Supporting information for:
Thermodynamics of Supramolecular Associations with Macrocyclic Water-Soluble Hosts

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Nomenclature of studied molecules

For $\beta$-Cd and CnS we represent only one fundamental unit that will be sufficiently repeat to build the desired molecule. The nomenclature used for water molecule is Ow for the oxygen atom and Hw for hydrogen atoms.

Figure S1: Atom type for (from left to right) the $\beta$-cyclodextrin, the p-sulfonatocalix[n]arene and the 4AAB.

Considering the H-bonds we apply the following notation: (donnor, hydrogen),receptor. For example "(N4, HN4),Ow" means that the HN4 hydrogen, links to N4 atom of the 4AA, forms a hydrogen bond with the Ow atom of a water molecule.
(C6S/4AA) association - results

Figure S2: a) Percentage of 4AA atoms inserted inside the C6S cavity as a function of the distance between centers of mass. b) $N_{\text{water}}$ corresponds to the number of water molecule inside the host cavity as a function of the distance between centers of mass of C6S and 4AA. The dotted lines represents the location of the deep minimum in the PMF profile for (C6S, 4AA).

Figure S3: Energy contributions as a function of the distance between centers of mass for (C6S, 4AA) at a) acidic pH and b) neutral pH. The blue curve corresponds to the Lennard-Jones energy, the green curve to the electrostatic part and the red one to the sum of all contributions. The dotted lines represents the location of the deep minimum in the PMF profile for (C6S, 4AA).
Figure S4: Number of H-bonds formed as a function of the distance between centers of mass for (C6S, 4AA) at a) acidic pH and b) neutral pH. The colored curves correspond to a given type of H-bond whereas the black curve corresponds to the sum of all H-bonds. The dotted lines represent the location of the deep minimum in the PMF profile for (C6S, 4AA).
**Inversion of the guest molecule**

To ensure which orientation the guest molecule takes during the simulation, we define the orientation coefficient $\alpha$. Let us consider simplified guest and host molecules (figureS5). We define $H(x_H, y_H, z_H)$ as the center of mass of the host molecule, $G(x_G, y_G, z_G)$ as the center of mass of the guest molecule and $A(x_A, y_A, z_A)$ as the position of the $N4$ atom of the guest molecule. Let us, now, consider distances between $H-G$ ($d_{HG}$) and $H-A$ ($d_{HA}$), we define $\alpha$ as the ratio of this two distances as follows:

\[
\alpha = \frac{d_{HG}}{d_{HA}} \quad (1)
\]

From this equation we can define three cases:

- **a) $\alpha < 1$** : In this case, $d_{HA}$ is higher than $d_{HG}$. This implies that the $N4$ atom of the guest molecule is further than benzene cycles of the guest from the host as illustrated in figureS5a.

- **b) $\alpha > 1$** : In this second case, $d_{HG}$ is higher than $d_{HA}$. This implies that the $N4$ atom of the guest molecule is closer than benzene cycles of the guest from the host as illustrated in figureS5b.

- **c) $\alpha = 1$** : In this last case, $d_{HA}$ equal to $d_{HG}$. This implies that the $N4$ atom of the guest molecule is exactly at the same distance than benzene cycles of the guest from the host. This case can happen when the guest molecule is far enough of the host molecule and there is not clear orientation of the guest molecule as illustrated in figureS5c.
Figure S5: Schematic representation of the orientation of 4AA when a) $\alpha < 1$, b) $\alpha > 1$ and c) $\alpha = 1$.

Figure S6: $\alpha$ coefficient computed for a) (C4S, 4AA) and b) (C6S, 4AA) at both acidic and neutral pH. We split the curves in three zones A, B and C.
Thermodynamic properties

The following section presents the curves obtained for $\Delta_r G$ and $\Delta_r H$ for our host/guest complexes as a function of the upper integration limit.

![Graph](image1)

Figure S7: Evolution of the enthalpy of association (red curve) and the free enthalpy of association (blue curve) for ($\beta$-Cd, 4AA) at pH=7. The red and blue dotted lines correspond to the experimental values for respectively enthalpy of association and free enthalpy of association.

![Graph](image2)

Figure S8: Evolution of the enthalpy of association (red curve) and the free enthalpy of association (blue curve) for (C4S, 4AA) at a) pH=1 and b) pH=7. The red and blue dotted lines correspond to the experimental values for respectively enthalpy of association and free enthalpy of association.
Figure S9: Evolution of the enthalpy of association (red curve) and the free enthalpy of association (blue curve) for (C6S, 4AA) at a) pH=1 and b) pH=7. The red and blue dotted lines correspond to the experimental values for respectively enthalpy of association and free enthalpy of association.