Supramolecular Catalysis of a Catalysis-Resistant Diels-Alder Reaction: Rapid Dimerization of Cyclopentadiene inside Cucurbit[7]uril

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In contrast to Diels-Alder reactions involving heteroatom-containing substrates, the *endo* dimerization of cyclopentadiene responds only very weakly to changes in microenvironment or the presence of potential catalysts (less than factor of 10 variation), although this pure hydrocarbon reaction has been used as an early model to predict the maximum possible catalytic effect (k_{cat}/k_{uncat} ca. 10^6 M) due to entropic contributions of a transition-state confinement (Page, M. I.; Jencks, W. P. *Proc. Natl. Acad. Sci. USA* **1971**, *68*, 1678). In the presence of cucurbit[*n*]uril homologues the reaction is selectively and almost maximally (k_{cat}/k_{uncat} ca. 4×10^5 M) accelerated by the intermediary sized cucurbit[7]uril in aqueous solution, while the other macrocyclic homologues display no acceleration or an inhibitory effect. The expected product inhibition due to the strong binding of the dicyclopentadiene reaction product can be overcome by addition of 10% methanol, which affords catalytic turnover numbers above 10. The reaction was monitored using ^{1}H NMR spectroscopy as well as UV spectrophotometry. The analysis of the kinetic data, combined with packing coefficient considerations, modelling of Lennard-Jones potentials, and dispersion-corrected DFT calculations, suggest that the catalysis is due to an entropy-dominated transition-state stabilization in the tightly packed ternary complex.

Introduction

Arguably, at least to an outsider, there is no area in catalysis which has been less practically relevant and at the same time more conceptually insightful than supramolecular catalysis with macrocycles.[1-3] The absence of successful application examples neither in industrial chemistry nor in synthetic methodology is contrasted by a wealth of advancements in regard to the understanding of the fundamental roles of effective molarity, substrate preorganization, transition-state stabilization, competitive binding, and product inhibition.[4,5] The reason that macrocycles such as cyclodextrins, calixarenes, cyclophanes, cavitands, capsules, molecular metallacages, and cucurbiturils have moved into the focus is that they have been considered as potential mimics of active sites which could eventually rival enzymatic functionality.[5-21] Concomitantly, Diels-Alder reactions[22-25] emerged as the gold standard to benchmark the catalytic activity of macrocycles.[7,9,13,19,26-30] In all case studies on supramolecular catalysis of Diels-Alder reactions, substrates with activating groups containing heteroatoms have been studied which are strongly dependent on the solvent environment or the presence of (Lewis) acidic or basic functional groups.[31,32]
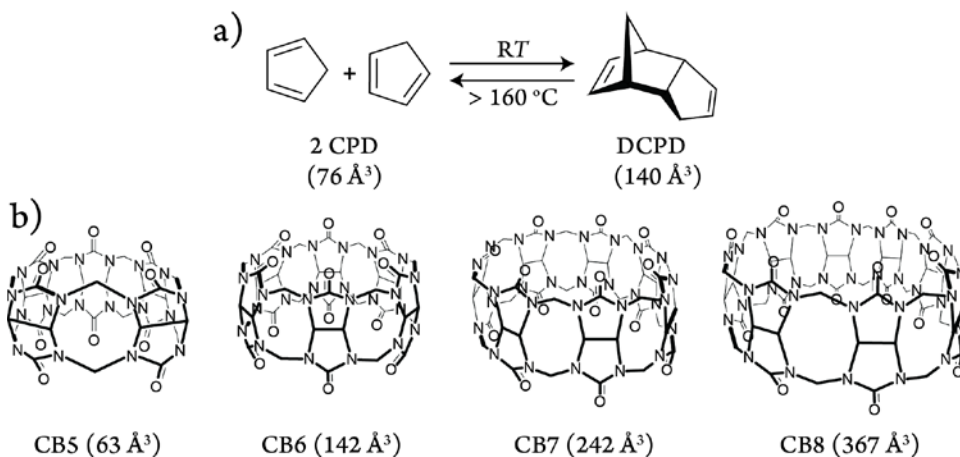

Chart 1. a) Diels-Alder reaction of cyclopentadiene, CPD, to *endo*-dicyclopentadiene, DCPD. b) Molecular structures of cucucurbit[*n*]urils, CB*n*, *n* = 5–8; molecular volumes and volumes of the inner cavity are given in parentheses.

The dimerization of cyclopentadiene (CPD) is the prototype of a Diels-Alder reaction of a simple hydrocarbon that follows the *endo* rule (Chart 1). At the same time, it is the textbook example of a Diels-Alder reaction that is extremely difficult to accelerate through the choice of the

reaction conditions;[33] the use of ionic liquids with 60% $AlCl_3$[34] leads only to a 6-fold rate enhancement, while ultrasound does not even reach a factor of 2.[35] This leaves only the universal possibility of increasing temperature or, since Diels-Alder reactions have negative volumes of activation, high pressure to speed up this slow reaction.[24] Moreover, in none of the numerous examples involving supramolecular catalysis of Diels-Alder reactions between heteroatom-containing dienophiles and CPD as diene[9,26,30,36-38] has an accelerated dimerization of the hydrocarbon been reported as an interfering side reaction. Accordingly, CPD dimerization has evaded, as other bimolecular reactions involving solely hydrocarbon substrates, noteworthy rate enhancements by means of supramolecular catalysis.

This "catalysis resistance" is striking, because the dimerization of CPD has been introduced 50 years ago by Page and Jenks as the theoretical target for biomimetic rate enhancements that could be traced back to a preferential binding of transition states and that could, on paper, reach k_{cat}/k_{uncat} values up to 10^6 M.[39] This maximum has never been reached in the five decades to come, even when using the more amenable heteroatom-containing Diels-Alder substrates (100-1000),[9,13,19,28,40-42] and also our presently reported value of 4×10^5 M, achieved by employing cucurbit[7]uril (CB7, Chart 1) in water as additive, comes only close. While an efficient catalyst for CPD dimerization is now at hand, our study corroborates the very stigma of the research field: One can hardly imagine a less useful catalyst than one for an ancient reaction that is well known to proceed slowly but smoothly on its own at ambient temperature on an industrial as well as laboratory scale.[43]

Table 1. Rate constants for CPD dimerization under different reaction conditions.[a]

	[CPD]/ mM	[CBn]/ mM	$k_{app}/10^{-6}$ $M^{-1} s^{-1 b}$	t/h	Conv./ %[c]
Neat	11.9×10^3	0	0.90^d	4	14
H_2O	4.0	0	7.2	360	3.6
CB5	2.0	4.0	9.4	504	3.4
CB6[e]	1.1	0.4	<5	504	<0.5
CB7[f]	**3.0**	**3.0**	**1.4×10^5**	**1**	**60**
CB8[e]	0.3	0.3	<9	504	<0.5

[a] Measured by ^{1}H NMR in D_2O at 25 °C (see Figure S2); rate constants were determined by plotting $1/[CPD]$ against time according to $1/[CPD] = 1/[CPD_0] + k_{app}t$. [b] 10% error. [c] Error in conversion is 5% of stated values. [d] Literature value: 0.83×10^{-6} M^{-1} s^{-1}, from ref. [44]; same value determined by UV spectrophotometry. [e] 20 mM and 50 mM NaCl were used to increase the solubility of CB6 and CB8, respectively. [f] Measured at pH 3.3, which is the pH obtained when dissolving 3 mM CB7 due to residual acid from its synthesis; the pH was not found to affect the reaction rate between pH 1.5-7.5.

Results and Discussion

The Diels-Alder reaction of CPD can be conveniently monitored by ^{1}H NMR (Figure 1 and Figure S2) or, alternatively, by UV (see Figures S5-S8). Neat CPD dimerizes slowly, with a rate of 9.0×10^{-7} $M^{-1}s^{-1}$, and this bimolecular reaction is known to vary only slightly in the gas phase[45] as well as a large range of solvents (factor of 3),[33,46-50] while we find an eight-fold increased rate in water (Table 1).[51] We next investigated the effects of CBn macrocycles. CBn are known for their high affinities to guest molecules,[52-54] driven by the hydrophobic effect for inner-cavity binding[53,55-58] and by cation-dipole interactions with the carbonyl portals.[18,54,56,59,60] In fact, guests with ammonium anchoring groups have been previously designed and studied with respect to catalytic reactions,[8,15,16,18-20,38,61-67] including the early [3+2] azide/alkyne cycloaddition example[8,68] of a reaction type which has later been referred to as (*in-situ*) click chemistry.[69] Their water solubility displays an even-odd anomaly, which limits the accessible concentrations of the even homologues.[59,70]
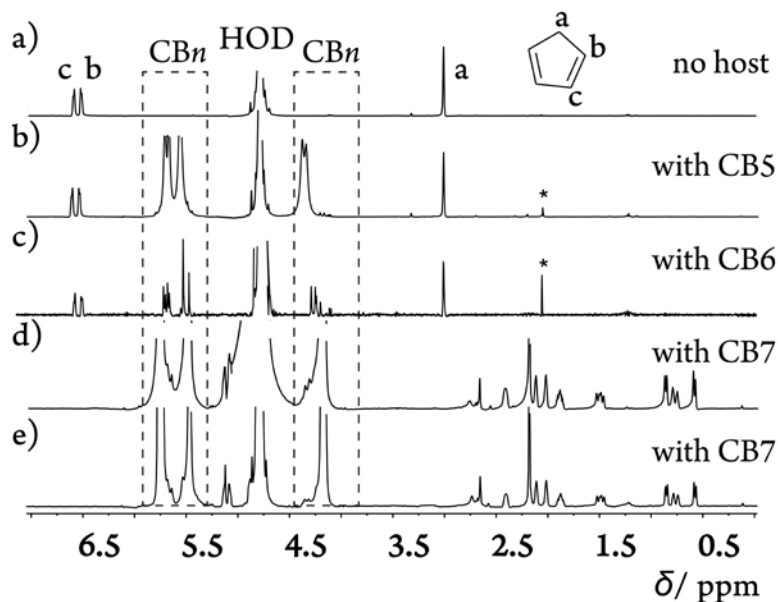
Figure 1. Dimerization of CPD (3 mM) monitored by ^{1}H NMR after 24 h a) as neat substrate in D$_2$O (no reaction), b) in the presence of CB5 (no reaction), c) in the presence of CB6 (in 20 mM NaCl, a complex was formed without reaction), d) in the presence of CB7 (rapid dimerization). Panel e) shows the ^{1}H NMR spectrum of DCPD complexed with CB7, which matches the one for product formation with CB7. Asterisk marks residual acetone from CBn synthesis.

In the presence of CB5, which is too small to encapsulate the substrate,[71] the ^{1}H NMR showed no changes of the CPD peaks, and no product was detected after 24 h (Figure 1b). The rate of CPD dimerization in the presence of CB5 remains similar to that in water (Table 1), where ca. 3.5% conversion was measured after 2-3 weeks. CB6 is sufficiently large to encapsulate an individual CPD molecule,[55] as confirmed by a slight up-field shift of the CPD protons and a splitting of the CB6 signals (Figure 1c). A CB6-isolated CPD substrate is inaccessible to dimerization and, expectedly, addition of CB6 inhibited the reaction markedly (Figure 1c). However, an equimolar amount of the intermediary sized CB7 accelerated the reaction by ca. 5 orders of magnitude, taking the dimerization in the neat liquid as reference point and using apparent bimolecular rates for an initial kinetic comparison (k_{app} values in Table 1 and Figure 2a). The conversion of CPD to DCPD in the presence of CB7 was sufficiently fast to allow ^{1}H NMR monitoring (Figure S2). A new set of peaks in the aliphatic region was observed after 24 h, which was assigned to the host-encapsulated dimerization product, *endo*-dicyclopentadiene (DCPD,

Figure 1d). Product identity was verified by ¹H NMR (Figure 1e) and GC. Finally, the use of the larger CB8 macrocycle shows, at best, a slight inhibitory activity, relative to water (Table 1). It immediately transpires that the size of the encapsulating macrocyclic cavity is critical to enable supramolecular catalysis of this previously catalysis-resistant Diels-Alder reaction. It should be noted that the high *endo* diastereoselectivity was retained under all reaction conditions,[22,72,73] that is, no *exo* product was detected.
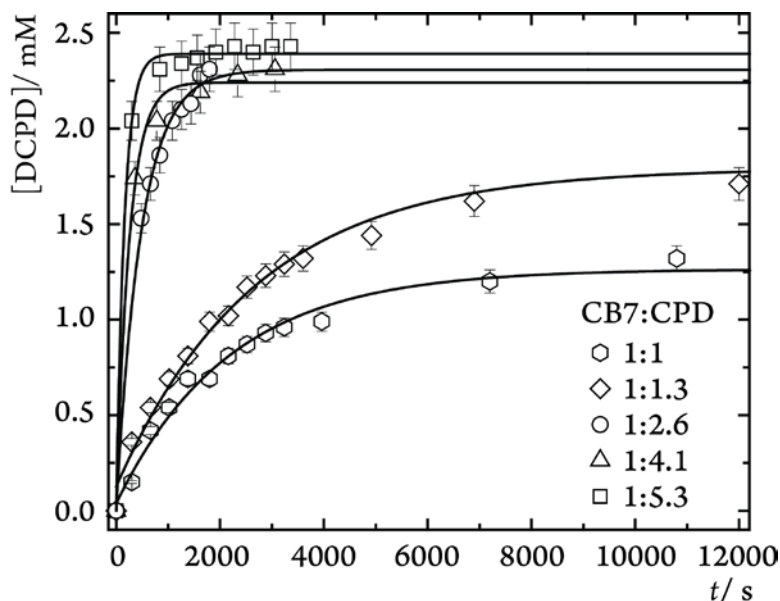

Figure 2. ¹H NMR monitoring of DCPD formation with time at different CB7:CPD concentration ratios (2.5 mM CB7, 2.5–13.3 mM CPD, pH 3.3).

We analyzed the catalytic action of CB7 in further detail. The variation of the concentration ratio between substrate and catalyst (Figure 2b) showed that the largest initial reaction rates were observed at a more than two-fold excess of the substrate, which pointed to the formation of a ternary host-guest complex, as required for dimerization. Moreover, while the rate increased with CPD concentration, the conversion stopped near a common plateau, which pointed to product inhibition,[26,41,74-76] that is, DCPD shows stronger cavity binding than CPD, which inhibits further reaction and catalytic turn-over. This complication is a general problem in macrocyclic catalysis involving Diels-Alder reactions, in which the (late) transition state is highly ordered and structurally resembles more the product than the reactants.[26,41,63,75,77-80] To overcome product inhibition, various "tricks" have been developed, such as domino reactions of the intermediary products to afford noncompetitive guests.[13,40,76,79,81,82] In our case, catalytic turnover could be

achieved through a complementary strategy, namely the choice of a slightly less polar solvent mixture (addition of 10% methanol). Practically, this lowers the binding constant of the more hydrophobic DCPD to CB7 sufficiently (from 4.8×10^7 M^{-1} in water to 9.0×10^5 M^{-1} in water:methanol 9:1, measured by ITC and indicator displacement titrations, see Figure S9) to allow the reaction to proceed with a turnover number of 10 or higher (Figure 3). As expected for catalytic reactions inside macrocyclic cavities, the addition of a strong competitive binder for CB7, namely adamantylamine,[18,58,83] caused quantitative inhibition of dimerization (see Figure S3).
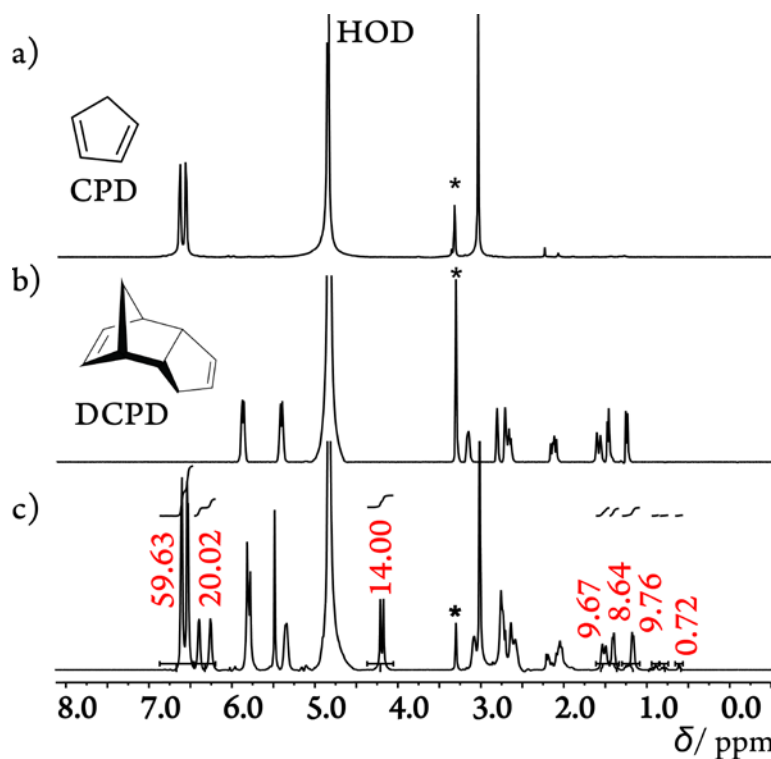

Figure 3. ^{1}H NMR spectra in D$_2$O:CD$_3$OD 9:1 mixtures after 24 h. a) CPD (30 mM); no product was formed. b) DCPD (10 mM). c) CPD (120 mM) dimerization inside the cavity of CB7 (3 mM); catalytic turnover was observed and ~30 mM DCPD was formed. Asterisk marks MeOH.
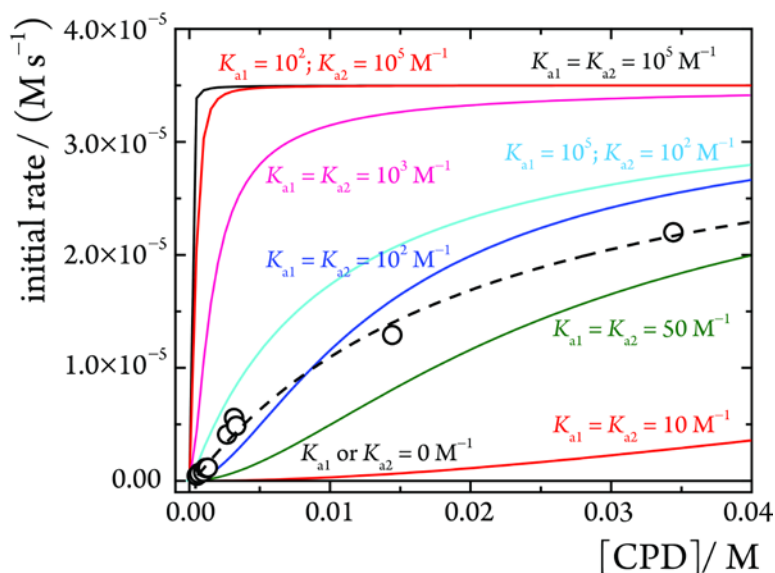
Figure 4. Simulated kinetics for the CPD dimerization inside CB7 (0.10 mM) assuming different sets of binding constants. Open circles show the experimental CPD dimerization rates, determined by UV spectrophotometry in a 9:1 $H_2O:CH_3OH$ mixture as a function of CPD concentration and the best fit to the kinetic model is shown by the dashed line. See Supplementary Information for fitting and simulation equation.

In order to quantify the catalytic effect, we performed a kinetic analysis under conditions where product inhibition could be largely neglected. In detail, we analyzed the dependence of the initial rates of the catalytic reaction on the substrate concentrations in the presence of 10% methanol with excess CPD,[30] see Figure 4. In the kinetic modeling, the formation of a ternary complex with a first ($K_{a,1}$) and a second (K_{a2}) binding constant is considered, from which an irreversible chemical reaction with a *unimolecular* rate constant (k_{cat}) occurs. A scenario with K_{a1} = 1.4×10^4 M^{-1} and K_{a2} = 46 M^{-1} provided the best fit, which is also reasonable in relation to the experimentally accessible binding constant of cyclopentane to CB7 (K_a = 1.96×10^5 M^{-1}, note that alkanes tend to show stronger affinities than alkenes).[53,55] Unfortunately, the binding constants for the formation of the ternary complex (K_{a1} and K_{a2}) could not be independently obtained through either ^{1}H NMR titrations or isothermal titration calorimetry (ITC), because of the rapidly occurring dimerization. The k_{cat} value for dimerization inside the ternary CB7 complex, which would correspond to the plateau value in Figure 4 ($k_{cat}[CB7]$), was found to be 0.35 ± 0.04 s^{-1}. This corresponds to a catalytic effect (k_{cat}/k_{uncat}) of 4×10^5 M, when referenced to the bimolecular

reaction rate in the neat liquid (Table 1); this value comes close to the predicted maximum for this specific Diels-Alder reaction (10^6 M).[84]
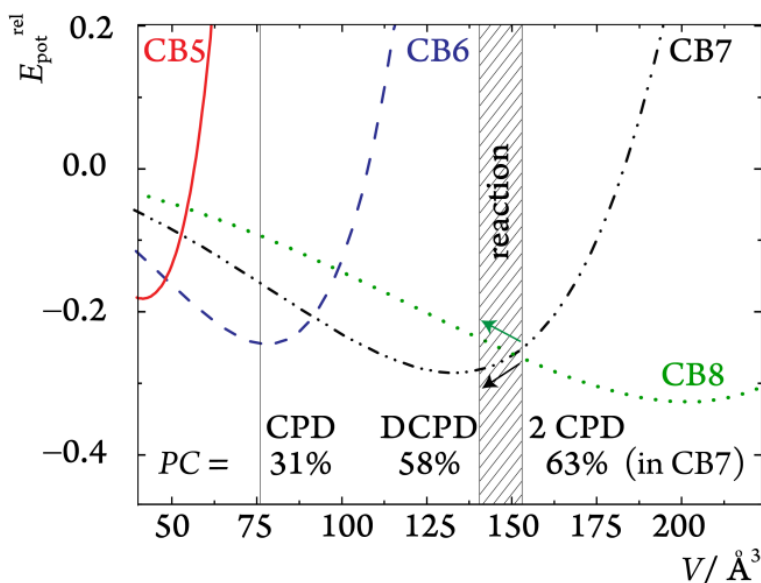

Figure 5. Model potentials for the interaction of a spherical guest positioned centro-symmetrically inside a host cavity *versus* guest volume (see ref. 16 for parameters and further details).

The catalysis and its selective observation for the intermediary sized host, CB7, can be empirically rationalized by packing coefficient considerations and modelling by Lennard-Jones type potentials, as applied in a previous gas-phase study for *retro*-Diels-Alder reactions (Figure 5).[16] The dimerization of CPD occurs essentially with the same rate and activation energy in the gas phase and in solution,[45] which strengthens the theoretical analysis. Note that the CB*n* molecular containers have varying inner cavity size and favor the binding of differently sized guest molecules, with maximal affinity always near the ideal packing coefficient (PC = 55%), the same as that found for the neat CPD liquid.[56,85] Even a single CPD molecule (V = 76 Å^3) is too large to bind to CB5, such that this macrocycle acts as a bystander in the dimerization (Table 1). CB6 can complex a single substrate molecule only, and thereby retards the reaction. CB7 and CB8 are both sufficiently large to encapsulate two CPD molecules (negative E_{pot}) but there is a fundamental difference in respect to the effects that the macrocycles have on the energy profile of the inner-phase dimerization reaction (arrows in Figure 5). From the molecular volumes of the substrates (2×76 Å^3) within the available cavity space of CB7 (242 Å^3) one can estimate a PC value of 63%

for the ternary complex. This means that for CB7, the dimerization occurs in the tight-packing regime ($PC > 55\%$), which leads to a transition-state stabilization ($PC = 60\%$) as the reaction proceeds to the product, which finds itself almost in an ideal packing state ($PC = 58\%$). This accounts for the experimentally observed catalysis with product inhibition. For CB8, the reaction proceeds in the loose-packing regime ($<55\%$); in this case, a further contraction in guest volume along the reaction coordinate decreases (from 41% to 38%) rather than increases the overall complex stability, in line with the observed (slight) inhibition of the dimerization reaction.

Beyond the empirical reasoning, the dimerization of CPD allows a particularly rigorous analysis of several other putative factors that could contribute to the observed catalysis inside CB7 and, in particular, it allows us to exclude several "trivial" causes. First, because the reaction is abundantly known to be largely insensitive to solvent properties,[33,46-48] neither the low *polarity* of the CB7 cavity (estimated to be similar to that of *n*-octanol, $\varepsilon = 10.3$)[86] nor its low *polarizability* (estimated to be below that of perfluorohexane, $P = 0.12$)[87] can account for the rate acceleration. Second, the reaction is unique in that it also proceeds in neat solution (Table 1), such that effects due to an *enhanced local concentration* inside CB7 can be convincingly excluded as being dominant: The concentration of CPD in the neat liquid is 4000 times higher than that tested in the presence of CB7, but its conversion is more than a factor of 4 lower, despite a 4 times longer reaction time. In fact, even by considering the tighter packing of CPD inside CB7 than in the neat liquid (63% versus 55%, see above), the local concentration in the cavity (13.6 M) is only slightly higher than that in the neat liquid (11.9 M), such that this effect is neglected.

Third, physicochemical properties of hydrocarbons are exceptionally well researched, such that not only the compressibility of CPD is well known,[88] but also the pressure dependence of its dimerization.[89] The increase in local concentration and packing of CPD inside CB7 (by ca. 15%) has the pertinent consequence of a strong increase in internal pressure inside the CB7 cavity, which is expected to accelerate the reaction due to its negative volume of activation ($V^{\ddagger}$ ca. 20 cm^{3}mol^{-1}).[89] From the known compressibility of CPD,[88] a 15% increased density can be correlated to a "mechanical" pressure of ca. 3 kbar experienced in the ternary complex. The inner phase of macrocycles has been frequently associated with unusual physical or phase properties,[87,90-93] and the specific idea that guests encapsulated inside macrocyclic cavities can experience an enhanced

internal pressure up to 10 kbar has been described, among others, by Rebek.[94] Note that such complexes in the tight packing regime may still experience an overall stabilization on the Lennard-Jones potential (Figure 5) – even diamantane, a C14 hydrocarbon (packing coefficient 79%), is stabilized inside CB7[52,58] – such that elevated internal pressures inside macrocycles can be formally assigned. The absolute value of 3 kbar is, however, only expected to result in a rate enhancement by a factor of ca. 12 near ambient temperature, according to the known pressure dependence of dimerization of neat CPD.[89] Accordingly, these three factors are at best circumstantial ones and another main one must be responsible for the observed 5 orders of magnitude enhancement in rates. To identify the cause, we resorted to computational modelling, akin to previous theoretical studies of reactions inside molecular containers.[30,95-99]

We chose the wB97XD/6-31G* level of theory, because it corrects for dispersion effects relevant in host-guest complexes,[16] and, as a density functional theory (DFT) method , is known to perform well for Diels-Alder transition states.[100] We did not include solvation models, because of the small solvent effects for the CPD dimerization and because of the constrictive binding by the CB7 macrocycle, which effectively insulates fully immersed guests from the outer environment.[87,101] As another asset, CPD dimerization has been studied in the gas phase,[45] such that direct benchmarking is possible. Indeed, the DFT calculations predict an activation enthalpy of 17.8 kcal mol^{-1} for the *endo* dimerization of free CPD in the gas phase (Table 2), which compares well with the experimental activation energy in the gas phase as well as that in solution (ca. 17 kcal mol^{-1}).[48,102]
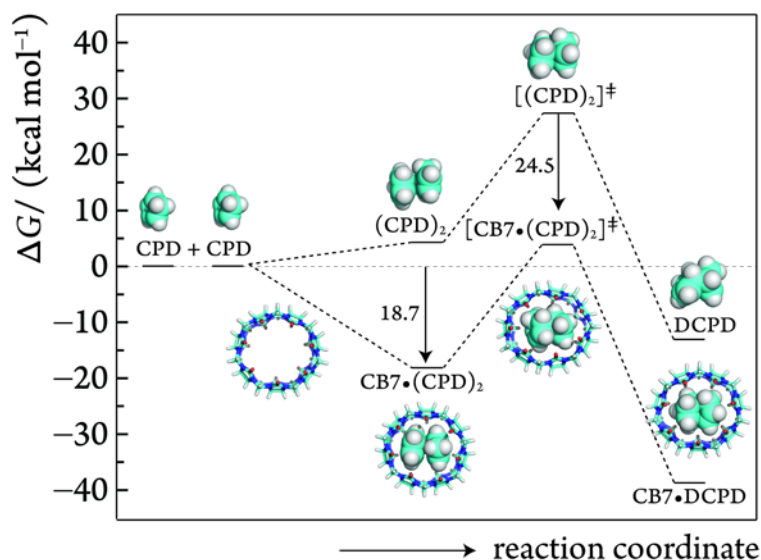
Figure 6. Calculated reaction coordinate (wB97XD/6-31G*, gas phase) with the relative free energies of the reactants ($\equiv$ 0), dimerization transition states, and products for the CPD dimerization reaction of free *versus* CB7-complexed CPD.

Table 2. DFT-calculated (wB97XD/6-31G*) thermodynamic data of the *exo* and *endo* transition states for dimerization of free *versus* CB7-complexed CPD (gas phase, in kcal mol^{-1}; calculated for the Ben-Naim reference state, see ref. [58,103].

	$\Delta H^{\ddagger}$	$T\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$
2 CPD free			
endo TS	17.8	−9.5	27.3
exo TS	21.2	−9.3	30.5
CB7•(CPD)₂ ternary complex			
endo TS	20.8	−0.7	21.5
exo TS	22.3	−1.9	24.2

The calculation of the free energies along the reaction coordinate in Figure 6 compares the (*endo*) Diels-Alder reaction for free CPD (top) with the CB7-assisted counterpart (bottom). The CB7-encapsulation related stabilization of two CPD molecules (18.7 kcal mol^{-1}) is smaller than those of the transition state and product (both ca. 25 kcal mol^{-1}), in line with the empirical Lennard-Jones modelling (Figure 5) and accounting for both key aspects, the effective catalysis

and product inhibition. Assuming that the dispersion interactions between the guest(s) and the CB7 host remain similar or even decrease slightly due to the negative reaction volume, this difference reflects the tighter packing in the substrate complex as a consequence of increased steric interactions (Pauli repulsion), which is being alleviated as the reaction proceeds. This effect can either be interpreted in terms of a destabilization of the reactants ("strain activation"),[8] a transition-state stabilization,[26,79] and partly in terms of a relief of internal pressure (see above). Interestingly, and fully in line with a preferential binding of the transition state, the size and shape of the CPD dimerization transition state resembles ferrocene, which binds strongly to CB7 ($PC =$ 58%, $K_a > 10^6$ M^{-1}).[56,101,104]

Turning towards the reaction kinetics, the free energy of activation for the *endo* cyclization is predicted to lie 3 kcal mol^{-1} below that for *exo* cyclization in both the free and complexed form; indeed, no change in diastereoselectivity was experimentally observed in the presence of CB7. In regard to the observed catalytic rate enhancement for the *endo* cyclization, complexation by CB7 lowers the free energy of activation for the Diels-Alder reaction by ca. 6 kcal mol^{-1} (Table 2). While this value is subject to change as the level or type of the dispersion-corrected DFT method is being varied, the wB97XD/6-31G* value compares reasonably well with the ca. 7.5 kcal mol^{-1} effective stabilization expected from the experimentally observed catalytic effect, calculated as $-RT\ln(k_{cat}/k_{uncat})$.

Noteworthy, the activation *enthalpy* for cyclodimerization is calculated to increase by ca. 3 kcal mol^{-1} in the ternary *endo* complex. This demonstrates that CB7 does not act as a perfect template as far as an accurate *endo* preorganization of the substrates is concerned, thereby disregarding this putative factor. However, the large unfavorable negative activation *entropy* calculated for the dimerization of neat CPD virtually vanishes upon complexation by CB7 (from -9.5 kcal mol^{-1} to -0.7 kcal mol^{-1} for the *endo* transition state, Table 2). This reveals that the catalysis is predominantly due to an entropic effect, in which CB7 acts primarily by a tight confinement of the substrate complex.[8,101] The binding of the reaction partners in the tight packing regime ($PC >$ 55%) appears to be instrumental for this confinement effect to unfold. Because we employed a dispersion-corrected DFT method, we were also able to calculate the van der Waals-associated $(CPD)_2$ dimer as an energy minimum, without surrounding CB7 (Figure 6). This allowed us to

assess the entropy loss due to dimer formation as –7.2 kcal mol^{-1} ($T\Delta S$), which corresponds largely to the entropic advantage for the CPD dimerization inside CB7. Accordingly, because the experimental rate enhancement of the Diels-Alder reaction of CPD approaches the projected maximum, and because the DFT calculations confirm a large entropic advantage for the inner-phase dimerization relative to the reaction of the unbound substrates, our experimental results may be seen as a late validation of the early theoretical work by Page and Jencks on the catalysis of CPD dimerization.[39] As an overarching conclusion, dramatic rate enhancements for associative bimolecular reactions are in general expected for active sites that bind their substrates in the tight-packing regime.

Conclusion

We present a case of a supramolecular catalysis involving a cycloaddition of two pure hydrocarbon substrates, which complements previous examples of Diels-Alder reactions with the more environmentally and catalytically responsive heteroatom substrates. The dimerization of cyclopentadiene can be selectively and strongly accelerated by the intermediary sized cucurbit[7]uril in aqueous solution. The analysis of the catalytic reaction through several spectroscopic methods, as well as dispersion-corrected DFT calculations, packing coefficient consideration, and modelling of Lennard-Jones potentials rule out effective molarity or internal pressure as causes, but point to a clear-cut case of transition-state stabilization, thereby providing experimental confirmation of a prediction which has been made 50 years back.[39]

Supplementary Information Available

Any Supplementary Information and Source Data files are available in the online version of the paper.

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Acknowledgment

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