

Summary

Supramolecular chemists have realized elaborate constructs that spontaneously organize from component molecules using dynamic intermolecular bonds. The analysis of these supramolecular constructs presents new challenges to experimental methods for structure elucidation by NMR and X-ray crystallography, especially when such structure become larger. The synthesis and design of new constructs has relied upon a trial-and-error approach guided by a few successful design principles, and structural information for such iterative processes is essential. Innovative techniques are required to reveal the structure of supramolecular constructs—including ill-formed byproducts and kinetic trapped species—that arise from the self-assembly of relatively simple molecular components. Investigations into self-assembly using *in silico* approaches such as molecular dynamics simulations (MD) or quantum mechanical calculations (QM) provide structural information that may be validated by experiment. This combination of computation and experiment may provide new avenues to develop these constructs from component molecules based on the predictive power of physics-based models.

In parallel to these developments, researchers in field of homogeneous catalysis increasingly use supramolecular approaches to exert new control over the reactivity of catalytic transition-metal complexes. For example, transition-metal catalysts incorporated within a supramolecular host (i.e., as a host–guest complex) may exhibit new reactivity and selectivity arising from the host. The changes in selectivity or reactivity of a reaction with varying host, substrate, or catalyst can hint at useful structural features of the host construct. However, the challenges in structure elucidation of supramolecular constructs by experimental methods are substantial when transition-metal catalysts and/or substrates are involved. Furthermore, the transient structures of the catalytic mechanism (that may be key to the observed changes in reactivity) are difficult to observe by typical X-ray or spectroscopic methods. This lack of structural knowledge typically leads to a trial-and-error approach to combine catalyzed reactions with host constructs until successful examples are found which can then be elaborated upon. Here too, *in silico* approaches can provide new avenues to investigate the environment of catalysts and substrates confined within supramolecular hosts, and also identify any interactions that may be relevant catalytic reactivity.

These *in silico* approaches provide well resolved structural information on an electronic (QM) or atomic levels (MD). Moreover, these methods enable the exploration of supramolecular constructs and their interactions with incorporated molecules via time-resolved structural information (trajectories) that reveal dynamic processes that are relevant to both supramolecular chemistry and homogenous catalysis. Importantly, these modeled trajectories provide data about observable phenomenon (i.e., host–guest complexation, catalytic activity, changes in diffusion) that are accessible by current experimental approaches. The combination of computational modelling and experimental studies is the heart of this thesis as a powerful tool to understand dynamics within supramolecular constructs.

In **Chapter 1**, we discussed the application of supramolecular chemistry in homogeneous catalysis, and elaborate on physics-based *in silico* approaches used in current research. Specifically, we detailed the motivation to use supramolecular constructs to exert new level of control on incorporated transition-metal catalysis via construct–catalyst and construct–substrate interactions. In the traditional design of transition-metal catalysts, where reactivity is controlled by electronic metal–ligand interactions while simultaneously steric substrate–ligand interactions evoke selectivity. Following the supramolecular approach, the selectivity of the catalytic center may be further influenced by construct–substrate interactions, enabling new reaction selectivity from existing transition-metal catalysts. We illustrated this supramolecular approach with known examples featuring resorcin[4]arene capsules and coordination cages used for both organic and transition-metal catalyzed transformations. We then discussed reports demonstrating the use of *in silico* approaches, QM or MD, to study the self-assembly or catalytic application of these same supramolecular constructs. These computational studies demonstrate how *in silico* methodology can provide high-resolution and dynamic structural information that rationalizes observed supramolecular and catalytic behavior of these constructs.

In **Chapter 2**, we demonstrated how pyridyl-ligand substitution at palladium (II) metal centers is facilitated by solvent or anion molecules present in solution. This simple reaction is critical to the self-assembly of coordination cages (and similar constructs) where slight variations in solvents and anions present in the reaction have significant effect on the efficacy of the assembly process. We studied this reaction with a model palladium (II) complex using an NMR-based thermochemical approach to quantify the influence of solvents and anions on activation energy (E_a) for pyridyl-ligand substitution. The proposed mechanism was supported by absorption spectroscopy and *in silico* approaches.

Specifically, we used QM calculations to determine the electrostatic volume (V_{esp}) of anions which correlated to an anion's ability to facilitate ligand substitution better than existing measures of anion coordination. The interactions between ions and the complexes were also studied using MD simulations that demonstrated how polar solvents diminished or abolished interactions between the anion and palladium (II) complex. These MD findings rationalized the observed effect of non-coordinating aprotic solvents to enable anion-facilitated substitution. Additional QM calculations were then used to interpret the spectral observations to discriminate between anion- or solvent-coordinated intermediate complexes in the pyridyl-ligand substitution mechanism. This study is a robust description of pyridyl-ligand substitution with significant implications for protocols used in the self-assembly of palladium-based coordination cages and similar supramolecular constructs.

In **Chapter 3**, we investigated the outcome of self-assembly for palladium-based coordination cages using an MD-based approach. Notably, we demonstrated a semi-autonomous QM-based methodology to develop forcefield parameters for MD simulations that are more accurate than semi-empirical or tight-binding calculations typically employed to study large supramolecular assemblies. We leveraged the accuracy of this approach to estimate the relative energy of possible supramolecular constructs, and the distribution of product coordination cages arising from self-assembly. This MD-based approach was able to predict the formation of a novel cage topology featuring 15 palladium (II) centers that was then identified by experimental synthesis. The applicability of this MD-based approach was further validated for cages formed from 2 dissimilar ligands, where the predicted distribution of product coordination was again experimentally observed. Lastly, using the finely resolved structural and thermodynamic information arising from MD and QM calculations we could uncover how steric hindrance within a ligand influences self-assembly through long-range interactions.

Overall, these findings demonstrate the applicability of MD-based approaches in the study of larger supramolecular constructs over longer time scales. Both the MD models of coordination cages and the approach for generating accurate forcefields were later leveraged to study catalytically active supramolecular assemblies (see below).

In **Chapter 4**, we demonstrated that the self-assembly of coordination macrocycles from their oligomer intermediates is driven by entropic contributions arising from solvent interactions. This phenomenon was further generalized to the formation of large cuboctahedral ($M_{12}L_{24}$) coordination cages with implications for other self-assembled supramolecular constructs.

Using thermochemical NMR measurements, we found that entropic contributions drove the formation of macrocyclic products from an observed oligomer intermediate despite the incorporation of a larger number of components. Then, using an extension of our earlier MD-based approach (discussed in Chapter 3) we considered entropic contributions arising from the incorporation of components (i.e., translational, rotational, and vibrational changes) in addition to those from solvation. By including the solvation dependent contributions our MD simulations reproduced the experimentally observed free energy differences, indicating that solvation influences play a large role in the self-assembly of constructs (beyond their smaller role discussed in Chapter 2). We applied this approach to the study of larger coordination cages, where we observed a similar entropic driving force from poorly-defined reticular intermediates to observed products.

These findings demonstrated how solvation entropy, which has been mostly overlooked in literature, drives the formation of coordination constructs including both macrocycles and spherical cages, providing critical insight into the self-assembly of these and similar constructs. Furthermore, this elaboration on our previously developed computational approaches enables the prediction of both kinetic and thermodynamic products of self-assembly which may be leveraged in future studies.

In **Chapter 5**, we observed a water-dependent expansion of hexameric undecyl-resorcin[4]arene capsules from MD simulations arising from a thermodynamically favorable and temporally persistent incorporation of 7 additional water molecules along the capsule's edge. This finding was further corroborated by NMR measurements of water association as a function of water concentration. Critically, these NMR spectra revealed further changes in the hydrogen bond network, which upon further experimental investigation suggested that the expanded form of the capsule was significantly more acidic. Remarkably, the catalysis of a novel Diels–Adler cycloaddition by the capsule corresponded to the formation of this expanded form as the kinetically active species. The findings of this study suggest that widely reported use of this capsule for organic transformations and transition-metal catalysis may be modulated by the structural changes evoked by increased hydration of the capsule's hydrogen bond network.

In this thesis, we have highlighted the use of thermochemical analyses and physics-based simulations to understand the dynamic structure of supramolecular constructs frequently used in catalytic applications. We have demonstrated that thermochemical investigation of self-assembly processes can reveal the specific roles of solvent and anion molecules in the self-assembly process at different scales. Further, we have demonstrated how thermodynamically-accurate MD approaches can be developed to study the products and intermediates of self-assembly. These experimental and *in silico* approaches can be further leveraged to identify structural changes in supramolecular assemblies, and then realize the effect of these changes on catalytic processes. Using the combination of these experimental and *in silico* approaches, we can better understand the synthesis of these supramolecular assemblies and explore the environment of transition-metal catalysts in confinement. The versatile techniques developed in this thesis will further assist the preparation of self-assembled supramolecular constructs by design, and their use in a variety of applications including catalysis.