : 2) for host (−)-**8**, ephedrine being the unique species complexed by this cavitand as shown in Fig. 9.

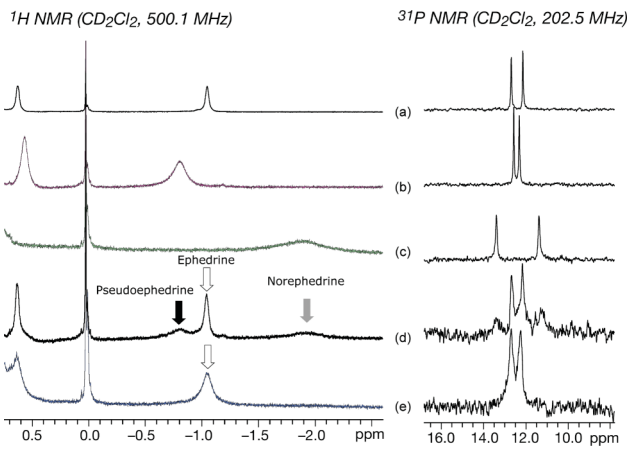


Fig. 9 Chemoselective complexation experiments followed by ^{1}H and ^{31}P NMR in CD_2Cl_2 at 233 K: (a) ephedrine@(−)-**8** (1 : 1); (b) pseudoephedrine@(−)-**8** (1 : 1); (c) norephedrine@(−)-**8** (1 : 1); (d) [ephedrine][pseudoephedrine][norephedrine]@(−)-**8** (1 : 1 : 1 : 3); (e) [ephedrine][pseudoephedrine][norephedrine]@(−)-**8** (1 : 1 : 1 : 1).

Conclusions

In summary, we have developed an efficient synthesis of inherently chiral cavitands following a strategy that can be extended to other dissymmetrical cavitands. Semi-preparative chiral HPLC was revealed to be an efficient means to optically resolve some of these hosts and their chiroptical properties have been investigated. Single crystal X-ray analyses were performed for the two chiral hosts (±)-**8** and (±)-**12** and confirmed the stereochemistry at the phosphorus atoms, which adopt the inward orientation of the P═O or P═S bonds, an important feature for efficient complexation of ammonium cations. The phosphonatocavitands are particularly

efficient in the recognition of neurotransmitter guests. NMR was used to study in solution the encapsulation process and showed for some of them enantioselective recognition towards adrenaline and ephedrine derivatives. Competition experiments between ephedrine, norephedrine and pseudoephedrine in the presence of cavitands **1** or **8** showed, in the case of (−)-**8** a complete chemoselectivity towards ephedrine.

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