Supramolecular Chemistry

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Combined Cation–π and Anion–π Interactions for Zwitterion Recognition

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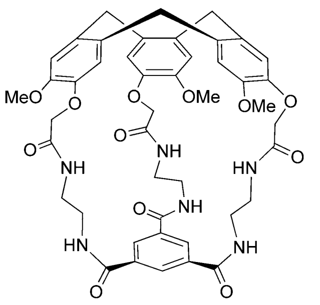
Noncovalent interactions involving aromatic rings play a key role in many processes of molecular recognition.[1] Among them, π–π[2] and cation–π[3] interactions have been widely studied and are known to be important bonding forces in biological systems, such as enzyme–substrate complexes,[4] the DNA double helix,[2,5] or protein folding.[6] Furthermore, these interactions are also involved in many supramolecular assemblies with artificial hosts.[3,7] On the contrary, anion–π interactions,[8] which take place between anions and electron-deficient or π-acidic aromatic systems, have been much less studied. The absence of such studies is due to their counter-intuitive nature, as anions are expected to lead to an electrostatic repulsion with aromatic π clouds.

The favorable nature of this interaction has however been demonstrated in pioneering works by NMR spectroscopy in the early 1990s,[9] and later by theoretical methods.[10] Since then, it has been shown a great deal of interest in theoretical chemistry[11] and in experimental areas, such as crystallography[12] and molecular recognition of anions.[13] Some receptors based on anion–π interactions also turned out to be promising for applications in both sensing and in the ^{19}F labeling of targeted tracer probes in nuclear medicine[10d] and in trans-membrane anion transport.[14] Theoretical studies have revealed that anion–π interaction energies are comparable to hydrogen bonds, and cation–π interaction energies (10–50 kJ mol^{-1}) and can reach up to -120 kJ mol^{-1}.[8,10c] However, to our knowledge, this interaction has never been associated to other noncovalent interactions to create a multitopic synthetic host able to bind to biologically relevant molecules.

Zwitterions, such as γ-aminobutyric acid (GABA) or taurine, play an important role in the transfer of neuronal information, which is the subject of numerous studies involving chemical, biochemical and clinical approaches. As these guests are strongly solvated species in aqueous media, their biomimetic encapsulation through endohedral weak interactions in a hydrophobic neutral molecular pocket is still a challenge.[15] Therefore, a promising strategy would be to design a host with a complementary cavity combining cation–π and anion–π interactions to respectively bind the positive charge and the negative charge of these zwitterionic neurotransmitters.

Hemicryptophanes, a class of molecular cage, are chiral heteroditopic host molecules that were found to be efficient receptors[16–20] and supramolecular catalysts,[21,22] and led to the design of novel molecular mechanical components as propellers[23] or gyroscopes.[24] Furthermore, we previously showed that these hosts were able to selectively encapsulate zwitterionic guests.[25]

Following this approach, we wish to report herein the synthesis of hemicryptophane **1** and its binding properties toward selected zwitterionic neurotransmitters in a competitive aqueous medium. ^{1}H NMR experiments and quantum calculations are presented to emphasize the competing cation–π and anion–π interactions involved simultaneously in the recognition process.



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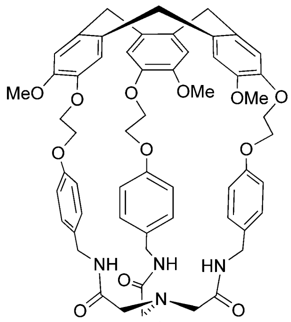

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Recently, we synthesized hemicryptophane **2**, which is formed from a cyclotriveratrylene (CTV) unit, which can stabilize an ammonium ion by cation–π interactions, and a triamide subunit that can stabilize a negative charge by three favorable hydrogen bonds.[26] The adequate organization of these binding sites in the host cavity allows **2** to bind ion pairs in chloroform with a cooperative effect,[18] and zwitterionic guests in an acetonitrile/water (90:10) medium with a 1:1 stoichiometry.[25] However, the three linkers are formed from electron-rich aromatic rings, which can produce electrostatic repulsions with an anion located in the cavity, destabilizing the host–guest complex. To tackle this problem, we replaced these aromatic rings by an electron-deficient system, which could improve the stability of the complex by favorable

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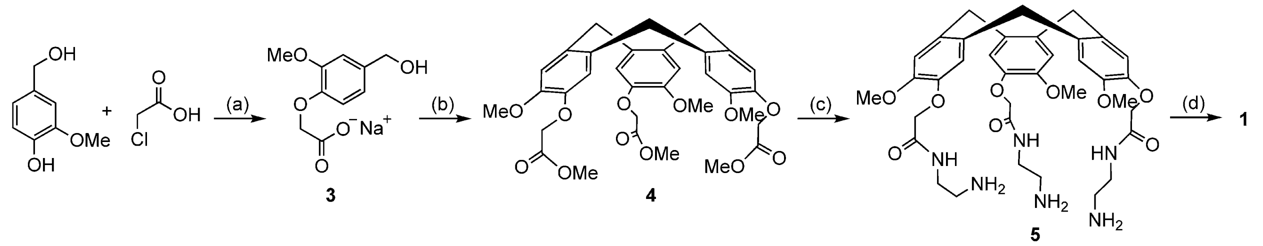


Scheme 1. Synthesis of **1**: a) NaOH, NaI, EtOH, reflux, 5 h, 73 %;[27] b) HCl and then MeOH, APTS, reflux, 3 days, 42 %; c) ethylenediamine, reflux, 48 h, 55 %;[27] d) benzene-1,3,5-tricarbonyl trichloride, triethylamine, CH_2Cl_2, slow addition over 6 days, 22 %.

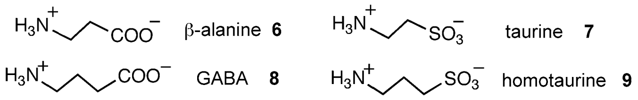
anion–π interactions. We also enhanced the number of hydrogen bond donors by adding three amide functions. In this way, host **1** was synthesized in four steps (Scheme 1). This synthesis is based on the formation of the previously reported intermediates **3**, **4**, and **5**.[27] First, the initial two-step formation of **4** was improved: the cyclization of the CTV unit and the formation of the ester groups were performed by a one-pot synthesis by first adding one equivalent of HCl and then a catalytic amount of *p*-toluenesulfonic acid in methanol. Thus, the yield was slightly improved (42 % vs. 37 %), but the main interest of this method was to avoid using explosive perchloric acid and to avoid chromatography purification as **4** precipitates in methanol and is recovered by a simple filtration. Compound **4** was then condensed in pure ethylenediamine to give **5**. Finally, a [1+1] macrocyclization between **5** and benzene-1,3,5-tricarbonyl chloride in the presence of triethylamine in dichloromethane allowed us to obtain host **1** in four steps and 4 % overall yield from vanillyl alcohol without any chromatography.

Single crystals of **1** suitable for X-ray analysis were obtained by slow evaporation from acetonitrile/water (50/50).[28] A representation of the molecular structure is given in Figure 1. Three water molecules are encapsulated into the cavity. Two of them interact with an amide group of the host through hydrogen bonding and one is in the proximity of the electron-deficient aromatic ring, thus anticipating the recognition properties of this host toward hydrophilic species.

Complexation abilities of **1** toward zwitterionic neurotransmitters **6**–**9** (Table 1) were investigated in an acetonitrile/water (80:20) mixture through ^{1}H NMR titration experiments. In all cases, only one set of signals was observed for the complex and for the guest, thus showing that host–guest exchange is fast on the NMR timescale. Upon addition of host **1**, it can be observed that the protons of taurine show significant upfield shifts (Figure 2). A similar behavior was observed for each guest owing to the shielding effect of the aromatic cavity (see the Supporting Information). The binding constants K_a were determined from the complexation-induced shifts of these protons, which displayed sharp signals, and no overlapping region (Table 1).

First, we can see from Table 1 that the binding abilities of host **1** toward zwitterions have been significantly improved as compared to host **2**. Indeed, binding constants are up to three

Table 1: Association constants K_a and complexation-induced shifts $\Delta\delta_{max}$ measured by ^{1}H NMR titration of guests **6**–**9** with host **1**.[a]



Guest	K_a [L mol^{-1}][b]	V_{VdW} [Å^3][c]	$\Delta\delta_{max}$(N$^+$CH$_2$) [ppm]	$\Delta\delta_{max}$(X$^-$CH$_2$) [ppm]
6	$1.5\pm0.1\times10^4$	86	−0.41	−0.25
7	$5.0\pm0.4\times10^5$	99	−0.39	−0.20
8	$2.3\pm0.1\times10^5$	103	−0.41	−0.20
9	$1.1\pm0.2\times10^5$	116	−0.31	−0.07

[a] CD_3CN/D_2O (80:20), 500 MHz, 298 K. [b] K_a values were determined by fitting ^{1}H NMR titration curves with WinEQNMR2.[29] [c] Van der Waals volumes were calculated using the method reported by Abraham et al.[30]

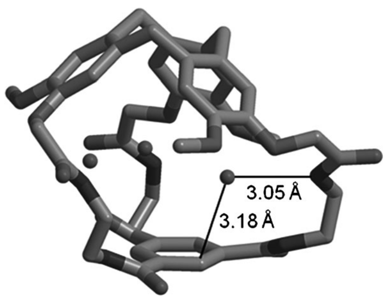


Figure 1. X-ray structure of **1**. Water molecules located outside of the cavity and hydrogen atoms have been omitted for clarity.[28]

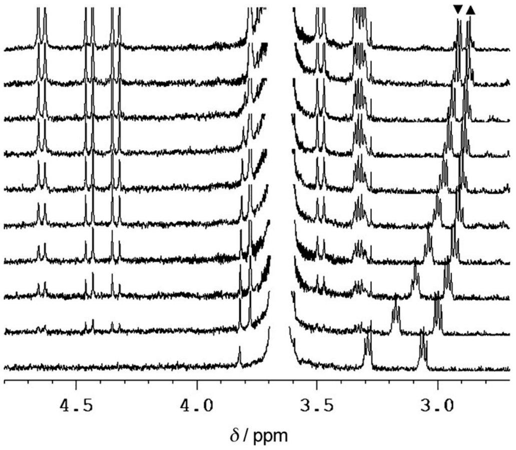


Figure 2. ^{1}H NMR spectra (80:20 CD_3CN/D_2O, 500 MHz, 298 K) of taurine **7** upon progressive addition of host **1** (0, 0.17, 0.30, 0.43, 0.56, 0.77, 0.92, 1.1, 1.5, and 2.8 equivalents from bottom to top). ▼ signal of NCH_2 protons of taurine, ▲ signal of SCH_2 protons of taurine.

orders of magnitude larger than those previously reported for hemicryptophane **2**, whereas the solvent is even more competitive (20% of water vs. 10% initially).[25] This is probably due to the addition of three hydrogen-bond donor amide groups and the π-acidic aromatic ring, which strongly stabilize the anion function located in the cavity. Second, taurine has the larger association constant. As we already observed with host **2**,[25] a good complementarity in term of size and shape between this guest and the host cavity can account for this result. When the Van der Waals volume of the guest departs from that of taurine the complexation ability decreases.

To understand how the guests interact with host **1**, we can analyze the observed complexation induced shifts ($\Delta\delta_{max}$; see Table 1). For the guests **6–8**, the protons at the α position to the ammonium show larger upfield shifts ($\Delta\delta_{max}(N^+CH_2) \approx 0.4$ ppm) than those at the alpha position to the anionic group ($\Delta\delta_{max}(X^-CH_2) \approx 0.2$ ppm). This result is consistent with the fact that the ammonium group is located in the upper part of the cavity, N^+CH_2 protons being so highly shielded by the three electron-rich aromatic rings of the CTV unit, and that the anionic group is located in the lower part of the cavity, X^-CH_2 protons being thus more smoothly shielded by the only electron-deficient aromatic ring of the host. It is interesting to note that these values are almost identical for these three guests, suggesting similar positioning in the cavity. The homotaurine **9** shows a similar behavior but with smaller complexation-induced shifts. This can be explained by a partial encapsulation of this guest, which is too bulky to fully fit in the cavity.

Finally, to emphasize the different interactions involved in the recognition, full geometry optimizations were performed using density functional theory (see the Supporting Information). The position of the guest in the taurine@**1** complex confirms our conclusions obtained previously from NMR spectroscopy. Indeed, the ammonium head is localized in the center of the CTV cap, whereas the sulfonate group occupies the lower part of the cavity (Figure 3). In this way, the guest fulfills the cavity to optimize the interactions with host **1**. First, the ammonium group binds to the CTV unit through cation–π interactions (the average $HN^+\cdots\pi$ distance with the aromatic rings of the CTV is 3.2 Å).[31] Then, the six hydrogen atoms of the amide groups of the host point toward the cavity, highlighting hydrogen bonds with the sulfonate group of the guest (the average NH···O distance is 3.3 Å). Finally, an anion–π interaction between the sulfonate group and the π-acidic aromatic ring is likely to occur. Indeed, an oxygen atom is 3.4 Å away from the center of the aromatic ring, and the angle of the $O^-\cdots$centroid axis to the plane is 76°.[10c]

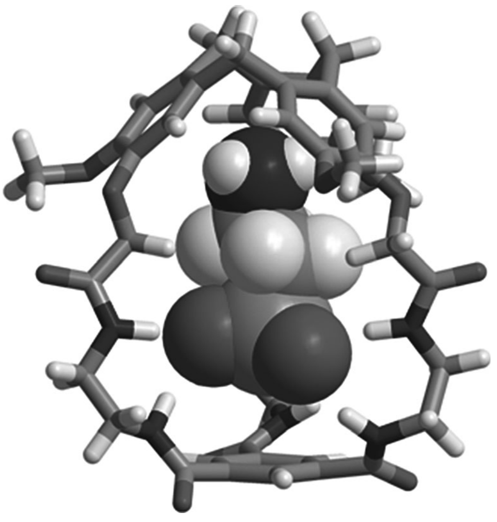


Figure 3. DFT optimized structure of taurine@**1** complex.

Considering the importance of these weak ion–π interactions, we felt that a deeper inspection would be insightful to quantitatively estimate their contributions and would emphasize their role in molecular recognition. Therefore, multireference wavefunction-based calculations were carried out to capture the contributions arising from the induced dipole in the aromatic rings in the presence of the charged ends of the zwitterion. In this respect, complete active-space self-consistent field (CASSCF) calculations allows such dispersive forces to be accounted for.[10a,c] Calculations were voluntarily limited to this level as we wanted to concentrate on the π electron-system fluctuations. Starting from the DFT-optimized structure, the zwitterion was displaced along the C_3 axis of the host. Using simplified structures for the receptor, the anion–π and cation–π energies (E_a and $3E_c$ respectively, E_c corresponding to the interaction energy with one aromatic ring of the CTV unit) were evaluated separately (see the Supporting Information). Finally, the total ion–π energy $E_{tot} = E_a + 3E_c$ was calculated as a function of the displacement z–z_{DFT}, where z is the guest position along the C_3 axis of the host and z_{DFT} corresponds to this position in the DFT optimized geometry (Figure 4). As expected, both interactions compete in the vicinity of the optimized geometry, leading to a minimum for $z - z_{DFT} = -0.1$ Å, characterized by a receptor–zwitterion interaction energy of -170 kJ mol^{-1}. It should be stressed that such energy, which accounts for the presence of four ion–π contributions, is not only compatible with previous calculations,[1b,10] but also supports the rather strong association constants experimentally observed. In

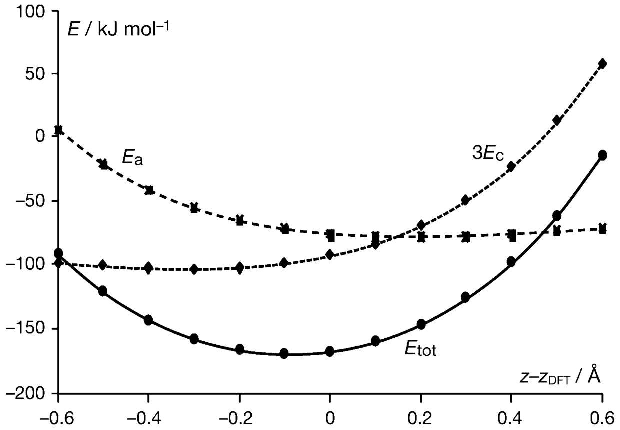


Figure 4. Cation–π ($3E_c$), anion–π (E_a), and total ion–π (E_{tot}) energy variations with respect to the zwitterion displacement z–z_{DFT} along the C_3 axis of the host.

conclusion, such dispersive forces are very efficient and can be combined in a synergistic manner to build up a recognition framework.

In summary, we have demonstrated that hemicryptophane **1** was able to encapsulate biologically relevant zwitterionic guests in a competitive aqueous medium only through endohedral weak interactions. High affinities have been obtained; the binding constants are up to three orders of magnitudes higher than those previously reported for this class of receptor. ^{1}H NMR experiments and DFT calculations emphasize the different interactions involved in these recognition processes. The combination of experimental and theoretical methods emphasizes the fact that cation–π and anion–π interactions can be associated to concomitantly stabilize a host–guest complex. Calculated energies ($-170\ \text{kJ mol}^{-1}$) show that combining both interactions in a single host molecule is promising for efficient molecular recognition of ionic compounds.

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Keywords: anion–π interactions · hemicryptophanes · host–guest systems · molecular recognition · taurine

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[28] Crystallographic data for **1:** $C_{45}H_{65}N_6O_{20.50}$, $M_r = 1018.03$, monoclinic, space group $C2/c$, $a = 18.952(1)$, $b = 13.291(1)$, $c = 39.927(2)$ Å; $\beta = 91.456(2)°$; $V = 10053.7(7)$ Å^3; $Z = 8$; $\lambda = 0.71073$ Å; $T = 180(2)$ K; 88780 reflections collected, 7149 unique reflections ($R_{\text{int}} = 0.1012$); $R1 = 0.0689$, $wR2 = 0.1740$

[$I > 2\sigma(I)$]; $R1 = 0.1383$, $wR2 = 0.2185$ (all data); residual electron density = 0.537 e Å^{-3}. CCDC 846246 (**1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[31] $N^+H\cdots\pi$ distance was measured between the nitrogen atom of the ammonium group and the centroid of the three aromatic rings of the CTV unit.