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Boronic Acid Hydrogen Bonding in Encapsulation Complexes

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Supporting Information

ABSTRACT: Hydrogen bonding is a key determinant of much macromolecular structure in nature, but individual donor and acceptor pairs are rarely observed in solution. Their weak interactions result in nanosecond lifetimes and rapid exchange of partners. Reversible encapsulation isolates molecules in very small spaces for milliseconds to hours and allows their characterization by NMR methods. Here we report a competitive study of hydrogen-bonding functions—carboxylic acids, primary amides, and boronic acids—within a multicomponent capsular assembly. The pairwise co-encapsulation of these molecules allows the direct observation of homodimeric boronic acids and their heterodimeric complexes with carboxylic acids and primary amides. The efficiency of boronic acids as hydrogen-bonding partners derives from their adaptable structures rather than from their intrinsic acid/base properties.

Reversible encapsulation provides a means of temporarily isolating molecules in the solution phase but removed from bulk solvent.[1] The walls of the capsule are solvent substitutes and provide mechanical barriers that allow the sequestration and stabilization of otherwise reactive intermediates. Many short-lived species (and even those unknown in solution) can be characterized in capsules: phosphine carbonyl adducts,[2] labile siloxanes,[3] organometallics,[4] fragile heterocycles,[5] and white phosphorus[6] are recent examples. Pairwise encapsulation of two molecules can create complexes within complexes,[7−9] and we recently described the encapsulation and characterization of carboxylic acid dimers.[10] Here we apply this method to evaluate isolated hydrogen-bonding interactions between boronic acids and their complexes with carboxylic acids and primary amides.

There are numerous types of capsules—covalently bonded[11,12] or self-assembled with hydrogen bonds,[13−22] metal/ligand interactions,[23,24] and even hydrophobic effects,[25]—but few have the capacity to position their guests in predictable orientations. The long and narrow capsule **1.2$_4$.1** (Figure 1) does so as a result of its shape and the polar environment near the center of the structure.[26] The capsule self-assembles spontaneously from the components (cavitand **1** and glycoluril **2**) in the presence of suitable guests. The arrangement of glycolurils results in a chiral assembly, but interconversion of the enantiomeric capsules occurs, a process that can be accelerated by polar guests near the network of hydrogen bonds or by coiled guests that apply pressure to the inside of the capsule.[27,28] The capsule is long enough to accommodate two molecules of *para*-substituted

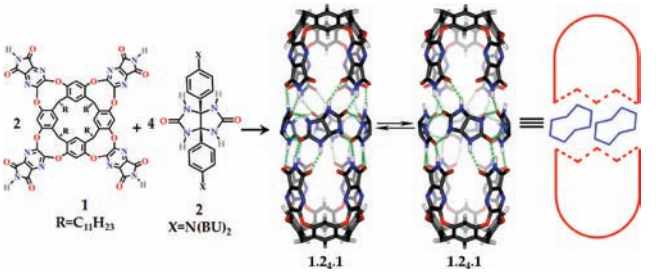

Figure 1. Chemical structures of the cavitand **1** and glycoluril **2** components and the calculated structures of the racemic extended capsule **1.2$_4$.1** (the peripheral alkyl and aryl groups have been removed for clarity). The cartoon representation of capsule used elsewhere is also shown.

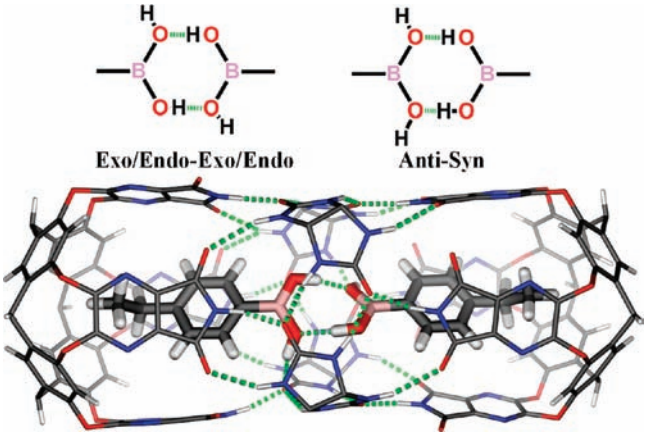

Figure 2. (Top) Structures of the exo/endo and anti/syn isomers of the H−B(OH)$_2$ hydrogen-bonded dimer. (Bottom) Energy-minimized structure (HF/6-31g*) of the exo/endo isomer of *p*-ethylphenyl boronic acid dimer in **1.2$_4$.1** (the peripheral alkyl and aryl groups have been removed for clarity).

phenyl boronic acids, molecules useful as components of self-assembled systems.[29]

The structure of the boronic acid dimer has been the subject of a recent theoretical study: the doubly hydrogen-bonded exo/endo conformer (Figure 2) was consistently calculated to be the lowest energy arrangement. The structure has planar (C_{2h}) symmetry with "spectator" and "involved" acidic hydrogens.[30] Computations also indicated that the alternate syn/anti dimer is

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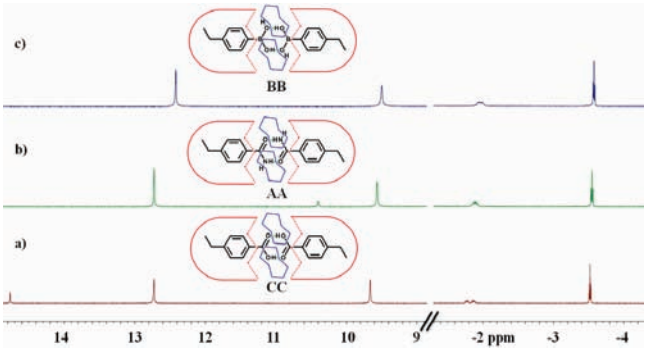

Figure 3. Partial ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}) of **1.2$_4$.1** with encapsulated homodimers of (a) *p*-ethylbenzoic acid (C), (b) *p*-ethylbenzamide (A), and (c) *p*-ethylphenyl boronic acid (B). The ethyl groups of the guests appear upfield (−1 to −4 ppm), and the N−H signals of the imides appear downfield (12.4 to 13.0 ppm). The signals between 9.5 and 9.7 ppm are the N−H's of the glycoluril **2**, and the signal at 14.77 ppm is the O−H--O of the encapsulated dimeric carboxylic acid (see SI for the complete NMR signal assignments).

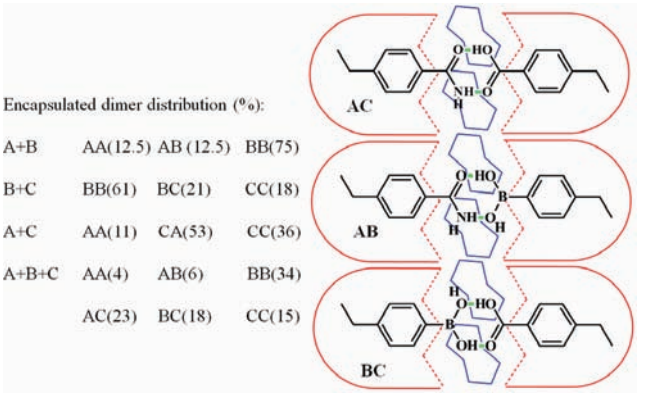

Figure 4. Distribution of encapsulated species in pairwise and three-way competition experiments with the *p*-ethyl derivatives of the amide (A), boronic acid (B), and carboxylic acid (C).

accessible in polar media (acetonitrile) and that the energetic barriers for interconversions between the dimeric structures are small. The superior stability of the exo/endo conformer is also found experimentally in the crystal structures of boronic acid homodimers (see Supporting Information (SI) for discussion).

We found that the *p*-methyl, methoxy, ethyl, and isopropyl derivatives all fit as symmetrical dimers inside **1.2$_4$.1** (Figure 3c and SI). The effect of the spectator acidic hydrogens on the interconversion of the capsular enantiomers is profound: for *p*-methylphenyl boronic acid the NH signals of the glycoluril spacer are so broadened that they are unrecognizable. This is a consequence of capsule racemization on the NMR time scale. For the *p*-isopropyl derivative, the diastereotopic methyl signals of the isopropyl group appeared as a broad doublet, likewise indicating rapid racemization of the capsule. Single peaks were observed for both the spectator and involved OH groups of the *p*-ethyl- and *p*-isopropylphenyl boronic acids at 7.72 and 8.12 ppm, respectively. Accordingly, interconversion of all isomers of the encapsulated dimer is rapid. The spectator H atoms indirectly affect the N−H signals of the imides nearby and shift them upfield; presumably, the acidic hydrogens interact with the ureido carbonyls and pull them away from the imides, weakening the network of hydrogen bonds.

The up- and downfield regions of the corresponding spectrum for *p*-ethylbenzamide in **1.2$_4$.1** are shown in Figure 3b. Both of the amide N−H signals are observed; the one involved in the hydrogen bond appears at 10.42 ppm and the spectator at 7.11 ppm. Compared to the signals of the free NH_2 at 5.0−5.5 ppm (not shown), the long-lived, encapsulated dimer results in a downfield shift ($\delta\Delta$) of ∼5 ppm. The signal of the free amide NH_2 represents the monomer, its dimer, *and* its complexes with other hydrogen bond acceptors (glycolurils) that are present in the bulk solution. These signals are averaged through rapid exchange of partners on the NMR time scale. The 2D ROESY spectrum did not show exchange cross-peaks between the involved and spectator amide NH signals.[31] However, exchange cross-peaks were observed for the two different NH signals of the glycolurils. The spectrum also shows the coalescence of the CH_2 signals of the guest, which indicates an intermediate rate of racemization of the capsule. The spectator amide hydrogens (and the carbonyl oxygen) of the guest can interact through bifurcated hydrogen bonds with the glycolurils as they rotate during the racemization of the capsule; as in the case of the boronic acid dimer, the bifurcated bonds lower the barrier to rotation of the glycolurils. Lowering the temperature slowed the racemization and sharpened the glycoluril N−H signals (see SI). The amide NH signal shifted downfield 0.1−0.2 ppm at 290 and 280 K, respectively. The spectrum of the corresponding *p*-ethylbenzoic acid is reproduced in Figure 3c.

The encapsulation of dimeric carboxylic acids, boronic acids, and carboxamides offers the opportunity to compare combinations and determine the most favorable interactions—*at least within the confines of the capsule*. We used guests of the same size (the *p*-ethyl derivatives) in order to minimize any effects of differences in "fit".

Pairwise competition experiments for the space in the capsule were performed between the amide (A), boronic acid (B), and carboxylic acid (C). Two equivalents of each guest (relative to the extended capsule) were used. Separate signals are seen for the N−H resonances of the benzamide and phenyl boronic acid, co-encapsulated with corresponding carboxylic acids (see spectra in SI). All three combinations can be seen as well as their respective homodimers. Statistically, the symmetrical homodimers are half as probable as the heterodimers with distributions of 25% and 50%, respectively. In the experiment (Figure 4), the carboxylic acid (C) and amide (A) form a heterodimer (AC = 53%), but its concentration is 4.8 times that of the under-represented amide dimer (AA = 11%) and 1.5 times that of the acid dimer (CC = 36%). This heterodimer matches the best donor with the best acceptor, yet its concentration is about twice what is statistically expected. The symmetrical carboxylic acid dimer is slightly more prevalent than what is statistically expected. The boronic acid homodimer BB is always favored, whether it competes with an acid or amide function, making this the best hydrogen-bonding pair in the series. The heterodimer of boronic acid and carboxylic acid (BC, 21%) is slightly favored over the homodimer of the carboxylic acid (CC, 18%).

Figure 4 also shows the distribution in the capsules when all three hydrogen-bonding partners are present. The same trend is seen: the best pair is the boronic acid homodimer at 34%, followed by the amide/carboxylic acid heterodimer at 23%, the boronic/carboxylic acid heterodimer at 18%, the carboxylic acid homodimer at 15%, and the amide/boronic acid hetereodimer at 6%. The amide homodimer AA is the least favorable occupant at 4%.

At first glance, the dominance of the boronic acid-containing complexes would indicate its superiority as a partner for hydrogen bonding. But statistical adjustments are necessary: the exo/endo boronic acid dimer has as many ways to form as does a carboxylic acid dimer; if syn/anti arrangements are included, then there are twice as many. In the direct competition study with all three functions present, the low concentrations of heterodimers with boronic acid show it *underperforms* as a partner for carboxylic acids and amides: it is neither a superior donor nor acceptor. The high concentration of boronic acid dimers surely reflects its statistical advantages but could also suggest a self-complementary balance of average donor and acceptor. The pK_a of benzene boronic acid is 8.8, scarcely more acidic than a phenol, but it acts as a Lewis acid.[32] In contrast, the carboxylic acid/amide pair is well-represented, as it matches the best donor and acceptor.[33]

The energetic evaluation of hydrogen-bonding interactions is inevitably context dependent, whether in enzyme interiors,[34,35] grooves of nucleic acids,[36] or synthetic receptors.[37] The space inside the center of assembly $\mathbf{1.2_4.1}$ is a different context, and one that is not easily characterized: it is not hydrophobic, since the ureido and imide groups present a wealth of dipoles and hydrogen-bonding opportunities for functions held nearby, but the polarity or dielectric is difficult to evaluate. Nonetheless, the confined space, exclusion of solvent, and prolonged lifetimes of the guests in the capsule provide means to observe the interactions of boronic acids, carboxylic acids, and primary amides. In solution, the rapid exchange of partners would thwart the dissection of these equilibria, but the simultaneous characterization of all the species showcases the potential of reversible encapsulation in physical organic chemistry.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H NMR and 2D NOESY/ROSEY spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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