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PAPER

Hemicryptophane host as efficient primary alkylammonium ion receptor

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Hemicryptophane **3** was found to be an efficient and selective primary alkylammonium receptor.
Binding constants are 1000-fold higher than those previously reported for hemicryptophane hosts.
Efficient complexation of dopamine emphasizes the use of this host for neurotransmitter complexation.
Density functional theory calculations were performed and highlight host–guest complementarities.

Introduction

The use of molecular containers for the complexation of neutral or charged guests is of increasing interest as they can lead to a better understanding of recognition phenomena by biological receptors and to the understanding of the practical applications of these containers as substrate selective sensors in drug delivery and in separations of complex mixtures.[1–9] In particular, efficient recognition of alkylammonium ions is the subject of numerous studies involving chemical, biochemical and clinical approaches.[10,11] Indeed, many bio-relevant ammonium derivatives intervene in important biological processes, such as the neurotransmitters, which exist at physiological pH in zwitterionic forms (*e.g.* the amino acids glycine or glutamic acid), or in ionic form (ammonium) (*e.g.* the biogenic amines dopamine, adrenaline, noradrenaline . . .).[12]

Compared to cryptophane hosts, which are constructed from two cyclotriveratrylene (CTV) units,[13] the related hemicryptophanes, introducing dissymmetry at the molecular cavity level, are ditopic host molecules which were found to be efficient receptors[14–18] and supramolecular catalysts,[19,20] and led to the design of novel molecular mechanical components such as propellers[21] and gyroscopes.[22] For instance, hemicryptophane **1**, called speleand (Fig. 1) and synthesized by Collet and Lehn, was able to complex methyl ammonium but the association constant was not determined.[14] Recently, we have shown that hemicryptophane **2** was able to encapsulate tetra-methylammonium with a binding constant K_{ass} = 380 M^{-1}.[16]

Hemicryptophane **3**, which contains a CTV unit, provides a rigid scaffold with a lipophilic cavity, and a C_3-symmetrical ligand derived from the tris(2-aminoethyl)amine (tren) moiety. The tren ligand is known to form an atrane structure when binding the nitrogens to a central element like a metal atom. The atrane structures have generated an interesting class of compounds, well represented across the periodic table.[23–25] For instance, the insertion of an atrane structure in cavity-containing host molecules led to original catalysts with unexpected reactivity.[26,27]

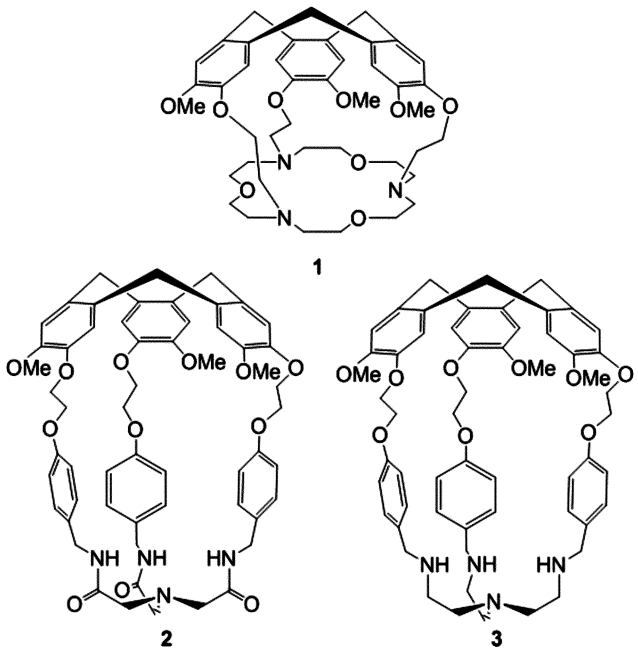

Fig. 1 Chemical structure of hemicryptophanes used for the complexation of ammonium cations: speleand, **1**;[14] triamide-hemicryptophane, **2**;[16] tren-hemicryptophane, **3**.

Furthermore, the tren moiety has been intensively used in cations and anion recognition. For instance, the cryptates are constructed from tren moieties that give them the expected three-dimensional structure.[28–32] More recently, calix[6]arenes capped with a C_{3v}-symmetrical azacrown bridge were designed to reinforce their complexation ability toward ammonium cations.[33] Herein, we report on the complexation of primary alkylammonium cations with host **3**. The binding constants are three orders of magnitude higher than those previously reported for other hemicryptophanes, highlighting its use as an efficient receptor for ammonium guests.

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Table 1 Association constants K_{ass} between receptor **3** and ammonium guests, as measured by ^{1}H NMR titration ($CDCl_3$/MeOD: 95/5, 500 MHz, 298 K)

Ammonium	K_{ass} (M^{-1})[a]	Ammonium	K_{ass} (M^{-1})[a]
$BnNH_3^+$ (**4**)	2.5 10^5	$MeNH_3^+$ (**5**)	6.3 10^4
t-$BuNH_3^+$ (**6**)	1.6 10^4	n-$PrNH_3^+$ (**7**)	1.0 10^4
Dopamine	2.5 10^4		

[a] K_{ass} were determined by fitting ^{1}H NMR titration curves on guests' aliphatic protons with WinEQNMR2.[34] Estimated error = 10%.

Results and discussion

The complexation of alkylammoniums picrate salts by host **3** was investigated in $CDCl_3$/MeOD (95/5) through ^{1}H NMR titrations. In all cases only one set of signals was observed for the host **3** and for the ammonium guests **4–7** (Table 1), showing that host–guest exchange is fast on the NMR time scale. It can be noticed that no shift was observed for the picrate ion, indicating that no interaction between host **3** and this anion can be considered. Complexation of benzylammonium **4** was studied first. The guest's protons displayed significant highfield shifts probably due to the shielding of the cavity (Fig. 2). Similar experiments were performed with the other ammonium guests **5–7**, and highfield shifts of the protons of the guests were also observed. These data are consistent with a recognition process occurring inside the hydrophobic cavity.

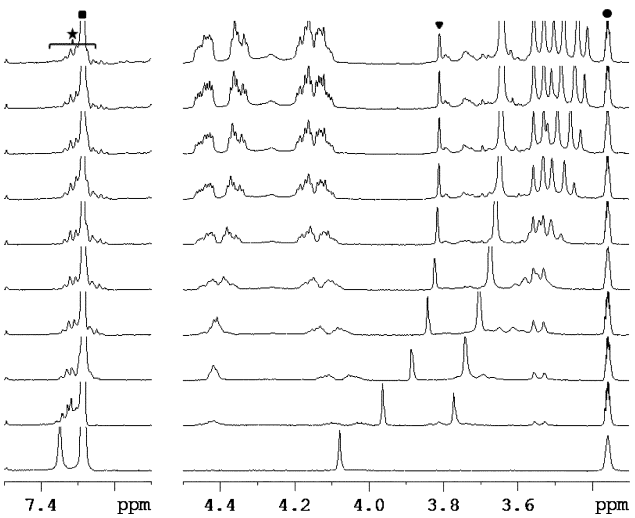

Fig. 2 ^{1}H NMR spectra (500 MHz, $CDCl_3$/MeOD: 95/5, 298 K) of $BnNH_3^+$ upon progressive addition of host **3** (0, 0.2, 0.5, 0.7, 1.0, 1.5, 2.0, 2.4, 3.0 and 3.9 equivalents from bottom to top). ▼: guest's aliphatic protons, ★: guest's aromatic protons, ●: methanol, ■: chloroform.

The binding constants K_{ass} were determined through the complexation induced shifts of the aliphatic protons of the guests since they displayed significant shifts, sharp signals and no overlapping region (Fig. 3). Furthermore, Job's plot experiments have been performed revealing a 1 : 1 binding association (Fig. 4). In spite of the use of a competitive protic solvent, high binding constants were obtained (Table 1), demonstrating the efficiency of host **3** in ammonium recognition. The affinity decreases according to the sequence $BnNH_3^+ > MeNH_3^+ > t\text{-}BuNH_3^+ \approx n\text{-}PrNH_3^+$. A combination of (i) a stabilizing hydrogen bonding network

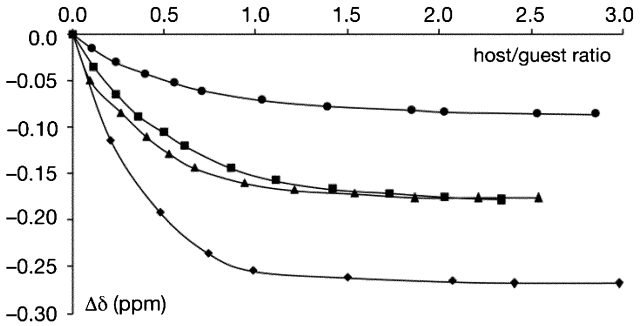

Fig. 3 ^{1}H NMR titration curves for the complexation of ammonium ions with host **3**. ◆: $BnNH_3^+$; ▲: $MeNH_3^+$; ■: *t*-$BuNH_3^+$; ●: n-$PrNH_3^+$.

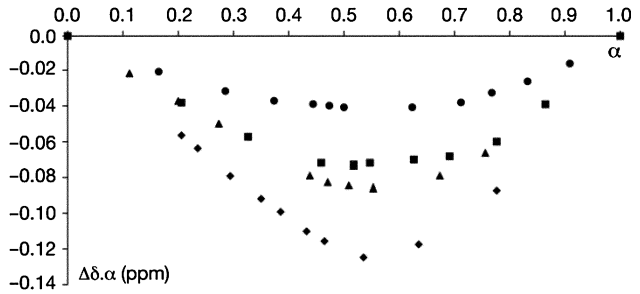

Fig. 4 Job's plots for the guest-**3** complexes; α is the guest's mole fraction. ◆: $BnNH_3^+$; ▲: $MeNH_3^+$; ■: *t*-$BuNH_3^+$; ●: n-$PrNH_3^+$.

between the encapsulated ammonium and the tren moiety and (ii) a good fit allowing both favourable CH–π interactions within the aromatic cavity and minimization of steric repulsions, can account for this experimental results. $BnNH_3^+$ shows the highest affinity (K_{ass} = 2.5 10^5 M^{-1}) since both stabilizing CH–π and π–π interactions are present. In the case of methyl ammonium, a much lower affinity is observed, probably due to the lack of π–π interactions. Sterically more demanding alkylammonium: n-$PrNH_3^+$ and *t*-$BuNH_3^+$ display the lowest association constants. Consequently, a $BnNH_3^+$/n-$PrNH_3^+$ selectivity of 25 is obtained. Therefore hemicryptophane **3** appears as an efficient and selective host receptor for ammonium guests.

To estimate the ability of hemicryptophane **3** to complex ammonium neurotransmitters, we investigated its recognition properties toward dopamine (Fig. 5). This neurotransmitter presents a primary ammonium group and an aromatic ring and should thus provide appropriate matching for the polar functions (through hydrogen bonding) and the apolar surfaces (through CH–π and

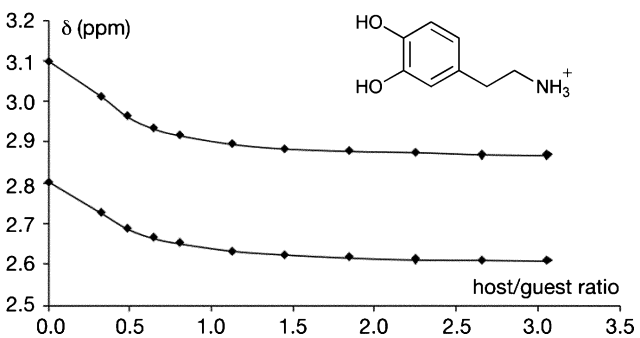

Fig. 5 ^{1}H NMR titration curves for the complexation of dopamine with host **3**. ◆: PhCH_2 signal of dopamine; ●: CH_2N signal of dopamine.

π–π interactions with the phenyl groups of the cavity). Moreover this neurotransmitter is achiral and thus will avoid the formation of diastereomeric complexes with the racemic host. Job's plot analysis indicates the formation of a 1 : 1 host–guest complex (Fig. 6). Moreover, significant highfield shifts were observed for the aliphatic protons of dopamine in the titration binding curves, probably due to the encapsulation of the guest in the aromatic cavity (Fig. 5). The WinEQNMR2 analysis reveals that **3** binds dopamine with a 1 : 1 association constant of 2.5 10^4 M^{-1}.

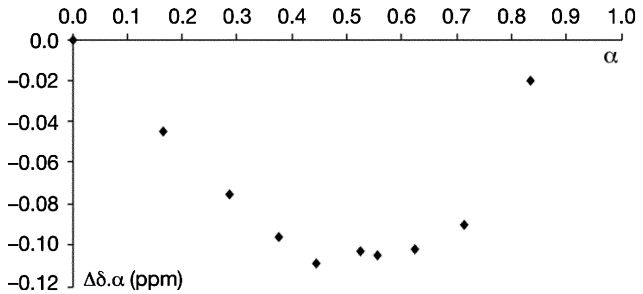

Fig. 6 Job's plot of dopamine with host **3**; α is the guest's mole fraction.

Further insight into this recognition process can be obtained from Density Functional Theory (DFT) calculations. In the optimized geometry of the complex, dopamine is encapsulated in the hemicryptophane cavity (Fig. 7a). The ammonium moiety is bound to the nitrogens of the tren moiety (the average $HN^+ \cdots N$ distance is 3.0 Å) and the aliphatic protons of the guest interact with the aromatic rings of the host with several $CH \cdots \pi$ distances in the range 2.75–2.85 Å). This is consistent with the highfield shift observed for these protons in the ^{1}H NMR spectra after addition of host **3**. Interestingly, one phenol group of the guest interacts with the CTV unit through an OH-π interaction ($HO \cdots \pi$ distance is 3.0 Å). In order to explain the selectivity between dopamine and benzylammonium **4**, it can be noticed from DFT optimized structures (Fig. 7a and 7b) that (i) ArH-π interactions are likely to occur between aromatic rings of host's walls and **4** (several $ArH \cdots \pi$ distances are in the range 2.6–2.8 Å), whereas the position of the dopamine's aromatic ring in the north part of the cavity does not allow such interactions; (ii) dopamine appears folded in the cavity highlighting more steric hindrances between the two partners.

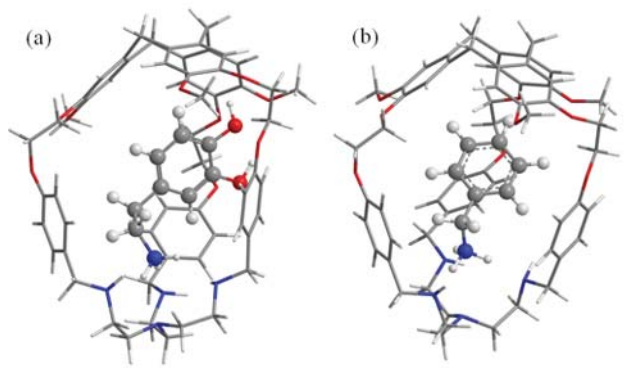

Fig. 7 DFT-optimized structures of (a) dopamine-**3** and (b) benzylammonium-**3** complexes.

Conclusion

In summary, we have demonstrated that hemicryptophane **3** shows a strong affinity for primary alkylammonium due to its ability to interact through both hydrogen bonding and CH–π interactions. Selectivity was found to be moderate but association constants are high for this class of receptors. Thus, dopamine was efficiently recognized by this host molecule. The DFT-optimized structure shows the encapsulation of this neurotransmitter and the interactions involved in this process. Studies are still in progress to resolve the racemic mixture and to investigate the potential activity of these hosts in chiral recognition.

Experimental section

Materials and instrumentation

Hemicryptophane **3** was synthesized according to the previously reported procedure.[35] Solvents were of commercial grade; $CDCl_3$ was stored over molecular sieves. ^{1}H NMR spectra were recorded at 298 K on a Bruker Avance 500 MHz spectrometer. ^{1}H NMR chemical shifts δ are reported in ppm, referenced to the protonated residual solvent signal.

Computational method

Ab initio evaluations were performed using the Gaussian 03 package17 within a restricted DFT framework. In order to access geometrical information upon the host–guest species, full geometry optimizations were performed using DFT calculations. A combination of BP86 functional and an all electron 6-31G* basis set including polarization functions has proven to be very satisfactory for similar issues.[36] We checked using the hybrid B3LYP functional that our results do not suffer from the arbitrariness of the exchange correlation functional. Such weak CH–π interactions are difficult to capture and would call for more elaborated but far too demanding methods.

^{1}H NMR continuous variation methods (Job's plot)

Stock solutions (2 mM in $CDCl_3/CD_3OD$ 95/5) of **3** and each of the guests were prepared and mixed in NMR tubes with different host/guest ratios. In this way, relative concentrations, α, were varied continuously but their sum was kept constant (1 mM for methyl-ammonium and 2 mM for other guests). ^{1}H NMR spectra were recorded for each sample and values of the host's chemical shift, δ, were measured. Job plots were obtained by plotting $\Delta\delta\alpha = (\delta_{obs}-\delta_{free})\alpha$ *versus* α, where δ_{free} is the chemical shift of the proton in the free host. The stoichiometry of the complexes was obtained from the value of the mole fraction α, which corresponds to a maximum of the curve: a 1 : 1 complexation is obtained for $\alpha_{max} = 0.5$.

^{1}H NMR titration of guests. solutions of guest picrate salts (1 mM in $CDCl_3/CD_3OD$ 95/5, 500 µL) were titrated in NMR tubes with 10 µL aliquots of a concentrated solution (10 mM in $CDCl_3/CD_3OD$ 95/5) of host **3**. The shifts $\Delta\delta$ of the guests' protons signals were measured after each addition and plotted as a function of the host/guest ratio. Association constants K_{ass} were obtained by nonlinear least squares fitting of these plots using WinEQNMR2 program.

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