ABSTRACT: The hexameric undecyl-resorcin[4]arene capsule (C11R6) features eight discrete structural water molecules located at the vertices of its cubic superstructure. Combining NMR spectroscopy with classical molecular dynamics (MD), we identified and characterized two distinct species of this capsule, C11R6-A and C11R6-B, respectively featuring 8 and 15 water molecules incorporated into their respective hydrogen-bonded networks. Furthermore, we found that the ratio of the C11R6-A and C11R6-B found in solution can be modulated by controlling the water content of the sample. The importance of this supramolecular modulation in C11R6 capsules is highlighted by its ability to perform acid-catalyzed transformations, which is an emergent property arising from the hydrogen bonding within the superstructure. We show that the conversion of C11R6-A to C11R6-B enhances the catalytic rate of a model Diels–Alder cyclization by 10-fold, demonstrating the cofactor-derived control of a supramolecular catalytic process that emulates natural enzymatic systems.

INTRODUCTION

Supramolecular catalysis derives inspiration from enzymes, translating natural features into synthetic systems to attain higher levels of control in chemical processes. Approaches toward bioinspired supramolecular catalysis include the biomimicry,4−6 second coordination sphere design,5 7 and confinement of the catalytic site.8−14

Along these lines, the positioning of catalytic active sites within well-defined capsules has been demonstrated to enable the control of catalyst properties to promote selective catalytic transformations.6,7 In natural systems, enzymatic activity that enables the self-steering of catalytic processes necessary for metabolism can be modulated via allosteric modifications by physiochemical inputs. Although it is an intrinsic feature of natural systems, analogous modulation of catalyst properties in synthetic mimics are rare.15−18

It is now more than 30 years ago that the Aoyama group described the host–guest chemistry of resorcin[4]arenes in nonpolar organic solvents.19−22 As further characterization developed, the hexameric nature of these capsules was realized and its capacity for host–guest interactions were extensively characterized.23−38 Analogous to an enzyme, C11R6 exhibits catalytic function from the elevated Brønsted acidity emerging from its supramolecular structure.39 Illustrated in Figure 1, this capsule is formed in nonpolar solvents (e.g., chloroform) through the self-assembly of six facial monomers in a cubic arrangement, featuring eight water molecules (one per vertex).23 The edges of C11R6 are held together by hydrogen-bond network edges between adjacent facial monomers, with each end point capped at the vertex with a water molecule, completing the cubic structure.23

The hydrogen-bond network of C11R6 results in the enhanced Brønsted acidity beyond that of the individual monomer units.39 This feature has driven the application of C11R6 as a supramolecular, organic Bronsted acid catalyst for chemical transformations under mild conditions.40−43 In addition, the hydrogen-bond rich environment of the internal cavity within C11R6 has been utilized as a supramolecular organocatalyst,44−46 demonstrating a host-selective reactivity based on substrate size, and substrate–bond activation via supramolecular interactions. The use of a supplemental protic acid cocatalyst (typically HCl) extends the scope of C11R6 activity,47−49 notably for application toward facile synthesis of high-value terpene derivatives.50−63 Further reactivity has been demonstrated in host-catalyzed Diels–Alder cyclization.64

Beyond the intrinsic Brønsted acidity of C11R6, this supramolecule possesses an internal cavity (ca. 1400 Å3),23 permitting the encapsulation of transition metal catalysts65 or organic catalysts66−71 within its cavity. In these instances, the internal surface of the capsule serves as a second coordination-sphere to modulate or enhance catalytic function.67
Both the acidity and host-capacity of \( \text{C}^{11}\text{R}_6 \) are derived from its structure\(^{23,39}\). Recent work by Payne and Oliver have demonstrated structural modification of \( \text{C}^{11}\text{R}_6 \) by the incorporation of alcoholic solvent molecules into the hydrogen bond network\(^{72}\), complementing previous studies by Cohen\(^{73-75}\) and Schnatwinkel\(^{76}\), which featured similar inclusion of long chain alcohols into the hydrogen-bond network. Interestingly, Katiyar has reported the association of free water to the capsule’s hydrogen-bond network\(^{77,78}\), beyond the 8 molecules needed for capsule assembly\(^{23,31,32}\). Studies by Merget suggest that the presence of additional water may impact the catalytic activity of \( \text{C}^{11}\text{R}_6 \) capsules in acid-promoted cyclization of terpenes\(^{60}\). Together these findings suggest that polar molecules such as water may act as cofactors able to modulate the structure and acidity of \( \text{C}^{11}\text{R}_6 \) analogous to the allosteric control of enzymes (e.g., cytochrome p450 oxidases, nitric oxide synthases, etc.). Understanding that these structural changes would provide insights into the previously observed water-dependent catalytic behavior and fine control the capsule’s catalytic activity.

In this work, we investigate the structural changes of \( \text{C}^{11}\text{R}_6 \) capsules through classical molecular dynamics (MD) simulations, which is further supported by \(^1\text{H} \) NMR spectroscopy. Using MD, we find that \( \text{C}^{11}\text{R}_6 \) interconverts between two assemblies as summarized by Figure 2. The \( \text{C}^{11}\text{R}_6\text{-A} \) assembly features 8 water molecules at the vertex positions—in line with previous reports of \( \text{C}^{11}\text{R}_6 \) structure\(^{23}\)—while \( \text{C}^{11}\text{R}_6\text{-B} \) has 14–15 water molecules, 6–7 of which spontaneously incorporate into a single edge of the cubic suprastructures, referred to here as “incorporated water” (Scheme 1). This computational finding is supported by NMR studies of water association, revealing a water-dependent equilibrium between the two capsule species differing significantly in their hydrogen-bond network. Differences between \( \text{C}^{11}\text{R}_6\text{-A} \) and \( \text{C}^{11}\text{R}_6\text{-B} \) assemblies are substantiated by \(^3\text{P} \) NMR chemical shifts of an encapsulated phosphine oxide, revealing different internal acidities quantified
by their Guttmann–Beckett acceptor number (AN). This difference in internal acidity allows the rate modulation of C11R6 catalyst Diels–Alder cycloaddition of maleimide and sorbic alcohol, demonstrating novel control of an abiotic homogeneous catalytic process.

RESULTS AND DISCUSSION

MD Simulations Reveal Distinct Species. Simulations containing explicitly solvated C11R6 with a total of 8–24 explicit water molecules were propagated as molecular dynamics trajectories for a total of 10 μs using optimized force field parameters (Figure S1). Unfortunately, simulations featuring randomly placed water molecules and undeckyl-resorcin[4]arene monomers (C11R6) failed to self-assemble over several μs of MD propagation (results not reported). Therefore, we found it necessary to include the 8 structural water molecules, placed at the vertex positions of the capsule, while the remaining water molecules were positioned randomly in the periphery of the capsule.

In simulations containing 8–12 water molecules, we observe the external attachment of free water to the C11R6 in line with previous reports. Simulations containing ≥14 water molecules reveal 6 additional incorporated water molecules along a single edge of the hydrogen-bond network of the C11R6 capsule (Scheme 1), as depicted in Figure 2b. Although these incorporated water molecules are highly organized and an integral part of the hydrogen bond network (Figure S16), single water molecules still exchange rapidly with water molecules from the bulk solvent and the 8 structural waters needed to form the capsule. The mobility of the incorporated water is highlighted by the concerted migration between the hydrogen bond edges of the capsule. This migration phenomenon was qualitatively observed as a rare event in our MD simulations (Figure S15), but occur at a sub-microsecond time scale.

The incorporation of additional water into the edge of the hydrogen bond network results in a breakage of the hydrogen bond between adjacent C11R6 faces, altering the connectivity of the supramolecular system. This change in connectivity and composition distinguishes C11R6-B from the typical C11R6-A assembly. Analysis of hydrogen-bonding in our MD trajectories (Figure S2) reveal a minimum of 6 extra incorporated water molecules are required to form C11R6-B.

Energetic analysis of the MD data using GIST (Figure 2a) distinguishes between both attached water and the incorporated water we observe in C11R6-B. While GIST does not provide complete free energy differences between C11R6-A and C11R6-B, it is useful in the analysis of favorable water structures found in our MD simulations. In simulations containing 8–12 water molecules the attached water is observed. Interestingly, the GIST-determined ΔA is similar to previously reported values (ca. ~2.0 kcal mol⁻¹), and from our analysis this is driven entirely by a favorable water–water interaction (Figure 2a, ΔUwater-water). The inclusion of water along the hydrogen bond edge is optimal in the presence of 14 water molecules, where an additional favorable water-capsule interaction (Figure 2a, ΔUwater-C11R6), resulting in a very favorable association (ΔA = −6.3 kcal mol⁻¹). While the incorporation of further water molecules within the suprastructure is possible, it incurs an increasing penalty from internal energy (Figure 2a, ΔU) and system entropy (Figure 2a, −TΔS).

The specificity of C11R6-B to incorporate 6 water molecules is a "goldilocks" number, originating from the required size of the hydrogen-bond network needed to fill a capsule edge (Figure 2b), resulting in favorable internal energy (Figure 2a). These "incorporated water" molecules are more mobile than their "structural water" counterparts, and are not as strongly localized. These simulations suggest that C11R6 is found in only two forms—C11R6-A containing 8 water molecules and C11R6-B containing 14 water molecules—and the ratio between the two may depend on water content.

1H NMR Identification of C11R6-A and C11R6-B. The formation of C11R6-A and C11R6-B was investigated by 1H NMR, by measuring spectra of C11R6 solution at various concentrations of water (44.12–103.01 mM; for details see Supporting Information (Figure S4). Long recycle delays (25 s) were necessary to obtain quantitative spectra for both water (T1 = 0.7–0.9 s, data not shown) and C11R6 (T1 = 1.39 s, data not shown).
Further characterization of the capsule using $^1$H NMR (Figure S3), DOSY (Figures 3b and S4), $^{31}$P NMR Investigation of Structure-Dependent Acid-Ity, and solution state FTIR (Figure S5) indicate that both assemblies are hexameric assemblies with a similar Stokes radius (16.6 Å) at [H$_2$O] = 44 and 103 mM consistent with previous reports of C$_{11}$R$_6$ capsule structure.23–38

The single observed peak of water (Figure 3) indicates that it is in a state of fast exchange between a free state in the bulk solution and a bound state, incorporated into the C$_{11}$R$_6$ capsule (Figure S14).82 As previous reports detail, the available water is completely incorporated into the cage at low (i.e., 44 mM) water concentrations;31–33,77 therefore, the measured chemical shift ($\delta = 5.1$ ppm) can be attributed to the structural water (Figure 1), as opposed to the free H$_2$O water-saturated chloroform.81

As the observed chemical shift is time-averaged,80 the proportion and quantity of water associated with C$_{11}$R$_6$ ($B_{wat}$) was determined directly from $^1$H NMR spectra (Figure 3a).

Figure 4 shows the total number of water molecules associated with C$_{11}$R$_6$ increases linearly with the proportion of C$_{11}$R$_6$-B ($\theta_B$) in the sample, with the slope showing an additional 7.27 ± 0.26 water molecules are incorporated per C$_{11}$R$_6$-B formed. Thus, combined with the 8 structural waters native to C$_{11}$R$_6$, a total of 15 water molecules are associated with C$_{11}$R$_6$-B. From our MD simulations (Figure 1) we surmise that these additional water molecules are incorporated into the hydrophobic bonding network of the capsule. This number is in agreement with MD models (Figure 2) that predict a minimum of 14 water molecules for the formation of C$_{11}$R$_6$-B (Figure 2). The water-dependent conversion between C$_{11}$R$_6$-A and C$_{11}$R$_6$-B was fit using an empirical model (Figure S13) to enable estimation of the proportion of C$_{11}$R$_6$-B capsules ($\theta_B$) via water content.

$^{31}$P NMR Investigation of Structure-Dependent Acid-Ity. Many catalytic applications of C$_{11}$R$_6$ rely on the intrinsic acidity derived from its supramolecular structure.39 The 33 Hz downfield shift of the C$_{11}$R$_6$-B phenolic protons (Figure 3a) suggest an increased acidity (compared to C$_{11}$R$_6$-A),82 a feature which is further supported by their apparent diffusivities observed by DOSY (Figure 3b).

![Figure 4](https://doi.org/10.1021/jacs.1c04924)  
*Figure 4. Plot of the total number of associated waters ($B_{wat}$) and proportion of C$_{11}$R$_6$-B capsules ($\theta_B$) determined from $^1$H NMR measurements (Figure 3a). The association of an additional 7.27 ± 0.26 water molecules concomitant to conversion is determined from the slope of the linear fit (red).*
Previous studies have shown that the Brønsted acidity of C11R6 assemblies can be modulated by changes in the solvent media.39 Unfortunately, these studies do not provide a clear understanding of the specific interactions that contribute to this acidity.

Therefore, we investigate the ability of structure-dependent acidity to modulate the interaction strength with tri-n-butylphosphine oxide (Bu3PO) as guest through 31P NMR (Figure S5).83,84 The encapsulation of Bu3PO was readily confirmed by 1H NMR, showing the development of broad upfield peaks (δ = -2.0–0.5 ppm), typically observed for encapsulated guests.24–38 The binding of Bu3PO within the capsule was further evidenced by 31P DOSY measurements (Figure S12), with similar diffusion for the C11R6 host and upfield peaks (log D = -9.0, see Figure 3b).

A downfield chemical shift in 31P NMR is expected when a Bu3PO forms a hydrogen-bond adduct with another species, such as when encapsulated within C11R6 and the degree of this shift is proportionate to the acidity of the hydrogen-bond donor.38,44 Three peaks (31Pδ ≈ 55.0–65.0 ppm) were consistently observed in the 31P NMR spectra of the encapsulated Bu3PO (Figures S9 and S10). The upfield peak (31Pδ ≈ 55.0–64.0 ppm) was assigned to the free Bu3PO by observed correlations to the protons of the free species by 1H–31P HMBC (Figure S11). A low intensity peak (31Pδ ≈ 64.0–65.0 ppm) was observed in all spectra, with a low intensity that waned with increasing water content. This spectral feature is particularly evident at a minimal water concentration (44.18 mM, Figure S8), where the majority of the Bu3PO (3.50 mM) was observed by 31P NMR at two concentrations, 3.50 mM (black) and 24.00 mM (red) in the presence of C11R6. Spectra were obtained at water contents spanning 43.76–110.19 mM (3.50 mM Bu3PO) and 43.05–86.53 mM (24.00 mM Bu3PO), which were subsequently converted to the proportion of C11R6-B (θB) by an empirical model (Figure S13). Inset, a 31P NMR spectrum showing peaks corresponding to encapsulated (▼, green) and free (▲, blue) Bu3PO.

Despite these limits in observation, the strength of the interaction between C11R6 and Bu3PO can be correlated to the downfield chemical shift of the single observable peak (31Pδ = 64.0–60.0 ppm). The strength of the interaction between Bu3PO and C11R6 can be determined by modulating the Brønsted acidity through changing the content of the sample (i.e., varying the water content of the sample) as shown in Figure S5. Two sets of experiments were performed where the C11R6-A/C11R6-B ratio was modulated through controlling water content (44.18–110.19 mM and 43.05–86.53 mM, respectively) in the presence of either a low (3.50 mM) or high (24.00 mM) concentration of Bu3PO. While the high concentration is analogous to catalytic conditions, at lower concentrations the Bu3PO probe selectively associates to the stronger interacting (i.e., more acidic) assembly. From these contrasting measurements we determine that the environment of C11R6-B is more acidic than C11R6-A, which may enhance its catalytic activity. We rationalize the increased acidity of C11R6-B by the increased availability of protons within the capsule from the weakly bound incorporated water molecules (Scheme 1).

Similar to 4 of the structural water molecules of C11R6-A,39 the 7 incorporated water molecules found in C11R6-B are capable hydrogen-bond donors, and may also act as acids stabilized by the edge hydrogen-bond network (Figure S16).

The Guttman–Becket acceptor number (AN) is a measure of Lewis acidity that quantifies the differences in acidity between the two capsules, and allows comparison of acid catalysts in solvent media.84 On the basis of 31P NMR spectra obtained at a minimal water concentration ([H2O] = 44.18 mM, Figure S8), we have estimated the Lewis acidity of C11R6-A (AN = S1), similar to B(OMe)3 (AN = S1).38 By extrapolating the chemical shift difference observed with Bu3PO (3.5 mM, Figure S5), we infer that exchange between this minor species and the observed major peak is unlikely based on the diverging chemical shift. On the basis of the low intensity of the 31P signal, we surmise that this spectral feature does not correspond to the free or encapsulated Bu3PO, and its identity is unlikely to interfere with measurements of the C11R6 capsule’s internal acidity. The remaining peak was attributed to the C11R6-associated Bu3PO (31Pδ ≈ 60.0–64 ppm) based on its apparent intensity (Figures S9 and S10). All three peaks were observed to move in a concerted fashion with changes in water content, which we ascribe to changes in bulk dielectric of the solvent medium.85

The free and encapsulated Bu3PO afford distinct peaks in slow exchange (Figure S5, inset). Similar to observations made with 1H NMR (Figure 3), differentiation between phosphate oxide encapsulated within C11R6-A and C11R6-B was not observed by 31P due to the similarities of the magnetic environments experienced by the phosphorus nuclei. Due to this similarity, the shift of the observable peak corresponds to the time weighted average of the Bu3PO encapsulated within C11R6-A and C11R6-B (see Figure S14a for an example of the exchange of indistinguishable nuclei).80 Further complications arise as a phosphate oxide guest within C11R6-A or C11R6-B may exchange hydrogen bonding partners within the capsule at a time scale faster than NMR measurement,86 resulting in a single observable peak with a shift that is the time weighted average of the hydrogen bonding states (see Figure S14b for a detailed example of the exchange of a rapid process). The result of these exchange processes is a single observable peak corresponding to Bu3PO encapsulated by C11R6-A or C11R6-B, in all states of hydrogen bonding (see Figure S14 for a detailed explanation).80

Figure 5. Chemical shift difference between free and encapsulated Bu3PO observed by 31P NMR at two concentrations, 3.50 mM (black) and 24.00 mM (red) in the presence of C11R6 (5.38 mM). Spectra were obtained at water contents spanning 43.76–110.19 mM (3.50 mM Bu3PO) and 43.05–86.53 mM (24.00 mM Bu3PO), which were subsequently converted to the proportion of C11R6-B (θB) by an empirical model (Figure S13). Inset, a 31P NMR spectrum showing peaks corresponding to encapsulated (▼, green) and free (▲, blue) Bu3PO.
estimate the Lewis acidity of C11R6-B assemblies (AN = 68 ± 1), similar to TiCl4 (AN = 70).36

**Structural Modulation of the C11R6-Catalyzed Diels–Alder Cycloaddition.** We investigated the catalytic activity of the two C11R6 assemblies in the Diels–Alder cycloaddition of maleimide and sorbic alcohol to produce 4-(hydroxymethyl)-7-methyl-3a,4,7,7a-tetrahydro-1H-isoinodole-1,3(2H)-dione (Figure 6, inset). The Diels–Alder reaction was explicitly chosen as a probe for the structure-dependent catalytic activity of C11R6 as it proceeds without the generation of water or acid as a byproduct. Specifically, catalysis was performed at different water concentrations ([H2O] = 8.76 ± 25.95 mM) enabling modulation of the C11R6-B proportion (θB = 0.12–0.44) within the mixture. The dependency of catalytic activity on the proportion of C11R6-B was revealed, with the result depicted in Figure 6.

The initial reaction rates reveal that increases in water content afforded a doubling of the observed reaction rate (0.65–1.15 h⁻¹), an effect not observed in the absence of C11R6 (Figure S7). As the ratio of C11R6-A and C11R6-B could not be directly observed by NMR, they were computed from the measured water content in concert with our empirical model (eq S1). The observed reaction velocity increases linearly (θB = 0.1–0.3) with the formation of C11R6-B until it plateaus (θB = 0.3–0.5), where another process becomes rate limiting. We propose that this rate limitation is due to the slow isomerization of sorbyl alcohol from its inactive s-trans isomer to the active s-cis isomer (Figure S17). From this limitation we surmise that C11R6 acts primarily as an acid-catalyst for the activation of maleimide. A linear fit of the reaction rate to the proportion of C11R6-B (θB) between 0.1–0.3 decomposes the overall reaction rate to the activity of either C11R6-A or C11R6-B assemblies. From this linear fit we find the more acidic C11R6-B (2.16 ± 0.29 h⁻¹) is significantly more active than C11R6-A (0.24 ± 0.06 h⁻¹). As the computed rate of C11R6-A catalyzed cycloadditions is close to the uncatalyzed reaction (0.21 ± 0.01 h⁻¹, Figure S7) we surmise that C11R6-B is the sole active catalytic species. This result highlights the similarities between biological and supramolecular catalytic systems, where subtle changes in the arrangement of (supra)molecular features yield significant changes in catalytic output under mild conditions.

**CONCLUSION**

On the basis of NMR spectroscopy and computational data we demonstrate that the self-assembled hexameric undecylresorcin[4]arene capsule C11R6 can be switched between two distinct species—C11R6-A and C11R6-B—respectively featuring 8 and 15 water molecules within their hydrogen-bond networks. The internal environments of the two assemblies were probed by the binding of Bu3PO, revealing substantial shifts in the 31P NMR peak of this guest through changing the C11R6-A/C11R6-B ratio by the addition of water to the sample. These NMR experiments suggest a stronger acidity of C11R6-B assemblies that translate into differences in catalytic activity. The catalytic activity of these two assemblies were investigated in a Diels–Alder cycloaddition reaction, revealing that C11R6-B exhibits greater catalytic output by an order of magnitude. This study demonstrates the ability of water to effect structural changes in C11R6 capsules by modulating the structure-derived catalytic properties of the supramolecular assembly. We envisage that the present work will enable subsequent study of other small-molecules as structural effectors of C11R6 (and related supramolecular structures) with the goal of gated and self-steering catalytic applications.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04924.

- Computational simulation parameters, experimental conditions, spectral data for all measurements (PDF)
- Coordinates and connectivity of a representative structure for C11R6-A (PDB)
- Coordinates and connectivity of a representative structure for C11R6-B (PDB)
- Coordinates, charge and connectivity of undecylresorcin[4]arene monomer subunit used in MD simulations (monomer.mol2); Force field parameters used for MD simulation provided in Amber format (sim.fr.cmod) (ZIP)

**AUTHOR INFORMATION**

**Corresponding Author**

Jooi N. H. Reek — Homogeneous, Supramolecular, and Bioinspired Catalysis Group, van’t Hoff Institute for Molecular Science (HIMS), University of Amsterdam (UvA), 1098 XH Amsterdam, The Netherlands; orcid.org/0000-0001-5024-508X; Email: j.n.h.reek@uva.nl

**Authors**

David A. Poole, III — Homogeneous, Supramolecular, and Bioinspired Catalysis Group, van’t Hoff Institute for Molecular Science (HIMS), University of Amsterdam (UvA), 1098 XH Amsterdam, The Netherlands

Simon Mathew — Homogeneous, Supramolecular, and Bioinspired Catalysis Group, van’t Hoff Institute for...
Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c04924

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank our colleagues Dr. Anne Jans, Eline Meijer, and Dr. Andreas Ehlers for their assistance and advice for this study. We thank the European Research Council (ERC Adv. Grant 339786-5354 NAT_CAT) and the sustainable chemistry research program from the University of Amsterdam for financial support.

REFERENCES


(83) Beckett, M. A.; Strickland, G. C.; Holland, J. R.; Sukumar Varma, K. A convenient n.m.r. method for the measurement of Lewis acidity at boron centres: correlation of reaction rates of Lewis acid initiated epoxide polymerizations with Lewis acidity. Polymer 1996, 37 (20), 4629−4631.
(86) Jakubczyk, M.; Adamczyk-Woźniak, A.; Sporzyński, A. Acceptor number of organoboron molecules quantitative determination of Lewis acidity. In Molecular Receptors; East Publisher House, 2011. pp 53−68.