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Enantio- and Substrate-Selective Recognition of Chiral Neurotransmitters with C_3-Symmetric Switchable Receptors

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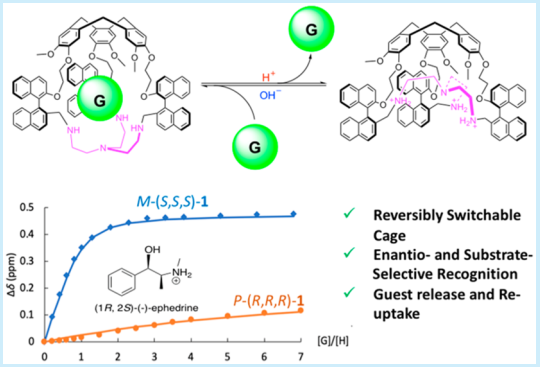
ABSTRACT: We report on the synthesis of C_3-symmetric enantiopure cage molecules **1**, which exhibit remarkable to exclusive enantioselective recognition properties toward chiral ammonium neurotransmitters. Strong changes in the substrate selectivity are also observed when different stereoisomers of **1** are used. Furthermore, protonation/deprotonation induces a reversible modification of the conformation of **1**, which switches from an imploded to an inflated form, leading to ejection and reuptake of the guest initially encaged inside the cavity.



Chiral recognition plays a crucial role in living systems and is also a key issue for researchers dealing with chiral separations or asymmetric catalysis. If chiral receptors and catalysts found in Nature display complex structures devoid of symmetry, their synthetic counterparts present frequently symmetry properties, like rotational axes.[1] Besides the beauty of symmetrical molecules, considerations of symmetry allow simplifying both the synthesis and the analysis and may improve the selectivity in enantioselective recognition or catalysis by reducing the number of diastereomeric host−guest complexes or transition states.[2] However, to perform chiral recognition, receptors or catalysts have to belong to the point groups C_n (including C_1) or D_n.[3] Since the seminal work of Kagan highlighting the advantages of C_2-symmetric ligands in asymmetric catalysis, numerous chiral ligands and receptors with 2-fold rotational symmetry have been reported.[4,5] In contrast, molecules with 3-fold rotational symmetry capable of chiral recognition remain rare.[6] The ability of C_3 symmetric hosts to discriminate enantiomers of ammoniums was even the subject of scientific controversy.[1a,6] However, the experimental work of Ahn et al. and then the studies reported by Hauberhauer et al. followed by the rationalization of Moberg put an end to this debate.[1a,7,8] However, very few C_3-symmetric hosts capable of chiral recognition of ammoniums have been reported to date, and the best selectivity reached only a modest value of 8.4 (87:13 ratio).[7,8] Therefore, experimental evidence that receptors with a 3-fold rotational symmetry are able to recognize ammoniums with enantioselectivity as high as those with 2-fold rotational symmetry remains to be brought.

Furthermore, as chiral ammoniums play a crucial role in biological systems, for instance, as neurotransmitters, there is also a challenge to build a receptor capable of displaying high substrate selectivity in favor of one neurotransmitter, because of its potential applications, in sensing or detection.[9] Moreover, if such a receptor is able to control the uptake and release of the guest by switching between two strongly different states upon the action of an external stimulus, this could offer new ways for drug delivery.[10]

Here, we report on the synthesis of C_3-symmetric molecular cages that display unprecedented enantioselective recognition properties for chiral ammoniums of biological interest. Binding constants up to 10^5 M^{-1} can be reached by receptor *M-(S,S,S)*-**1**, whereas low (100 M^{-1}) to no binding was observed with its enantiomer *P-(R,R,R)*-**1**. Changing the stereochemistry of the receptor also induced strong changes in the substrate selectivity: receptor *M-(S,S,S)*-**1** bound ephedrine more strongly than adrenaline, whereas the opposite trend was observed for its enantiomer *P-(R,R,R)*-**1**. Moreover, this cage could be reversibly switched from an inflated form to an imploded one upon protonation/deprotonation, allowing for an easy control of the uptake and release of the enantiomerically pure neurotransmitters.

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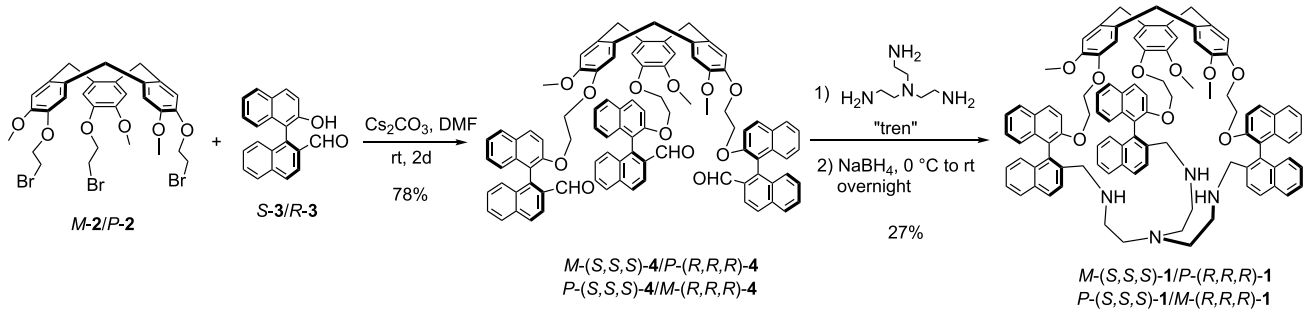
Scheme 1. Synthesis of the Four Enantiomerically Pure C_3-Symmetric Cages 1



Scheme 1 shows the synthetic route followed to obtain the four C_3-symmetric stereoisomers of cage **1**. Cyclotriveratrylene (CTV) **2** was obtained enantiomerically pure according to our previously reported procedure.[11,12] Racemic 2′-hydroxy-[1,1′-binaphthalene]-2-carboxaldehyde derivative **3** was synthesized using the methodology described by Xie et al.,[13] and a subsequent resolution with a chiral HPLC afforded the enantiopure compound (*S*)-**3** and (*R*)-**3** (Figures S1−S3). Their absolute configuration was then assigned using ECD spectroscopy (Figures S4 and S5). Then, *M*-**2** or *P*-**2** was reacted with (*S*)-**3** or (*R*)-**3** in DMF using $CsCO_3$ as a base to yield enantiomerically and diastereomerically pure *P*-(*S,S,S*)-**4**, *P*-(*R,R,R*)-**4**, *M*-(*S,S,S*)-**4**, and *M*-(*R,R,R*)-**4**. Finally, a reductive amination gave the expected hemicryptophane cages *P*-(*S,S,S*)-**1**, *P*-(*R,R,R*)-**1**, *M*-(*S,S,S*)-**1**, and *M*-(*R,R,R*)-**1** in 27% yield as single isomer in each case.[14] The NMR spectra indicate that all the stereoisomers of cage **1** display, on average, a C_3 symmetry in solution (Figures S14 and S19).

Crystals of *P*-(*R,R,R*)-**1** suitable for X-ray diffraction analysis were obtained by slow evaporation from a concentrated solution of the cage in $CHCl_3/CH_3OH$. Because of traces of HCl in $CHCl_3$, the *P*-(*R,R,R*)-**1** compound crystallized as its protonated counterpart *P*-(*R,R,R*)-**1**·$3H^{3+}$ with protonation on each secondary amine (Figure 1). Interestingly, this triprotonated structure exhibits a C_3 symmetry but with an unexpected imploded conformation: the tren (tris(2-aminoethyl)amine) moiety appears fully collapsed inward the CTV unit, leading to a compound devoid of cavity. C−H···O and C−H···π interactions between the NCH_2CH_2 protons of the tren unit and both the oxygen atoms and aromatic rings of the CTV could account for the stability of this imploded state (C−H···O and C−H···π_{Ar} distances of 2.94 and 3.03 Å, respectively). The ^{1}H NMR spectrum of this protonated form was obtained either by dissolution of these crystals in $CDCl_3$ or by addition of 3 equiv of picric acid to compound *P*-(*R,R,R*)-**1** (Figures S6 and S25). One can see that, despite the protonation of the amines, one signal of the NCH_2 protons is strongly high-field shifted when compared to the same protons in the deprotonated *P*-(*R,R,R*)-**1** cage (from 1.05 ppm (deprotonated) to −0.26 ppm (protonated), Figure 2)). This is consistent with the imploded conformation of the protonated compound observed in the solid state, where one of the diastereotopic protons of the NCH_2 units appears in the shielding area of the CTV moiety. Furthermore, cross-peaks between the protons of the NCH_2 of the tren moiety and those of the aromatic rings of the CTV core were evidenced on the NOESY map (Figure S30) indicating short distances between the two units. On the contrary, when the similar NOESY experiment was performed on the deprotonated cage, no NOE correlation between the tren moiety and the CTV unit was shown, suggesting a well-defined cavity in the cage compound *P*-(*R,R,R*)-**1** (Figure S23). More insight into this strong difference in the conformation of *P*-(*R,R,R*)-**1** and *P*-(*R,R,R*)-**1**·$3H^{3+}$ is further given by the ability of *P*-(*R,R,R*)-**1** to complex tetramethylammonium (Me_4N^+) with a binding constant of 373 M^{-1}, whereas no complexation could be detected with its protonated counterpart *P*-(*R,R,R*)-**1**·$3H^{3+}$.[15] All these NMR experiments strongly support that the imploded conformation of *P*-(*R,R,R*)-**1**·$3H^{3+}$ is maintained in solution whereas its basic partner *P*-(*R,R,R*)-**1** presents a hollow core. As pH switch can be used as a specific stimulus to perform reversible nanomechanical processes at molecular level,[16] we then investigated whether the protonation/deprotonation of cage **1** could enable the control of the dynamic motion from an inflated state to a fully imploded one. We were pleased to note that the alternating use of HCl (aq) and NaOH (aq) resulted in a reversible switch from a fully inflated form to a collapsed one and that at least five cycles could be performed between these two states (Figure S7).

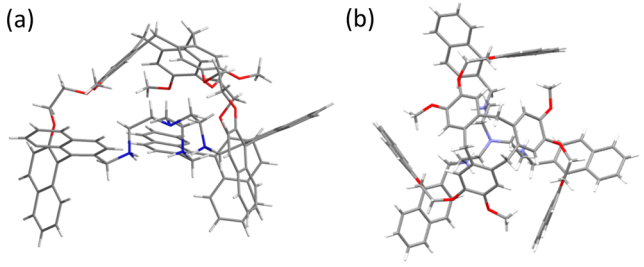


Figure 1. X-ray structure of *P*-(*RRR*)-**1**·$3H^+$: (a) side view and (b) top view.

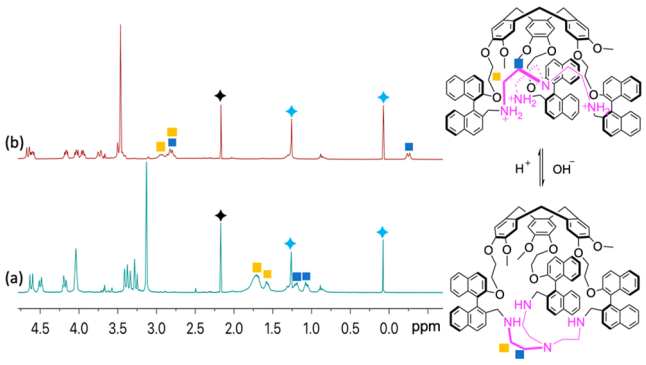


Figure 2. ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) spectra of (a) *P*-(*R,R,R*)-**1** and (b) *P*-(*R,R,R*)-**1**·$3H^{3+}$. The black and blue ◆ represent acetone and grease, respectively.

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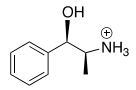
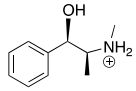
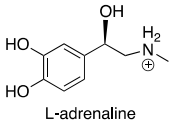
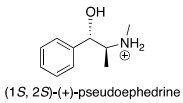
Thus, the pH acts as an effective and simple stimulus to switch **1** reversibly from a collapsed state to a reinflated cage.

Once the conformational issues of the deprotonated and protonated cages **1** were solved, we examined the ability of the four inflated C_3-symmetric receptors *P-(S,S,S)*-**1**, *P-(R,R,R)*-**1**, *M-(S,S,S)*-**1**, and *M-(R,R,R)*-**1** to complex chiral ammonium neurotransmitters: (1*R*,2*S*)-(−)-ephedrine, (1*R*,2*S*)-(−)-norephedrine, (1*S*,2*S*)-(+)-pseudoephedrine, and L-adrenaline. ^{1}H NMR titration experiments were performed, and the modeling of the resulting titration curves gives rise to the binding constants given in Table 1. In most of the cases, the best fit was achieved with a 1:1 host/guest stoichiometry, except for (i) norephedrine guest and *M-(S,S,S)*-**1** host and (ii) pseudoephedrine guest and *M-(S,S,S)*-**1** and *P-(R,R,R)*-**1** hosts where two complexes were formed subsequently with a 1:1 and then a 1:2 host/guest ratio. The two enantiomeric hosts *M-(R,R,R)*-**1** and *P-(S,S,S)*-**1** displayed good substrate selectivities with $K_{ephedrine}/K_{adrenaline}$ of 2.3 and 2.5 and with $K_{norephedrine}/K_{adrenaline}$ of 34.8 and 33.5, respectively.[17] However, when complexed with tested guests, only low enantioselectivities were achieved, the best result being obtained with pseudoephedrine, with a modest enantioselectivity $K_{P\text{-}(S,S,S)\text{-}1}/K_{M\text{-}(R,R,R)\text{-}1}$ of 4.2. In contrast, the two other enantiomeric cages *M-(S,S,S)*-**1** and *P-(R,R,R)*-**1** exhibited unprecedented enantioselectivity as C_3-symmetric receptors: with the primary ammonium norephedrine, an enantioselectivity value ($K_{M\text{-}(S,S,S)\text{-}1}/K_{P\text{-}(R,R,R)\text{-}1}$) of 445 was measured and with the secondary ammonium ephedrine an exclusive enantioselectivity was observed with a binding constant close to 19 000 M^{-1} for the *M-(S,S,S)*-**1** host, while no binding occurred with its enantiomer counterpart *P-(R,R,R)*-**1**.

Table 1. Association Constants of the Enantiopure Receptors 1 with Ammonium Guests in $CDCl_3/CD_3OD$ 95/5 at 298 K

Guest[a]	Host	K (M^{-1})[b]	Enantio-selectivty[c]
 (1*R*, 2*S*)-(-)-norephedrine	*M-(S,S,S)*-**1**	$K_1 = 73786 \pm 14\%$	
		$K_2 = 16608 \pm 11\%$	445
	P-(R,R,R)-**1**	$166 \pm 2.2\%$	
	M-(R,R,R)-**1**	$23880 \pm 10.0\%$	
	P-(S,S,S)-**1**	$28349 \pm 13.5\%$	1.2
 (1*R*, 2*S*)-(-)-ephedrine	*M-(S,S,S)*-**1**	$18798 \pm 7.7\%$	> 19000
	P-(R,R,R)-**1**	-[d]	
	M-(R,R,R)-**1**	$1560 \pm 2.4\%$	
	P-(S,S,S)-**1**	$2124 \pm 1.7\%$	1.36
 L-adrenaline	*M-(S,S,S)*-**1**	$2465 \pm 9.8\%$	1.9
	P-(R,R,R)-**1**	$4654 \pm 13.3\%$	
	M-(R,R,R)-**1**	$687 \pm 1.0\%$	
	P-(S,S,S)-**1**	$847 \pm 0.8\%$	1.3
 (1*S*, 2*S*)-(+)-pseudoephedrine	*M-(S,S,S)*-**1**	$K_1 = 5048 \pm 24.5\%$	
		$K_2 = 385 \pm 17.8\%$	8.7
	P-(R,R,R)-**1**	$K_1 = 43738 \pm 5.0\%$	
		$K_2 = 512 \pm 2.5\%$	
	M-(R,R,R)-**1**	$347 \pm 3.4\%$	
	P-(S,S,S)-**1**	$1459 \pm 7.6\%$	4.2

[a]Picrate was used as counterion. [b]K values were determined by fitting the ^{1}H NMR titration curves of proton of the guest using Bindfit, the error bars arise from the fitting.[18] [c]Defined as $K_{(one\ enantiomer)}/K_{(other\ enantiomer)}$.[17] [d]No complexation was observed.

The ^{1}H NMR titration curves shown in Figure 3 clearly evidence the difference in the binding properties of these two enantiomers toward ephedrine. Changing only one stereogenic center in the guest structure, i.e., switching from ephedrine to pseudoephedrine, led to complete reverse of the enantioselectivity: an enantioselectivity of 8.2 in favor of *P-(R,R,R)*-**1** was observed with pseudoephedrine as a guest. As a consequence, the host *P-(R,R,R)*-**1** exhibits a strong substrate selectivity toward pseudoephedrine: a $K_{pseudoephedrine}/K_{norephedrine}$ ratio of 263 is reached and the substrate selectivity is even exclusive when pseudoephedrine is compared to ephedrine. Interestingly, the lower enantioselectivity obtained with L-adrenaline as substrate induced changes in substrate selectivities: the *M-(S,S,S)*-**1** enantiomer preferentially binds norephedrine or ephedrine than adrenaline (with $K_{norephedrine}/K_{adrenaline}$ of 30, and $K_{ephedrine}/K_{adrenaline}$ of 8, respectively), whereas the enantiomer *P-(R,R,R)*-**1** is adrenaline-selective with a selectivity $K_{adrenaline}/K_{norephedrine}$ of 28 and even exclusive when compared to ephedrine. Thus, switching from one enantiomer to another completely changed the substrate selectivity, allowing building selective receptors for a given neurotransmitter by simply using the mirror image of a cage.

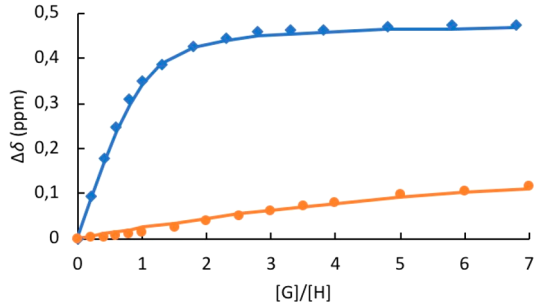


Figure 3. Titration curves of hosts *M-(S,S,S)*-**1** (blue) and *P-(R,R,R)*-**1** (orange) with (1*R*,2*S*)-(−)-ephedrine. The complexation-induced shifts ($\Delta\delta = \delta_{uncomplex} - \delta_{complex}$) of the guest's proton at 5.18 ppm were recorded and plotted as a function of the ratio [G]/[H] (dots). Curves were fitted with the Bindfit program (solid lines).

As cage *P-(R,R,R)*-**1** and obviously its enantiomer *M-(S,S,S)*-**1** are able to switch from a globular form to a fully imploded conformation upon an acidic stimulus (vide supra), we wondered if this nanoscale molecular motion could occur with a guest already encapsulated in the cavity, thereby expelling the included guest outside the cavity. Addition of picric acid to a solution of encapsulated ephedrine led immediately to the imploded structure of the cage *M-(S,S,S)*-**1** associated with the release of the ephedrine guest in the media (Figure 4). This result demonstrates that this molecular motion of the cage is possible despite the high stability of the initial host−guest complex (K = 19 000 M^{-1}). After subsequent addition of triethylamine, the host was reinflated and able to encage the ephedrine guest simultaneously, giving

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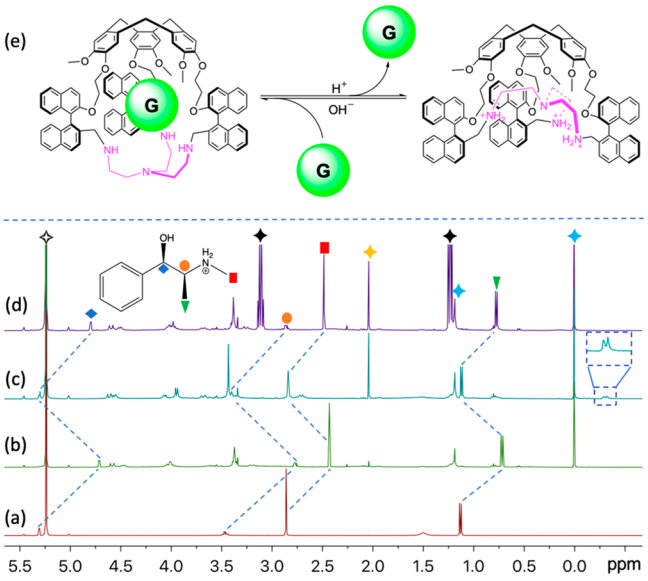

Figure 4. (a–d) ^{1}H NMR (400 MHz, CD_2Cl_2, 298 K) spectra of: (a) (1*R*,2*S*)-(−)-ephedrine; (b) (1*R*,2*S*)-(−)-ephedrine and equimolar of *M*-(*S*,*S*,*S*)-**1**; (c) (1*R*,2*S*)-(−)-ephedrine and equimolar of *M*-(*S*,*S*,*S*)-**1** and 3 equiv of picric acid, the peak at −0.3 ppm was zoomed to highlight the imploded conformation of *M*-(*S*,*S*,*S*)-**1** after protonation; (d) (1*R*,2*S*)-(−)-ephedrine and equimolar of *M*-(*S*,*S*,*S*)-**1** and picric acid and excess of Et_3N. (e) Schematic representation of reversible uptake and release of guest by *M*-(*S*,*S*,*S*)-**1** upon protonation/deprotonation. White, black, yellow, and blue ◆ represent $CHDCl_2$, Et_3N, acetone, and grease, respectively.

back the initial host–guest complex. Thus, simple protonation/deprotonation induces a strong change of the conformation of the receptor allowing for the control of the reversible trap and release of the ephedrine neurotransmitter.

In summary, we have described the synthesis of four new C_3-symmetric enantiopure cages and their enantioselective recognition toward chiral ammonium neurotransmitters. The enantioselectivity reached with these new enantiopure cages is unprecedented for a receptor with 3-fold symmetry as well as the selectivity change observed for a given substrate with enantiomeric receptors. A nanomechanical process from an imploded to a reinflated form upon protonation/deprotonation was demonstrated. This motion occurs both with the host alone and with the host–guest complex, which allows simple control of the uptake and release of the enantiopure neurotransmitter.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04440.

Experimental details, reaction conditions, characterizations, NMR and ECD spectra, and titration curves (PDF)

Accession Codes

CCDC 1956216 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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