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Project Title: *Understanding Host-Guest Dynamics of Supramolecular Assemblies Relevant to Potential Applications in Catalysis*

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Overview. We are carrying out a theoretical and computational investigation to address the question *What determines the dynamical timescales for host-guest supramolecular assemblies?* The long-term objective is to understand the factors that affect the dynamics of assembly opening, closing, guest exchange, and host-guest rearrangements important for catalytic applications. Host-guest supramolecular assemblies hold significant promise as potential catalyst structures: This project is focused on the resorcin[4]arene and pyrogallol[4]arene hexameric assemblies that are held together in weakly polar solvents by hydrogen bonding (Fig. 1). It has been demonstrated that these assemblies can encapsulate reactants, lower the free energy of activation for a desired chemical transformation (with or without an additional catalyst), and release the nascent products.

Progress. The majority of our efforts have focused on the resorcinarene hexameric assembly that forms in wet chloroform and includes in its structure eight water molecules. The role of these water molecules has not been fully understood and our first efforts aimed at elucidating it. Specifically, we used molecular dynamics (MD) simulations to investigate the location of the excess waters (those in the solution but not involved in the assembly structure) relative to the capsule. The water diffusion coefficient was used as the key observable because it was measured *via* NMR in solutions of the resorcinarene hexameric assembly as a function of water content¹ in measurements that likely represent the most detailed interrogation of water interactions with the assembly.

Our MD simulations reproduced, both qualitatively and quantitatively, the measured behavior of the average diffusion coefficient of all the waters present as a function of water content in the chloroform solution.² The water molecules are found to diffuse more quickly overall as the the number of waters per hexameric assembly is increased. However, this is *not* described by a model in which water molecules are either part of the assembly structure or free in the chloroform solution, as has been frequently assumed before. Rather, a significant number of additional, non-structural waters are attached to the assembly. We find that both our simulations and the NMR measurements¹ are well described by an adsorption isotherm model that is characterized by the total number of waters bound to the assembly and the free energy of binding. Fitting the model to the data predicts approximately six water molecules are hydrogen bonded to the assembly, in addition to the eight that are part of the capsule structure. More importantly, these results demonstrate how measured diffusion data can be used to determine water association with the assembly.

The simulations can also be used to directly determine the number of waters attached to the

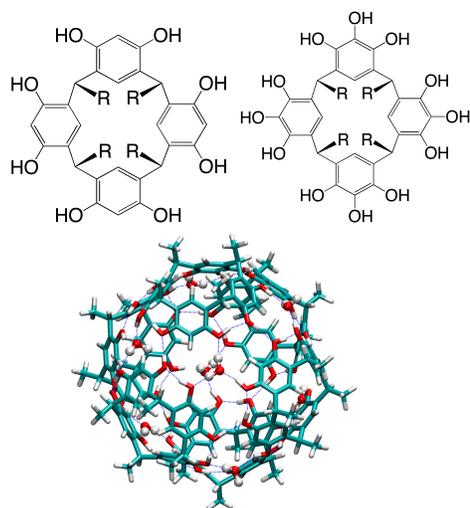


Figure 1: Monomers in the two hexameric assemblies under study: resorcin[4]arene (left) and pyrogallol[4]arene (right) and resorcinarene capsule structure (bottom)

assembly and their location. The total number of capsule-associated waters is fully consistent with the values derived from analysis of the diffusion coefficients. Further, three populations of water molecules are identified in addition to those in the structure of the assembly. The most favorable location for waters is encapsulated within the assembly, followed by direct hydrogen bonding to the structural waters. Interestingly, additional waters are not found to significantly hydrogen bond to the resorcinarene monomers but only to the structural waters, which are always observed to be present in the assembly. Finally, at high water contents ($\gtrsim 20$ waters per assembly) transient long hydrogen-bonded chains of waters are found that can involve as many as seventeen water molecules.

The MD simulations have also been used to examine the dynamics of the water;³ it was previously observed that water exchange between the assembly and solution is fast on the NMR timescale.¹ We find that water molecules are indeed rapidly exchanging between encapsulated, structural, attached, and long-chain positions. The timescales range from a few tens of picoseconds – *e.g.*, for encapsulated waters to move into one of the eight positions in the assembly structure – to a few nanoseconds for a water free in solution to hydrogen bond to the assembly. These simulations thus provide a detailed picture of the behavior of water molecules in the capsule environment, one that shows them as plentiful and rapidly exchanging between sites both inside and outside the assembly. We have also found that the populations and dynamics of water are affected by the properties of an encapsulated guest molecule, as has been suggested from NMR studies.⁴

As a comparison, MD simulations were carried out for the pyrogallolarene hexameric assembly. This capsule, by virtue of its additional hydroxyl groups does not require water for formation and, in fact, can be destabilized by the presence of water. Our simulations show that significantly fewer water molecules ($\sim 1 - 2$) attach to the pyrogallolarene capsule compared to the resorcinarene one (~ 6). Moreover, we have observed water encapsulation within the pyrogallolarene assembly that involves an opening in the hydrogen-bonded “seam” between two monomers.

Host-guest exchange in the resorcinarene assembly occurs on timescales that are long relative to feasible MD simulations. However, exchange of solvent molecules between the solution and capsule interior is observed when hydrogen bonding interactions are artificially weakened; these simulations are being used as the starting point for Hamiltonian replica exchange and transition path sampling simulations to identify the mechanisms and determine the timescales for guest encapsulation and release in both the resorcinarene and pyrogallolarene assemblies.

This project has opened up an exciting new avenue for research within our research group. The graduate students involved have gained valuable experience in MD simulations, rate theory, and numerical methods as well as in mentoring undergraduates involved in the work.

References

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