

Molecular Recognition in an Aqueous Medium Using Water-Soluble Prismarene Hosts

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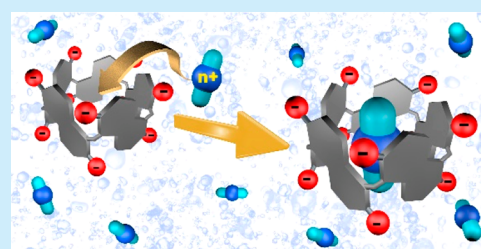


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Supporting Information

ABSTRACT: The synthesis of water-soluble prism[*n*]arenes (*n* = 5 and 6) bearing anionic carboxylato groups on the rims is described. The binding properties of this novel class of water-soluble hosts are studied by nuclear magnetic resonance and calorimetry. The complexation of singly and doubly charged ammonium guests with the more rigid pentamer is enthalpically driven by secondary interactions, while the thermodynamic fingerprint for the larger hexamer reveals driving forces that strongly depend on the guest charge and/or size.

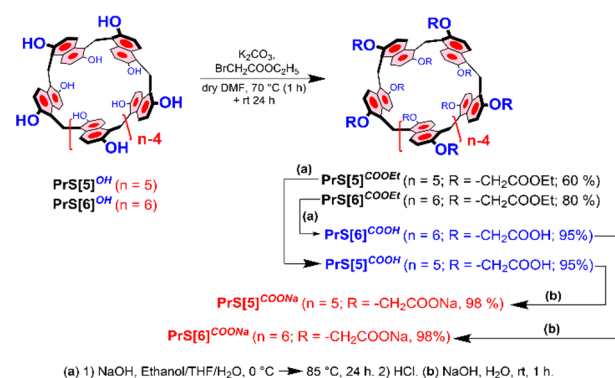


Naphthalene-based macrocycles have recently attracted a great deal of attention in supramolecular chemistry, because of their structural and conformational features.^{1–5} In this context, very recently our group reported a new class of deep-cavity macrocycles named prismarenes.^{6–9} Prismarenes are constituted by five or six 1,5-methylene-bridged naphthalene units and are obtained by an acid-catalyzed condensation of 2,6-dialkoxynaphthalene and formaldehyde.^{6,8}

Water-soluble hosts¹⁰ based on classical cyclophane macrocycles such as calixarenes and pillararenes^{10,11} have been widely investigated for their complexation properties in aqueous media. On the contrary, water-soluble naphthalene-based macrocycles have remained largely less studied, and only very recently have Jiang¹² and co-workers reported the recognition of hydrophilic guests by water-soluble naphthotubes. As is known,¹² the structural and conformational features of water-soluble hosts play a crucial role in determining their binding affinity in water for charged guests, and therefore, it would be very beneficial to investigate the strength and thermodynamic nature of the forces driving the complexation processes. Thus, we envisioned that the inclusion of charged guests inside the deep hydrophobic cavity of prismarenes could reveal intriguing thermodynamic features closely connected to their structural properties. On the basis of these considerations, in this work, we report the synthesis of novel water-soluble carboxylato-prismarenes PrS[*n*]^{COO⁻} [*n* = 5 and 6 (Scheme 1)] as well as their recognition properties in aqueous solution toward ammonium guests 1–7 (Figure 1) determined by NMR and calorimetric investigation. The synthesis of water-soluble prismarenes PrS[*n*]^{COO⁻} (*n* = 5 and 6) is outlined in Scheme 1.

Per-hydroxylated prismarenes⁹ PrS[5]^{OH} and PrS[6]^{OH} were alkylated with ethyl bromoacetate in the presence of

Scheme 1. Synthesis of Water-Soluble Prismarenes



K_2CO_3 as the base and dry DMF as the solvent. This procedure gave ethoxycarbonylmethoxy-prismarenes PrS[5]^{COOEt} and PrS[6]^{COOEt} in 60% and 80% yields, respectively (Scheme 1). The hydrolysis of PrS[5]^{COOEt} and PrS[6]^{COOEt} in the presence of NaOH afforded carboxylic acid-substituted prismarenes PrS[5]^{COOH} and PrS[6]^{COOH}, respectively, in 95% yield. ¹H NMR spectra of carboxylic prismarenes PrS[5]^{COOH} and PrS[6]^{COOH} at 298 K are in agreement with their *D*₅ and *D*₆ symmetry, respectively, observed also for the parent PrS[*n*]^{COOEt}.

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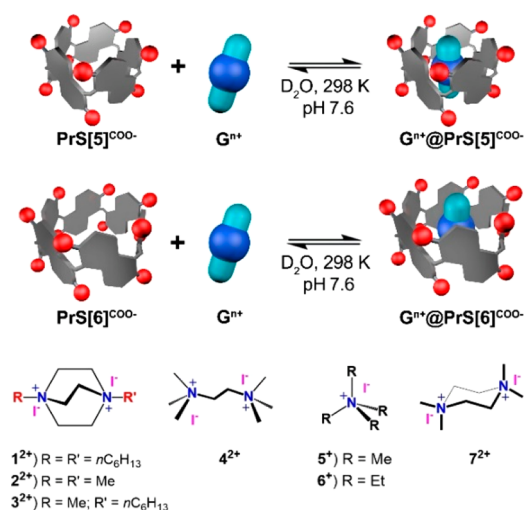


Figure 1. Schematic complexation equilibrium of PrS[5]^{COO-} (top) and PrS[6]^{COO-} (bottom) with ammonium guests at 25 °C in a buffered aqueous solution (pH 7.6).

Finally, neutralization of PrS[5]^{COOH} and PrS[6]^{COOH} by treatment with an aqueous NaOH solution afforded PrS[5]^{COONa} and PrS[6]^{COONa} salts, respectively, which exhibited good solubility in aqueous medium. In agreement with the *D*₅ symmetry of the molecule, the ¹H NMR spectrum of PrS[5]^{COO-} in a D₂O solution (Figure 2c, pH 7.6, phosphate

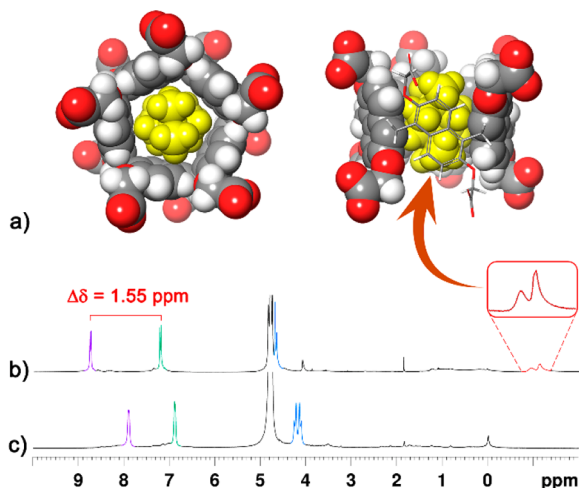


Figure 2. (a) Different views of the DFT-optimized structure of the 7²⁺@PrS[5]^{COO-} complex at the B97D3/SVP/SVPFIT level of theory. (b and c) ¹H NMR spectra (400 MHz, buffered D₂O solution, pH 7.60, 298 K) of PrS[5]^{COO-} and of an equimolar solution of PrS[5]^{COO-} and 7²⁺·2I⁻, respectively.

buffer) at 298 K showed the presence of an AX system at 7.89 and 6.88 ppm (Figure 2c; *J* = 8.0 Hz; $\Delta\delta$ = 1.01 ppm), attributable to the aromatic H atoms of the macrocycle, while at 4.74 ppm, a singlet was detected, attributable to the methylene bridges. Finally, OCH₂ groups resonated as an AB system at 4.25 and 4.14 ppm.

The addition of ammonium cations 1–7 as iodide salts to a D₂O solution (pH 7.6, phosphate buffer) of PrS[5]^{COO-} gave substantial changes in its ¹H NMR spectrum (Supporting Information), indicative of the formation of *endo*-cavity complexes (Figures 1 and 2 and the Supporting Information),

in slow exchange on the NMR time scale. In detail, when *N,N,N',N'*-tetramethylpiperazonium salt 7²⁺·(I⁻)₂ and PrS[5]^{COO-} were mixed in an equimolar ratio in D₂O (Figure 2b,c), the formation of the 7²⁺@PrS[5]^{COO-} *endo*-cavity complex was confirmed by the presence of upfield-shifted H atom signals of 7²⁺ to negative values of chemical shift (Figure 2b,c and the Supporting Information). Interestingly, the $\Delta\delta$ value between the aromatic doublets of PrS[5]^{COO-} increased from 1.01 ppm for the free host to 1.55 ppm [$\Delta\delta$ = 8.80 ppm – 7.25 ppm = 1.55 ppm (Figure 2b)] upon inclusion of 7²⁺ inside the cavity of the carboxylato-prism[5]arene (Figure 2a). Diagnostic cross-peaks were present in the NOESY spectrum of the 7²⁺@PrS[5]^{COO-} complex between the shielded methylene protons of 7²⁺ at negative values of chemical shift and ArH protons of the host PrS[5]^{COO-}. These results are strongly indicative of the inclusion of the piperazonium cation inside the cavity of the host.^{6,8} Analogously, upfield-shifted ¹H NMR signals were observed upon complexation of ammonium guests 1–6 inside the cavity of the PrS[5]^{COO-} host [Figure 1].

The DFT-optimized structure of the 7²⁺@PrS[5]^{COO-} complex (Figure 2a and the Supporting Information) at the B97D3/SVP/SVPFIT level of theory reveals that the PrS[5]^{COO-} host adopts a conformation in which the aromatic walls assume canting angle¹³ values of ~90° and therefore define a regular pentagonal prism. The piperazonium cation (yellow in Figure 2a) is accommodated inside the internal cavity of PrS[5]^{COO-} and establishes several (approximately nine) C–H··· π interactions with an average C–H··· π centroid distance of 2.6 Å.¹⁴

ITC calorimetric studies¹⁵ confirm that PrS[5]^{COO-} forms 1:1 complexes with ammonium guests 1–7 (Figure 1). In fact, the macrocycle cavity of PrS[5]^{COO-} is unable to encapsulate more than one guest while the negatively charged rims prevent the possible assembly of capsular structures^{16,17} due to the strong electrostatic repulsion between the two facing PrS[5]^{COO-} molecules.

The inclusion complexes exhibit affinity constant values ranging from 10³ to 10⁵ M⁻¹, and the results in Table 1 and Figure 3 suggest that the stability of the Gⁿ⁺@PrS[5]^{COO-} complexes is significantly affected by the structural features of the differently charged Gⁿ⁺ guests.

The largest binding affinities were achieved for the complexation of doubly charged cations 7²⁺ and 4²⁺, with log *K* values of 5.3 (2) and 5.1 (2), respectively. With regard to the complexation of singly charged ammonium guests, PrS[5]^{COO-} displays a greater affinity for tetramethylammonium 5⁺ than the larger tetraethylammonium 6⁺ with a 5⁺/6⁺ selectivity ratio of 9.5. The larger binding affinity of PrS[5]^{COO-} for dicationic than for monocationic ammonium guests suggests that Coulombic favorable COO⁻/N⁺ interactions play a crucial role in an efficient complexation, along with cation– π interactions. 1,4-Dimethyl-DABCO 2²⁺ has the smallest affinity for PrS[5]^{COO-}, while the presence of longer *n*-hexyl chains in 1,4-dihexyl-DABCO 1²⁺ and 1-hexyl-4-methyl-DABCO 3²⁺ increases the stability of their respective complexes by ~0.6 log unit. The binding parameters (Figure 3a) highlighted that the inclusion of all ammonium cations in the hydrophobic cavity of PrS[5]^{COO-} is due to enthalpically favorable attractive forces (including electrostatic, cation– π , and CH– π interactions) that drive the recognition process. The sizable enthalpy gain [ΔH^0 ranges from –15.21 to –33.91 kJ mol⁻¹ (see Figure 3)] overrides the cost in energy needed for the

Table 1. Log K Values and Thermodynamic Parameters^a for Host–Guest Complex Formation at 298 K in an Aqueous Solution (pH 7.6, 70 mM phosphate buffer)

guest	PrS[5] ^{COONa}			PrS[6] ^{COONa}		
	log K	$\Delta H^{\circ b}$	$\Delta S^{\circ c}$	log K	$\Delta H^{\circ b}$	$\Delta S^{\circ c}$
5 ⁺	4.51 (9)	−15.21 (2)	36 (2)	3.5 (2)	−1.33 (6)	63 (4)
6 ⁺	3.50 (3)	−24.66 (1)	−15.8 (6)	3.3 (2)	−1.54 (6)	58 (4)
4 ²⁺	5.1 (2)	−26.45 (2)	9 (3)	3.10 (5)	−7.95 (2)	32.7 (9)
1 ²⁺	4.5 (1)	−30.02 (2)	−14 (3)	3.41 (6)	−12.21 (2)	25 (2)
3 ²⁺	4.5 (1)	−33.65 (3)	−27 (3)	3.29 (1)	−12.63 (1)	20.5 (4)
2 ²⁺	3.87 (6)	−18.53 (2)	13 (2)	2.91 (3)	−14.92 (1)	5.7 (6)
7 ²⁺	5.3 (2)	−33.91 (3)	−12 (4)	3.05 (3)	−16.71 (1)	2.3 (6)

^a σ in parentheses. ^bExpressed in kilojoules per mole. ^cExpressed in joules per degree per mole.

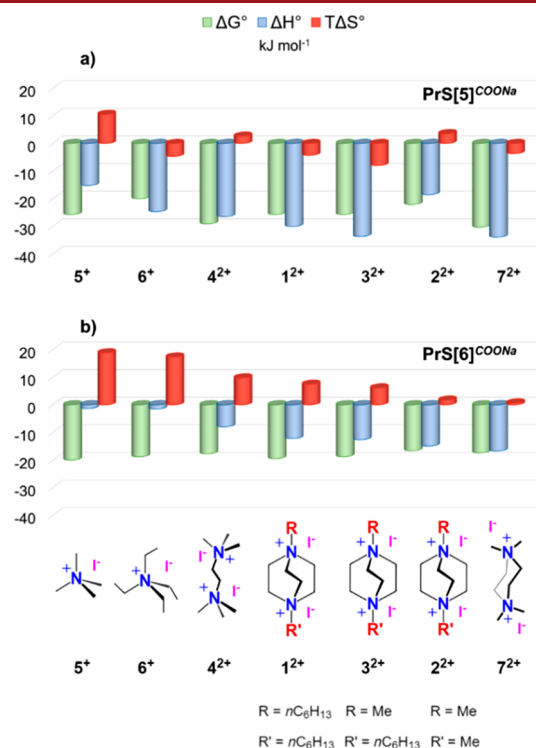


Figure 3. Thermodynamic parameters for host–guest complex formation of (a) PrS[5]^{COO}− and (b) PrS[6]^{COO}− with positively charged guests at 25 °C in a buffered aqueous solution (pH 7.6).

desolvation of all of the interacting components. The complexations of piperazonium 7²⁺ and DABCOHeMe 3²⁺ are more exothermic (Figure 3a) than those of other guests but with an entropic penalty that accounts for the loss of degrees of freedom due to host–guest complex formation and/or to a lower level of desolvation upon inclusion in the aromatic cavity of the host. Desolvation is still a relevant process for the binding of ⁺NMe-based cations such as 2²⁺ and 4²⁺ and, interestingly, for tetramethylammonium guest 5⁺, which all benefit from a favorable entropic contribution (see Figure 3a). Significantly, the *endo*-cavity complexes of doubly charged guests such as 7²⁺, 2²⁺, 1²⁺, 3²⁺, and 4²⁺ with PrS[5]^{COO}−, which show large enthalpic gains (Table 1), have packing coefficients (PC) of 57%, 63%, 65%, 66%, and 56%, respectively, in the optimal 55 ± 9% PC range as reported by Rebek and Mecozzi.¹⁸

NMR and calorimetry measurements indicated that PrS[6]^{COO}− also forms only 1:1 inclusion complexes with all of the charged guests despite its larger cavity. Also in this case, upon

addition of cations 1–7 as iodide salts to a D₂O solution (pH 7.6, phosphate buffer) of PrS[6]^{COO}−, a new set of upfield-shifted signals emerged in its ¹H NMR spectrum (Supporting Information) due to the formation of complexes slowly exchanging on the NMR time scale.

The association constants (Table 1 and Figure 3) determined for the formation of the Gⁿ⁺@PrS[6]^{COO}− complexes (Figures 1) are all on the order of 10³ M⁻¹ and lower than the values found for the analogous Gⁿ⁺@PrS[5]^{COO}− complexes. This difference in affinity could be attributed to the lower Gⁿ⁺/PrS[6]^{COO}− complementarity, due to the larger size of the hexamer cavity that causes a scarce steric fit with Gⁿ⁺ in Figure 1. Although the binding free energies for all of the G²⁺@PrS[6]^{COO}− complexes are comparable (approximately −18 kJ mol⁻¹), intriguing differences can be revealed when the enthalpic and entropic contributions are determined. The inclusion of doubly charged guests G²⁺ inside the PrS[6]^{COO}− cavity is an enthalpically driven process occurring by electrostatic interactions between the carboxylate and cationic groups, along with multiple cation– π and CH– π interactions with the π -electron rich PrS[6]^{COO}− cavity (Figure 3b). Interestingly, enthalpically favored G²⁺@PrS[6]^{COO}− complexes have packing coefficients (PC) of 63% (1²⁺), 48% (2²⁺), 60% (3²⁺), and 40% (4²⁺), within the optimal 55 ± 9% PC range.¹⁸ However, the structural features of doubly charged guests G²⁺ seem to strongly influence the enthalpic term (ΔH° gain follows the order 7²⁺ > 2²⁺ > 3²⁺ > 1²⁺ > 4²⁺). In fact, in the case of DABCO cations 1²⁺–3²⁺, longer *n*-hexyl chains in 1²⁺ confer larger hydrophobicity and a smaller charge to radius ratio, resulting in a lower overall charge density. Consequently, for the formation of the 1²⁺@PrS[6]^{COO}− complex, electrostatic and/or cation– π interactions are less efficient than for the other DABCO cations 2²⁺ and 3²⁺.¹⁹ Similar binding affinities of PrS[6]^{COO}− were measured for the complexation of singly charged cations 5⁺ and 6⁺, with log K values of 3.5 (2) and 3.3 (2), respectively.

The K value of 1990 M⁻¹ (log K = 3.3) measured by ITC for the formation of the 6⁺@PrS[6]^{COO}− complex was confirmed by integration of the slowly exchanging ¹H NMR signals for the free and complexed guest [K = 1815 M⁻¹ (Figure S32)]. The inclusion of monocations 5⁺ and 6⁺ in the PrS[6]^{COO}− cavity is an entropically favored and driven process ($T\Delta S^{\circ}$ ~ 18 kJ mol⁻¹ on average). Desolvation of the 5⁺ and 6⁺ cations, which are strongly hydrated in their free state, as well as the release of water molecules from the solvent-filled cavity of PrS[6]^{COO}− to the bulk of the solvent upon complexation account for a favorable increase in entropy. Moreover, the less suitable fit between these smaller monocationic guests and the

larger host cavity, which results in greater prismarene walls flexibility, further contributes to the large entropic gain observed. As one can see from Figure 3b, moving from doubly charged guests to singly charged cations 5^+ and 6^+ , the decrease in the ΔH^0 contribution is compensated by an increased $T\Delta S^0$ term. This result indicates, for the *endo*-cavity complexation of $\text{PrS}[6]^{\text{COO}^-}$ with charged guests, an enthalpy–entropy compensation effect (EEC), which is commonly observed in supramolecular recognition systems.²⁰ As reported in the literature,²⁰ EEC plots (see the Supporting Information) permit one to gain insight into complexation thermodynamic fingerprints. In detail, the slope and the intercept ($T\Delta S_0^0$) of the plot of $T\Delta S^0$ versus ΔH^0 (Supporting Information) might provide relevant information for changes in the conformation and desolvation of the host and guest.²⁰ Generally, slope values of <1 might be expected for macrocycles characterized by a more rigid structure in which secondary host–guest interactions prevail. A slope closer to unity could be indicative of a rearrangement of the hydrogen-bond network²¹ and conformational changes in the macrocycle structure. In agreement with these observations, the complexation of $\text{PrS}[6]^{\text{COO}^-}$ exhibits a slope of 1.12 (7) and a $T\Delta S_0^0$ value of 19.6 (8) kJ mol^{-1} , which both account for greater host flexibility and a larger number of water molecules in the interior and exterior of the hexamer $\text{PrS}[6]^{\text{COO}^-}$ cavity than in the case of the pentamer. In fact, the complexation thermodynamic fingerprint for $\text{PrS}[5]^{\text{COO}^-}$ shows a lower enthalpy–entropy compensation effect; a slope of 0.7 (1) and an intercept of 19 (3) kJ mol^{-1} can be attributed to the higher conformational rigidity of the pentamer. In agreement with these deductions, $\text{G}^{n+}@\text{PrS}[5]^{\text{COO}^-}$ complexes show packing coefficients in the optimal $55 \pm 9\%$ PC range, indicative of a good steric fit between size and shape of the cations G^{n+} and the narrower cavity of the pentamer.

In conclusion, here are described the synthesis of novel water-soluble carboxylato-prism[*n*]arenes ($n = 5$ and 6) and their *endo*-cavity complexation properties toward organic ammonium cations $\text{G}^{n+}@\text{PrS}[n]^{\text{COO}^-}$ ($n = 5$ and 6) in water. Calorimetry studies showed that the complexation processes are driven by thermodynamic factors depending on prismarene size and cation charge and shape. The inclusion of ammonium cations 1–7 in the cavity of $\text{PrS}[5]^{\text{COO}^-}$ is driven by enthalpically favorable attractive forces. The larger $\text{PrS}[6]^{\text{COO}^-}$ hexamer forms *endo*-cavity complexes with association constants lower than those found for $\text{PrS}[5]^{\text{COO}^-}$. *Endo*-cavity inclusion of a singly charged ammonium guest by carboxylato-prism[6]arene is entropically favored; desolvation of the cations and the release of water molecules from the solvent-filled cavity of the hexamer account for the large entropic gain. On the contrary, the encapsulation of doubly charged guests inside the cavity of $\text{PrS}[6]^{\text{COO}^-}$ is enthalpically driven mostly due to electrostatic, cation– π , and CH– π interactions.

The synthesis of water-soluble prismarenes, described here for the first time, and the thermodynamic fingerprints of their complexations in aqueous medium could pave the way for the construction of new prismarene-based supramolecular systems with intriguing properties.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.2c00819>.

Detailed synthetic procedures, one- and two-dimensional NMR spectra, HR mass spectra, details of DFT calculations details, and details of ITC titrations (PDF)

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Notes

The authors declare no competing financial interest.

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