Toward Understanding CB[7]-Based Supramolecular Diels-Alder Catalysis

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Cucurbiturils (CBs) are robust and versatile macrocyclic compounds, often used as molecular hosts in complex supramolecular systems. In previous work, remarkable catalytic activity has been observed for asymmetric cycloadditions under very mild conditions. Herein, we investigate the nature of supramolecular catalysis using DFT calculations and QM/MM techniques. We discuss induced conformational changes, electrostatic shielding effects from the highly polar aqueous environment and cooperativity in hydrogen bonding of the substrates in explicit water using QM/MM simulation techniques. Our results show little specificity for the chosen molecules, suggesting an excellent opportunity to expand the scope for catalytic use of these supramolecular macrocyclic containers.

Keywords: QM/MM, Diels-Alder (DA) chemistry, catalysis, confinement & solvent effect, quantum chemistry ab initio

INTRODUCTION

Sustainable catalysis is evolving to limit the environmental impact of chemical industries. Organocatalytic and supramolecular systems are successfully developed offering mild reaction conditions and great selectivity. These are often aimed at mimicking enzymes that achieve the highest catalytic efficiencies as well as specificity. Cucurbit[n]urils (CB[n], n = 5–8), are great supramolecular hosts, creating a microscopic environment while maintaining good solubility in water (Barrow et al., 2015). Besides participating in host-guest chemistry (Zhang et al., 2012; Wu et al., 2017, 2019; Olesińska et al., 2019; Huang et al., 2020), they were successfully utilized in catalytic applications (Wang et al., 2011; Taylor et al., 2013; Zheng et al., 2015; Palma et al., 2017; Ren et al., 2018; Rad et al., 2019), surface chemistry (Wagner et al., 2020), and sensing and detection (Huang et al., 2012; Kasera et al., 2012; Biedermann et al., 2015; de Nijs et al., 2017, 2019).

Substrate binding within CB[n]-cavities is usually observed spectroscopically (through a variety of NMR techniques, surface Raman spectroscopy as well as UV/Vis and PL spectroscopies) (del Barrio et al., 2016; Sigle et al., 2016) and using isothermal titration calorimetry (ITC) experiments. However, thermodynamic parameters and binding constants attainable by these experiments do not alone explain the catalytic effect and more structural insights are needed to further explore these phenomena. Computational studies can account for many aspects of the catalysis (Harvey et al., 2019) enhancing our understanding of the origins of these effects. Cucurbiturils are subject to many computational works, often in conjecture with experiments, contributing to interpretation of spectroscopy (Chio et al., 2019), electronic properties (Sin et al., 2020) and in particular binding free energies and structures (Yin et al., 2016; Senthilnathan et al., 2018; Olesińska et al., 2019; Wu et al., 2019). As hosts, CBs were featured in many blind prediction challenges (Muddana et al., 2012, 2014; Lee et al., 2017; Rizzi et al., 2018).
Herein we focus on the CB-modulated catalysis of intramolecular Diels-Alder cycloaddition reactions (Palma et al., 2017) (Figure 1). N-allyl-2-furfurylamines are known model substrates for Diels-Alder reactions (Andrés et al., 1997; Gschwend et al., 2002). Based on the cavity size and our previously reported binding studies, CB[7] was found to be the best host homolog to offer enhanced water solubility allowing for higher concentrations, conformational restriction and tight binding. In physiological conditions, low conversion is achieved, while in the presence of CB[7], the cycloaddition rates are significantly sped up, and the reaction goes to completion within minutes. Importantly, at 10 mol% catalyst loading, the reaction still occurred at an increased rate, indicating a catalytic turnover in the order of organocatalysts. This work was the first example of carrying out this reaction in aqueous environment without incorporation of protecting groups and was compared to the activity of natural Diels-Alderase (Ose et al., 2003; Byrne et al., 2016).

We have previously found that binding in CB favors the closed conformation of the reactants, in agreement with experimental NMR measurements. The confinement of the reacting molecules have also been taken into account by computations (Chakraborty and Chattaraj, 2018). However, these binding effects amounting to 1–2 kcal/mol, only partially explain the catalytic effects of 4–5 kcal/mol, which have so far been unresolved. We now investigate the reaction mechanism determining detailed underlying electronic structures to assess catalysis. Using continuum electrostatic model to account for the water environment, we obtained a good agreement between experimental and calculated reaction barriers without CB. However, in CB, the catalytic rate enhancement is not reproduced without taking into account explicit water molecules. Our QM/MM calculations reconcile these differences, and we are able to assess the catalytic effects upon binding in CB. Our results show that the catalytic effects are arising as a combination of confinement, electrostatic shielding and shifting the pKₐ of the ligand. In view of future design, we also demonstrate that DFT calculations can provide detailed electrostatic maps that elicit an optimal environment for efficient catalysis.

**RESULTS**

We considered the cycloaddition reaction in four substrates (1a–d) obtained from substitution from N-allyl-2-furfurylamine molecule (Figure 1). To assess the catalytic effects, we compared reaction rates between water and in the presence of one equivalent of CB[7] (Figure 1B), which presents a 1:1 binary complex. To obtain the barriers, we identified reactant, product and transition states (RS, PS, and TS). We did not investigate the binding affinity of the substrates in CB[7], since the complexation is experimentally confirmed. As experimental reference results for the catalytic effects, we used barriers derived based on first order kinetics presented in reference (Palma et al., 2017). The introduction of CB[7] induces a ca. 5 kcal/mol drop in the activation free energy (Table 1).

**Protonation of the Substrates**

First, we considered the effect of protonation on the amine moiety on the rate of cycloaddition. Since positively charged compounds are generally the most potent to bind into CB structures, due to the favorable interaction with the carbonyl...
groups, the protonation equilibrium is likely to be upshifted in the presence of CB[7].

In experiments, pH was \( \sim 7.4 \), while the pK\(_a\) of the amine is estimated \( \sim 10 \) based on the DFT free energies and empirical prediction (details in Supplementary Material). Henceforth, we consider a protonated substrate for all calculations. Nevertheless, we compared the neutral 1a compound in our preliminary calculations obtaining that it undergoes the cycloaddition with a barrier of 30.6 kcal/mol, while after protonation decreases this to 28.6 kcal/mol. This points to the beneficial effects due to the increased pK\(_a\) of the amine in the CB environment, but does not fully account for the catalytic effects observed.

### Reaction Without CB[7]

We calculated the reactant and transition states for all four differently substituted substrates to obtain the reaction barriers in solution. Geometry optimizations were carried out in the gas phase for the TS and for several reactant (Figure 2) and product conformers, followed by a continuum dielectric model to account for free energies in the water environment.

Considering the binding poses within the CB[7] cavity, the substrate needs to adopt a folded structure, which is readily aligned for cycloaddition (HIC, hair-pin induced conformation) (Palma et al., 2017). Therefore, we calculated the most stable open and HIC conformers of the reactant state for 1a that show a 1 kcal/mol free energy difference only. This demonstrates that additional effects beyond a HIC starting geometry also stabilize the transition state in the presence of CB.

Our calculated free energy barriers, summarized in Table 2, show a very good agreement with the experimental kinetic rates for all four compounds. The reaction barrier with the Me substituted 1b substrate is somewhat higher in the calculations.
as compared with experiment, whereas the other three ligands match the barriers within 0.2 kcal/mol. We also compared the free energy barriers using a range of functionals that all performed similarly. Small improvements can be observed using Minnesota functionals when we compare the barrier heights for the H and Me substituted ligands, 1a vs. 1b (Supplementary Table 2).

**Reaction in the CB[7] Cavity**

Initial MD simulations were used to obtain several conformers of host-guest complexes as starting points in DFT optimization for the stationary reactant, transition, and product states. Most interestingly, the presence of CB[7] leads to similar barriers as obtained in implicit water calculations without CB[7] (see Supplementary Material). To account for the missing catalytic effects, we therefore decided to incorporate explicit water molecules in the DFT calculations.

We initially investigated the effects of a single water molecule for the catalytic barrier (Figures 3A,B). We placed the water molecule near the ammonium cation moiety given their strong interactions, and reoptimized the stationary structures. This resulted in small rearrangements in the binding mode of the substrate in the cavity, as the NH$_2$ does not directly interact with the CB[7]'s carbonyl oxygens, but through the explicit water instead (Figure 3C). The free energy barrier of the reaction in this model is 24.6 kcal/mol, which is in satisfactory agreement with the experimental results.

In comparison, analogous geometry optimizations for the non-catalytic system without CB[7], in the presence of a single water molecule does not change either the stationary structures or the barriers significantly (Supplementary Tables 1, 2). This suggests a cooperative influence of the solvent and the CB[7], which can only be incorporated with explicit solvation. Therefore, the stationary points along the reaction were calculated for all four substrates in the presence of one water molecule besides the macrocycle. The results are summarized in Table 2 showing a good agreement between this model and the

| TABLE 2 | Comparison of experimental (as shown in Table 1) and calculated barriers calculated by DFT. |
|---------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| X       | Exp. barrier/kcal mol$^{-1}$    | Comp. barrier/kcal mol$^{-1}$   | Exp. barrier/kcal mol$^{-1}$ with 1 eq CB[7] | Comp. barrier/kcal mol$^{-1}$ with 1 eq CB[7] |
|---------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| H       | 28.7                            | 28.6                            | 26.8                            | 26.7                            |
| Me      | 28.6                            | 29.5                            | 26.9                            | 26.9                            |
| Br      | 23.6                            | 22.5                            | 22.7                            | 23.0                            |
| Cl      | 24.6                            | 26.6                            | 22.3                            | 21.7                            |

Without the CB[7], the model considered implicit solvent, while the catalytic system consisted of a single explicit water molecule in addition. Values are in kcal/mol, calculations were done at the B3LYP-D3/6-31G*//B3LYP-D3/6-311++G(3df,3pd) level.
experiments. The level of theory for this series was benchmarked to cover other functionals and Pople basis sets, maintaining the same trends in all cases (Supplementary Tables 1, 2).

**QM/MM Calculations in Explicit Water**

To study the reaction featuring multiple water molecules, the most stable conformers of 1a were solvated in explicit water and subjected to reaction path scans using QM/MM calculations. The activation energy was 25.9 kcal/mol in solution, and 20.8 kcal/mol in complex with CB[7], minimized at the level B3LYP/6-31+G* and the energies recalculated with the basis set 6-311++G(3df,3pd).

The energy profiles depicted in Figure 4 exhibit a ca. 5 kcal/mol decrease in activation energy when the substrate is bound to CB[7], accounting for the overall catalytic effect fully. The only main difference in the reaction paths is observed for the reactant state regions. The reactant minima are located at reaction coordinate values 6.4 Å in water and 6.0 Å with CB[7]. Therefore, the RS conformations are more contracted inside the cavity before the cycloaddition, underlining the importance of pre-selecting conformers which easily undergo the cyclization. The overall barriers are somewhat lower than the ones presented in Table 2, which can be attributed to the different approach of solvent modeling.

Similarly, we also performed QM/MM calculations on the 1b substrate with a methyl substituent, as well as a nitro group (1e, Supplementary Figure 4) to analyze the trends in the barrier heights and the catalytic effects (Supplementary Figures 3, 5, respectively). We obtained a barrier height of 26.5 kcal/mol in water and 20.5 kcal/mol in CB[7] for 1b, showing a somewhat slower reaction in water, but faster in CB[7]. The QM/MM calculations thus improved the agreement with the experimentally observed catalytic effect for 1b, as also seen for compound 1a.
Overall, a clear trend is observed both in experiments and in calculations in water, without CB[7]. More electron withdrawing groups reduce the barrier more, therefore we predict the fastest reaction in water with the nitro group. Figure 5 interestingly, this trend is absent from the reactions with CB[7]. In this case, experimental barriers are comparable, no clear trend is observed.

![Figure 5](image1.png)

**Figure 5** | Experimental and calculated trends for reaction barriers obtained in water (left) and catalyzed by CB[7] (right). Compounds 1b, 1a, 1c, 1d, and 1e are shown ordered in increasing electron withdrawing ability. The experimental (dark blue in water and red in CB[7]) and calculated (gray and light blue in water and orange and green in CB[7], for implicit water and QM/MM, respectively) energy barriers are shown in kcal/mol.

![Figure 6](image2.png)

**Figure 6** | Map of reaction barrier changes upon the addition of a probe $-1$ point charge (calculated at B3LYP/6-31+G*). Yellow regions indicate an increased barrier height for the reaction, whereas green regions favor nucleophilic groups at these locations for reducing the barrier heights as shown in color scale (capped at $\pm 10$ kcal/mol). CB[7] is overlaid with the results to highlight the area shielded from the polar environment.
This is not observed in implicit solvent calculations with CB[7], and the prediction for the methyl substituent is affected the most. Therefore, the lack of explicit solvent in this case probably cannot accurately account for the ligand’s geometry and bound position within the CB[7], which leads to the less accurate estimate of the catalytic effects. On the other hand, when using QM/MM, the presence of the water molecules allows us to obtain a significantly closer agreement with experiment for the catalytic effects. In this case, although the barriers both in water and in CB[7]-catalyzed environment are slightly underestimated, the overall catalytic effect is more accurately reproduced.

**Point Charge Analysis**

The well-defined Diels-Alder transition states enable us to study the shielding effect of CB[7] in an environment where molecular details are removed, and only electrostatic interactions are considered more generally. We placed probe point charges around the continuum solvent optimized reactant and transition states on a grid around the molecule and recalculated the energy barriers. We defined a cubic 3D grid up to 3.0 Å around the substrate with a 0.5 Å spacing to evaluate the electrostatic influence on the reaction barrier. Placing a $-1$ probe charge (given the cationic substrate) around the reacting molecule outlines the pattern on the catalytic effect depicted in Figure 6.

The surface was obtained by selecting the grid points that are located at within 2.0–2.3 Å distance from the ligand, where solvent molecules would surround the substrate. Yellow regions indicate an increased barrier height for the reaction when negatively charged groups, such as the oxygen of water molecules would be present, whereas green regions favor electrophilic groups at these locations for reducing the barrier heights. Our results using a $+1$ probe charge on the grid points results in analogous complementary effects (Supplementary Figure 6).

**DISCUSSION**

DFT calculations using continuum solvent models reproduce catalytic barriers to excellent accuracy as compared with experimental values. The results are consistent between tested functionals and basis sets within the acceptable error margin of DFT. However, the reaction barriers in binary complex with CB[7] are not able to capture the catalytic effects observed experimentally. Therefore, we used explicit water molecules as well as QM/MM calculations that successfully resolve the differences. Nevertheless, the absolute barriers are underestimated by the QM/MM minimizations, which can possibly be resolved by free energy calculation methods such as finite temperature string simulations.

**FIGURE 7** | Reactant complexes (RS, top) and transition states (TS, bottom) of ligands 1a–d in the presence of CB[7] (lines) and a single explicit water. Distances of C-C outer (left) and C-C inner (right) are shown in Å. Non-polar hydrogens are hidden for clarity.
Our calculations suggest that the reaction path is slightly modified in CB[7] as there the compressed reactant state conformation is stabilized upon complexation. Explicit water molecules in this case enable us to obtain the correct binding orientation within CB[7], which lead to the decreased reaction barriers. Furthermore, electrostatic effects are also beneficial that shield the substrate from interactions with water.

Our results in conjunction with the experimental rates suggest that the four substituents have a similar catalytic effect (Figure 7). This is also seen from the similar geometric distances: C-C inner and C-C outer bonds observed in the stationary states determining the catalytic barrier heights. Therefore, these results can be generally applied to a range of molecules with analogous intramolecular Diels-Alder reaction mechanism that also contain an amine group, facilitating the binding and directing the orientation of the substrate. Extensions might include intermolecular reactions (Jon et al., 2001; Ren et al., 2018), where a larger CB[8] group might be necessary to accommodate both reacting partners.

The increasing electron withdrawing effects of the substrate substituents lead to faster reaction rates in water, as observed both in calculations and in experiment, including our predicted nitro substituent (Figure 5). Interestingly, the catalytic effects also depend on geometric factors of these substituents, as the methyl and nitro groups deviate from the trend observed for the H, Br, and Cl series. The methyl group has a slightly enhanced catalytic effect, whereas the nitro group is relatively slower in CB[7].

To more generally assess electrostatic factors governing the reaction, we probed the catalytic effects of single point charges placed on a 3D grid around the substrate. We found that the regions, where the nearby negative charges unfavorably affect the reaction, largely overlap with the area that the CB[7] shield from solvent upon complexation. These results are consistent upon using positive probe charges that show complementary effects. We envision that these maps quantifying electrostatic effects for the reaction barrier will also enable future design for improving catalysis.

CONCLUSIONS

One of the first catalytic reactions where CBs were successfully used to enhance the rates of are the examples of Diels-Alder reactions. Our computational study elaborates the catalytic effect of cucurbit[7]uril on the cycloaddition reaction. The supramolecular host binds the substrate creating a favorably anisotropic environment preparing the cycloaddition both conformationally and electrostatically.

With DFT calculations and implicit solvation, we are able to reproduce the kinetics of the non-catalytic cycloaddition with great accuracy. However, the supramolecular catalytic effect is only interpretable by describing the environment more precisely, taking the solvent and their interaction with the substrate and the catalyst into account at the atomic level. Our results hence underline the limitations of implicit solvation and the cooperativity between the catalyst and the solvent.

In particular, a clear trend was observed in water for different substituents. The more electron withdrawing substituent used, the lower the barrier. This trend was not observed in the presence of CB[7] experimentally. In this case, the geometric effects due to interactions with solvent molecules likely play an additional important role in determining the reaction barriers, due to the ligand occupying the CB[7] cavity in slightly different positions. This is also supported by the fact that implicit solvent calculations continue to show a similar trend even in the presence of CB[7], whereas QM/MM calculations with explicit water, and computational models with added explicit water molecules more accurately reproduce the barrier heights for several substrates. Overall, both experimental and calculations suggest that the largest catalytic efficiency is achieved for the 1a and 1b substrates.

We recognize the natural direction of expanding the scope of this type of supramolecular catalysis based on the utilization the hydrophobic cavity and the H-bonding network formed by the solvent, polar groups and the portal of the CBs. Our general approach of mapping the influence of the electrostatics of the ligand’s environment using simple 3D grid of point charges can aid this design of catalysts or additional substrates, where specific host-guest complex-based catalysis can expand to.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

OS and ER conceptualized the research, IS did the MD simulations, DB carried out the QM and QM/MM simulations and processed the results. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2020.587084/full#supplementary-material
REFERENCES

Andrés, C., Maestro, G., Nieto, J., Pedrosa, R., García-Granda, S., and Pérez-Carreño, E. (1997). Diastereoselective intramolecular Diels-Alder reaction of the furan diene. A facile access to enantiopure epoxy tetrahydroisoindolines. Tetrahedron Lett. 38, 1463–1466. doi: 10.1016/S0040-4020(97)01058-0

Barrow, S. J., Kasera, S., Rowland, M. J., Del Barrio, J., Scherman, O. A., Jesús Del Barrio, J., et al. (2015). Cucurbituril-based molecular recognition. Chem. Rev. 115, 12320–12406. doi: 10.1021/acs.chemrev.5b00341

Becke, A. D. (1993). Density-functional thermochemistry. III. The role of exact exchange. J. Chem. Phys. 98, 5648–5652. doi: 10.1063/1.469413

Best, R. B., Zhu, X., Shim, J., Lopes, P. E. M., Mittal, J., Feig, M., et al. (2012). Optimization of the additive CHARMM All-Atom protein force field targeting improved sampling of the backbone ψ, θ and side-chain χ_1 and χ_2 dihedral angles. J. Chem. Theory Comput. 8, 3257–3273. doi: 10.1021/ct300400x

Biedermann, F., Hathaiz, D., and Nau, W. M. (2015). Associative chemosensing by fluorescent macrocycle–dye complexes – a versatile enzyme assay platform beyond indicator displacement. Chem. Commun. 51, 4977–4980. doi: 10.1039/C4CC02277D

Brooks, B. R., Brooks, C. L., Mackerell, A. D., Nilsson, L., Petrella, R. J., Roux, B., et al. (2016). CHARMM: the biomolecular simulation program. J. Comput. Chem. 37, 1545–1614. doi: 10.1002/jcc.21287

Byrne, M. J., Lees, N. R., Han, L.-C., van der Kamp, M. W., Mulholland, A. J., Stach, J. E. M., et al. (2016). The catalytic mechanism of a natural Diels–Alderase revealed in molecular detail. J. Am. Chem. Soc. 138, 6095–6098. doi: 10.1021/acs.jc化.6b00323

Chakraborty, D., and Chattaraj, P. K. (2018). Confinement induced asymmetric thermodynamic and kinetic facilitation of some Diels–Alder reactions inside a CB[7] cavitation. J. Comput. Chem. 39, 151–160. doi: 10.1002/jcc.25094

Chio, W.-I. K., Peveler, W. J., Assaf, K. I., Moorthy, S., et al. (2019). Selective detection of nitroexplosives using molecular recognition within self-assembled plasmonic nanojunctions. J. Phys. Chem. C 123, 15769–15776. doi: 10.1021/acs.jp化.9b03263

de Nijs, B., Kamp, M., Szabó, I., Barrow, S. J., Benz, F., Wu, G., et al. (2017). Smart confined plasmonic nanojunctions. J. Phys. Chem. Lett. 8, 3257–3273. doi: 10.1021/acs.jpclett.7b00535

Jon, S. Y., Ko, Y. H., Park, S. H., Kim, H. J., and Kim, K. (2001). A facile, stereoselective [2 + 2] photoreaction mediated by cucurbit[7]uril. Chem. Commun. 1, 1938–1939. doi: 10.1039/b10153a

Kasera, S., Biedermann, F., Baumberg, J. J., Scherman, O. A., and Mahajan, S. (2012). Quantitative SERS using the sequestration of small molecules inside precise plasmonic nanostructures. Nano Lett. 12, 5924–5928. doi: 10.1021/nl303345z

Lee, J., Tofoleau, F., Pickard, F. C., König, G., Huang, J., Damjanović, A., et al. (2017). Absolute binding free energy calculations of CB[8]clip host–guest systems in the SAMPLES blind challenge. J. Comput. Aided. Mol. Des. 31, 71–85. doi: 10.1007/s10822-016-9968-2

Marenich, A. V., Cramer, C. J., and Truhlar, D. G. (2009). Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. J. Phys. Chem. B 113, 6378–6390. doi: 10.1021/jp810292n

Muddana, H. S., Varnardo, C. D., Bielawski, C. W., Urbach, A. B., Isaacs, L., Geballe, M. T., et al. (2012). Blind prediction of host-guest affinities: a new SAMPLE3 challenge. J. Comput. Aided. Mol. Des. 26, 475–487. doi: 10.1007/s10822-012-9554-1

Muddana, H. S., Yin, J., Sapra, N. V., Fenley, A. T., and Gilson, M. K. (2014). Blind prediction of SAMPLE4 cucurbit[7]uril binding affinities with the mining minima method. J. Comput. Aided. Mol. Des. 28, 463–474. doi: 10.1007/s10822-014-9726-2

Olesińska, M., Wu, G., Gómez-Coca, S., Antón-García, D., Szabó, I., Rosta, E., et al. (2019). Modular supramolecular dimerization of optically tunable aryl viologens. Chem. Sci. 10, 8806–8811. doi: 10.1039/C9CS03057C

Ose, T., Watanabe, K., Mie, T., Honma, M., Watanabe, H., Yao, M., et al. (2003). Insight into a natural Diels–Alder reaction from the structure of macrophage synthase. Nature 422, 185–189. doi: 10.1038/nature01454

Palma, A., Artel眯a, M., Wu, G., Lu, X., Barrow, S. J., Uddin, N., et al. (2017). Cucurbit[7]uril as a supramolecular artificial enzyme for Diels–Alder reactions. Angew. Chem. Int. Ed. 56, 15688–15692. doi: 10.1002/anie.201706487

Phillips, J. C., Braun, R., Wang, W., Gambart, J., Tajkhorshid, E., Villa, E., et al. (2005). Scalable molecular dynamics with NAMD. J. Comput. Chem. 26, 1781–1802. doi: 10.1002/jcc.20289

Rad, N., Danyluk, O., and Sashuk, V. (2019). Reversing chemoselectivity: simultaneous positive and negative catalysis by chemically equivalent rims of a cucurbit[7]uril host. Angew. Chemie Int. Ed. 58, 11340–11343. doi: 10.1002/anie.201905027

Ren, X., Yu, Z., Wu, Y., Liu, J., Abell, C., and Scherman, O. A. (2018). Cucurbit[7]uril-based high-performance catalytic microrreactors. Nanoscale 10, 14835–14839. doi: 10.1039/C9NR02900H

Rizzi, A., Murkli, S., McNeill, J. N., Yao, W., Sullivan, M., Gilson, M. K., et al. (2018). Overview of the SAMPLE6 host–guest binding affinity prediction challenge. J. Comput. Aided. Mol. Des. 32, 937–963. doi: 10.1007/s10822-018-0170-6

Senthilnathan, D., Solomon, R. V., Kiruthika, S., Venuvanalingam, P., and Sundararajan, M. (2018). Are cucurbiturils better drug carriers for bent metalloccenes? Insights from theory. J. Biol. Inorg. Chem. 23, 413–423. doi: 10.1007/s00775-018-1547-7

Shao, Y., Gan, Z., Efipanovsky, E., Gilbert, A. T. B., Worrmit, M., Kussmann, J., et al. (2015). Advances in molecular quantum chemistry contained in the Q-Chem 4 program package. Mol. Phys. 113, 184–215. doi: 10.1080/00268976.2014.952696

Sigle, D. O., Kasera, S., Herrmann, L. O., Palma, A., de Nijs, B., Ren, X., et al. (2016). Observing single molecules complexing with cucurbit[8]uril through nanogap surface-enhanced raman spectroscopy. J. Phys. Chem. Lett. 7, 704–710. doi: 10.1021/acs.jpclett.5b02535

Taylor, R. W., Coulston, R. J., Biedermann, F., Mahajan, S., Baumberg, J. I., and Scherman, O. A. (2013). In situ SERS monitoring of photochemistry within a nanojunction reaction. Nano Lett. 13, 5985–5990. doi: 10.1021/nl403164c
Vanommeslaeghe, K., and MacKerell, A. D. Jr. (2012). Automation of the CHARMM General Force Field (CGenFF) I: bond perception and atom typing. J. Chem. Inf. Model. 52, 3144–3154. doi: 10.1021/ci300363c

Wagner, A., Ly, K. H., Heidary, N., Szabó, I., Földeš, T., and Assaf, K. I. (2020). Host–guest chemistry meets electrocatalysis: cucurbit[6]uril on a Au surface as a hybrid system in CO₂ reduction. ACS Catal. 10, 751–761. doi: 10.1021/acscatal.9b04221

Wang, Y.-H., Cong, H., Zhao, F.-F., Xue, S.-F., Tao, Z., Zhu, Q.-J., et al. (2011). Selective catalysis for the oxidation of alcohols to aldehydes in the presence of cucurbit[8]uril. Catal. Commun. 12, 1127–1130. doi: 10.1016/j.catcom.2011.03.029

Wu, G., Oleśińska, M., Wu, Y., Matak-Vinkovic, D., and Scherman, O. A. (2017). Mining 2:2 complexes from 1:1 stoichiometry: formation of cucurbit[8]uril–diarylviologen quaternary complexes favored by electron-donating substituents. J. Am. Chem. Soc. 139, 3202–3208. doi: 10.1021/jacs.6b13074

Wu, G., Szabó, I., Rosta, E., and Scherman, O. A. (2019). Cucurbit[8]uril-mediated pseudo[2,3]rotaxanes. Chem. Commun. 55, 13227–13230. doi: 10.1039/C9CC07144J

Yin, H., Wang, R., Wan, J., Zheng, Y., Ouyang, D., and Wang, R. (2016). Molecular encapsulation of histamine H₂-receptor antagonists by cucurbit[7]uril: an experimental and computational study. Molecules 21:1178. doi: 10.3390/molecules21091178

Zhang, J., Coulston, R. J., Jones, S. T., Geng, J., Scherman, O. A., and Abell, C. (2012). One-step fabrication of supramolecular microcapsules from microfluidic droplets. Science 335, 690–694. doi: 10.1126/science.1215416

Zheng, L., Sonzini, S., Ambarwati, M., Rosta, E., Scherman, O. A., and Herrmann, A. (2015). Turning cucurbit[8]uril into a supramolecular nanoreactor for asymmetric catalysis. Angew. Chemie Int. Ed. 54, 13007–13011. doi: 10.1002/anie.201505628

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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