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Research paper

Bambusurils as effective ion caging agents: Does desolvation guide conformation?

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ABSTRACT

Water soluble bambusurils can bind and isolate inorganic anions in the center of the hydrophobic cavity, with high affinity and selectivity. This makes them appealing anion carriers and ion transporters for a wide range of biomedical applications, including in ion-channel diseases of the muscles, bones and brain. For understanding the bambusuril ion caging ability in aqueous media, molecular dynamics simulations, including free energy calculations are used. It is seen that the ion is hermetically sealed inside the cavity, as a result of a concerted action involving conformation and desolvation of both ion and bambusuril cavity.

1. Introduction

The design of water-soluble receptors for anions is particularly challenging and significant advances have been made, taking advantage of specific effects that include the hydrophobic effect, C—H hydrogen and halogen bonding [1,2]. The nature of the solvent plays a fundamental role in the selectivity and strength of the anion binding process. Electrostatic interactions are particularly important in stabilizing anions in solution and generally dominate over other recognition forces. The development of anion transporters to promote the translocation of anions across lipid membranes is an emerging field, with a key role in ion channel diseases such as cystic fibrosis [3]. In parallel, the use of anions to template self-assembled structures has also significantly progressed, and has been recently revisited [4]. The synthesis of anion-templated rotaxanes and catenanes [4,5] has provided new systems, again making a direct connection to host-guest supramolecular systems. Recently, rotaxanes forming strong complexes with halides in water through a combination of halogen and hydrogen bonding have also been investigated [6,7]. In most of these applications, compatibility with aqueous media is mandatory; however, in some cases, water may hinder the binding affinity. This has fostered the development of new host-anion systems, but the establishment of tools to rationalize the relation between structural variations and affinity to different anions, still remains necessary. Our investigation is focused on three bambusuril (BU) derivatives, dodecamethylbambus[6]uril ($Me_{12}BU[6]$) dodecabenzylbambus[6]uril, $Bn_{12}BU[6]$, and dodeca(4-carboxybenzyl)bambus[6]uriL, $(BnCOOH)_{12}BU[6]$. The respective cyclic structures [8], illustrated in Scheme 1, consist of six equal glycoluril units, adopting alternate conformations, interconnected by methylene bridges and differ in peripheral substitutions, in which the disubstituted glycoluril units, containing aliphatic [9,8,10,11] (e.g. methyl) or aromatic [21,33] (e.g. benzyl and benzoyl) groups are used to construct the macrocycle.

These molecules clearly possess a high potential in biomedicine and pharmaceutics, due to their remarkable guest binding behavior, able to form stable complexes with various anionic molecules including several halide ions [10,21] Depending on the substitution, it is possible to tune the properties of the macrocycle, including solubility and molecular affinity. Other BU analogs [12–14] have been obtained by internal substitutions, in which the portal or equatorial oxygen atoms of the carbonyl groups are replaced by different heteroatoms (e.g. sulfur [12] and nitrogen [14], see Fig. 1 for some representative structures of these macrocycles optimized at the AM1 and HF/6-31G* level.

The interior of BUs acts as anion receptor, whereas little is known about the binding properties of their portals. The convex arrangement of glycoluril units in BUs, directs the methine hydrogen atoms inwards, conferring to the internal core a positive potential. The presence of only one row of mehylene bridges increases the flexibility and adaptability of the cavity to the size of the anion [15,8]. In this typical conformation, the methine hydrogens form a pocket with the possibility of establishing C—H···X^- interactions. The internal diameter and the respective height of $Me_{12}BU[6]$ may reach a typical maximum of 6.4 Å and 12.7 Å, respectively [8]. The binding modes of $Me_{12}BU[6]$ and their arrangement in the solid-state have been established by Sindelar and co-workers [10] using X-ray diffraction.

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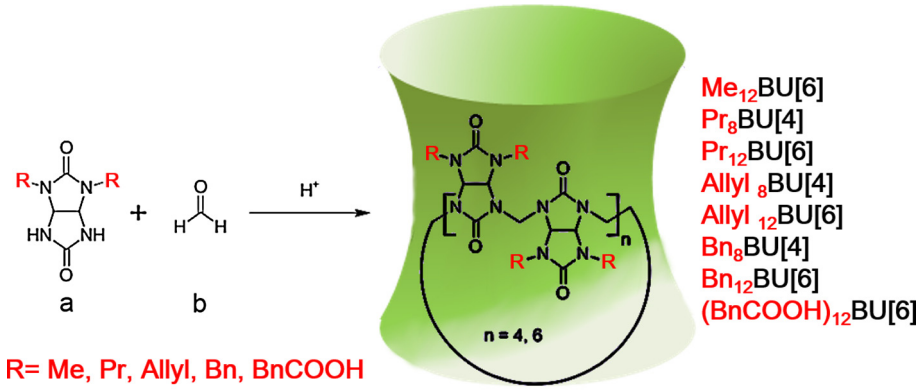

Scheme 1. Schematic representation of the general synthesis of bambusuril derivatives from the acidic-catalyzed condensation between 2,4-disubstituted glycoluril (a) and formaldehyde (b).

The preparation of this methyl substituted BU consists of an acid-catalyzed condensation between 2,4-dimethylglycoluril and formaldehyde [8]. Me_{12}BU[6] is a strong anion binder but the respective synthesis depends on the anion template effect as described in Refs. [8,16,17,18]. The strategy is based on the use of the anion of interest as a templating agent to bind the glycoluril units into assemblies that have high selectivity for the templating anion. The latter can be considered as an entity that contains the required features to promote the organization of the building blocks in a specific manner. This process is both thermodynamically and kinetically driven [17]. The host-guest interactions of these molecules in aqueous environments and in non-polar solvents have also been investigated using thermal calorimetry and ^{1}HNMR data. A recent work on the topic [18] focuses on the binding properties of dodecabenzylbambus[6]uril (Bn_{12}BU[6]) in the presence of multiple anion mixtures in chloroform, with association constants of up to 10^{10} M^{-1}. In aqueous solutions, BUs have been suggested, among others, for the preparation of sensors able to detect the occurrence of abnormal salt concentrations in human body, upon contact with very small amounts of blood or urine [19,20]. Further interest has grown with the preparation of the first water soluble derivative, $(BnCOOH)_{12}$BU[6] [21]. This molecule, functionalized with twelve carboxybenzyl groups, is able to bind anions in buffered water solution with high affinity (stability constants up to 10^7 M^{-1}) [21] and unusual selectivity. The structure and complexation profile of this BU molecule with grafted carboxylate groups have been inspected by ^{1}H-NMR titration and isothermal titration calorimetry (ITC). The association constants for the formation of 1:1 complexes between $(BnCOOH)_{12}$BU[6] and various halide ions have been determined [21] through competition experiments with another anion (often the chloride ion). The complex is stabilized by multiple weak C—H···anion interactions, resulting in exceptionally strong complexes in water. These efforts reflect the multitude of possibilities that can be explored with this type of macrocycles. This work provides both description and rationalization of some of the relevant features involved in the BU host-guest interactions, comprising conformation, hydration and free energy patterns, which are indispensable among others to predict their potential as building blocks for supramolecular structures.

2. Simulation details

2.1. General procedure

The exploratory MD simulations were performed with the Gromacs package (version 4.6.5) by using all-atom amber99sb forcefield. The starting geometries of the Me_{12}BU[6], Bn_{12}BU[6] and $(BnCOOH)_{12}$BU[6] hosts were constructed resorting to Avogadro and Pymol (Version 1.7.7.2) and optimized by the semi-empirical Antechamber/SQM method. Electrostatic charges were obtained from AM1-BCC [22,23] calculations. For the rigid Me_{12}BU[6], these methods provide good approximations for its structure in solution. However, some degree of distortion is expected for the benzyl (Bn_{12}BU[6]) and carboxybenzyl ($(BnCOOH)_{12}$BU[6]) derivatives, as has been reported for other flexible hosts, such as cyclodextrins [24]. The distortion/collapse of these flexible hosts may suggest that a high energy is required to fill their cavities and preclude the interior vacuum state [24]. The main idea in what follows is to evaluate in silico how the conformation and the hydration pattern of each BU molecule is affected by the presence of bulky substituents and by the formation of the inclusion complexes. For this purpose, five different systems are considered: three of them taken as references, account for the solvation of each single molecule of Me_12BU[6], Bn_{12}BU[6] and $(BnCOOH)_{12}$BU[6], while in the other two the inclusion complexes of the charged host $(BnCOO^-)_{12}$BU[6] with one and two chloride ions are considered. In each case, the molecules were accommodated in a cubic box (7.5 nm edge-length) containing explicit TIP3P water molecules. All the calculations were carried out in NPT ensemble with periodic boundary conditions at a constant temperature of 298 K, and a pressure coupling of 1.0 bar, respectively, to V-rescale and Berendsen external baths. A standard time step of 2 fs was used for both equilibration and production runs. Non-bonded interactions were computed on the basis of a neighbor list, updated every 10 steps. Long range electrostatic contributions were computed using the particle mesh Ewald (PME) method [25]. For Lennard-Jones energies, a cut-off of 0.9 was applied. To obtain a starting configuration, each system was firstly subjected to an energy minimization step. Equilibrium properties, structure and dynamics of BU systems were calculated over the 35 ns simulation runs after the systems were equilibrated for 5 ns. The bonds were constrained by the LINCs algorithm [26]. The simulated time was found to be enough to provide a robust statistics for the host solvation and the last 5 ns were subjected to the standard analysis. These include time-dependent RMSD for (i) all BU atoms and (ii) a defined cavity backbone, excluding the twelve carboxybenzyl groups and geometric clustering performed to identify similar structures, sampled during the MD simulations. The algorithm for geometric cluster analysis is based on the hierarchical (top-down) approach, as described by Daura and coworkers [27], and allows evaluating the conformational prevalence of each BU structure. This simple clustering approach reduces the complexity of the structural information, revealing patterns which are hidden, at the scope of dynamic properties. To find clusters of structures in each MD trajectory,