

# Force and Stress along Simulated Dissociation Pathways of Cucurbituril-Guest Systems

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## SUPPORTING INFORMATION

### Analysis of interactions between water molecules and CB[7]-B5

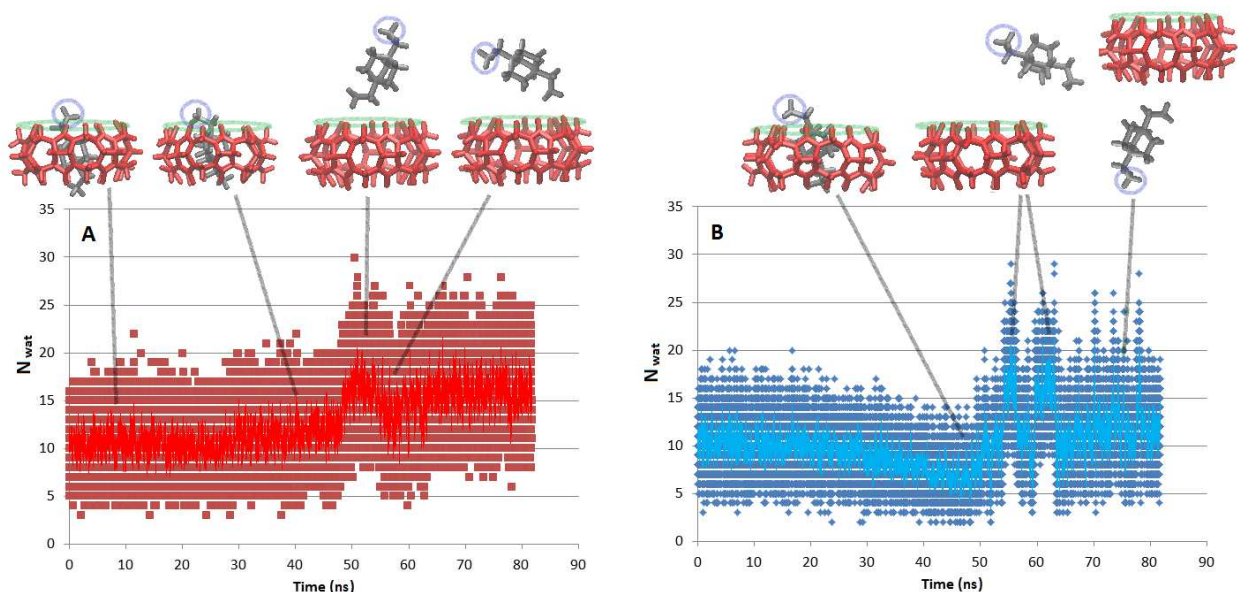
We employed the data from our CB[7]-B5 steered MD simulations in explicit solvent to analyze the interactions of the host and guest with solvent molecules. We initially examined changes in hydration structure during the dissociation process by computing the number of water molecules,  $N_{\text{wat}}$ , within a 5 Å spherical volume around the charged  $N_1$  (Fig. S1-A) and  $N_2$  (Fig. S1-B) guest nitrogens. To facilitate visualization, the moving average for each case has also been included in Figs. S1-A and B as a bright colored line plot. Representative snapshots of the host-guest complex are also included, with atom  $N_1$  and the host's top portal (orientation based on Fig. 1 of the main text) highlighted with a blue circle and a light green oval, respectively. The value of  $N_{\text{wat}}$  around  $N_1$  remains fairly constant until the guest suddenly leaves the host (~ 47 ns). In contrast, the number of water molecules around  $N_2$  decreases initially, as this nitrogen is pulled out of solvent and into the host's cavity (Fig. S1-B, first snapshot on the left).

After the guest leaves the host, at about 47 ns, it remains close the host's top portal, where it tends to adopt either a perpendicular or a parallel orientation with respect to the plane of the portal. The perpendicular orientation, illustrated by the third snapshot, from left to right, in Fig. S1-A, has an increased number of waters around  $N_1$ , while the parallel orientation,

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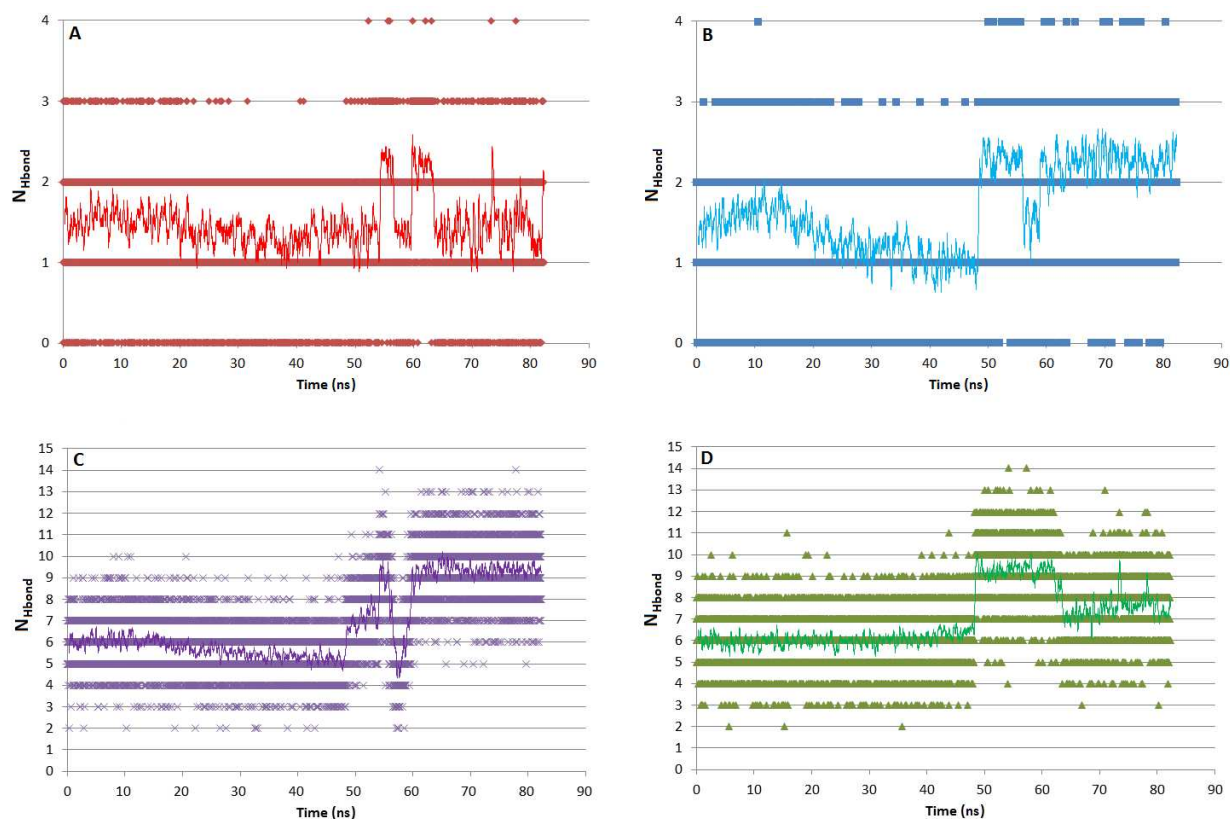
illustrated by the fourth snapshot in Fig. S1-A, has a slightly more shielded  $N_1$  atom, and a somewhat inaccessible  $N_2$  atom. Interestingly, at about 63 ns, the guest suddenly moves to the bottom portal and samples the space around it for the remaining of the simulation (see Fig. S1-B, last snapshot on the right). The two notable spikes in  $N_{\text{wat}}$  observed in Fig. S2-B at about 55 and 63 ns correspond to conformations in which the  $N_2$  is directed away from the host, and hence fully solvated. For comparison, we note that a 10 ns conventional MD simulation of the B5 molecule in TIP4P-Ew led to an average value of  $N_{\text{wat}} = 16$ , for both  $N_1$  and  $N_2$ .



**Figure S1.** Number of waters ( $N_{\text{wat}}$ ) within a 5 Å spherical volume around atom  $N_1$  (A) and atom  $N_2$  (B) vs. time for steered MD simulations of the CB[7]-B5 complex in explicit solvent. Above these plots, we have included representative conformations of particular instances along the process, corresponding to the times pinpointed by the gray lines.

We also used the *g\_hbond* tool in GROMACS, with default parameters, to compute the number of hydrogen bonds ( $N_{\text{Hbond}}$ ) between water molecules and the  $N_1$  (Fig. S2-A) and  $N_2$  (Fig. S2-B) atoms, as well as between water molecules and the host's top (Fig. S2-C) and bottom (Fig. S2-D) portal oxygens. A moving average for  $N_{\text{Hbond}}$  is also included in each plot. Overall, it is evident that the behavior of  $N_{\text{Hbond}}$  for  $N_1$  and  $N_2$  is consistent with that of  $N_{\text{wat}}$  in graphs S1-A and B, respectively. Not surprisingly, Figures S2-C and S2-D show that  $N_{\text{Hbond}}$  tends to

increase for both portals once the guest exits the host. The sharp dip in  $N_{\text{Hbond}}$  at around 58 ns in Fig. S2-C corresponds to the period where the guest lies flat across the top portal, preventing it from interacting with water. The guest is later driven towards the bottom portal, resulting in a decrease in  $N_{\text{Hbond}}$  for the bottom oxygens and an associated increase in  $N_{\text{Hbond}}$  for the top oxygens. For comparison, 10 ns MD simulations in explicit solvent for free B5 and CB[7], led to an average value of  $N_{\text{Hbond}} = 2$  for  $N_1$  and  $N_2$ -water interactions, and  $N_{\text{Hbond}} = 9$  for the top and bottom oxygens-water interactions. The analysis portrayed in Fig. S2 was complemented by the calculation of hydrogen bond maps (not shown) showing the frequency with which all water molecules interact with each of the four groups studied. These maps did not indicate the presence of any long-lived hydrogen bonds, suggesting that no waters remain embedded within the complex during the course of the simulation.



**Figure S2.** Number of hydrogen bonds ( $N_{\text{Hbond}}$ ) between water and the  $N_1$  (A) and  $N_2$  (B) ammonium groups, and the top (C) and bottom (D) portal oxygens.

Finally, we explored the ability of water molecules to form bridging interactions between the guest's ammonium groups and the carbonyl oxygens of the host's portals during the course of the dissociation. In particular, we calculated the number of water-mediated hydrogen bonds ( $N_{\text{watmed}}$ ) between the  $N_1$  ammonium and the top oxygens, and the  $N_2$  ammonium and the bottom oxygens, for the initial 0-60 ns period during which the guest remains closest to the host; snapshots for analysis were extracted every 10 ps, leading to a total of 6000 structures. Interestingly, these interactions are rarely observed ( $N_{\text{watmed}} = 57$  for the top portal, and  $N_{\text{watmed}} = 21$  for the bottom portal), suggesting that the insertion of bridging water molecules plays only a minor role in the forced dissociation of this host-guest complex. The notable infrequency of water bridges, which are not explicitly accounted for in implicit solvent models, is also consistent with the equivalence observed between the explicit and implicit solvent dissociation mechanisms, and supports the use of GBSA as a suitable solvent model here.