A theoretical analysis of a classic example of supramolecular catalysis†

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Computational chemistry is used to study a 1,3-dipolar cycloaddition between an azide and an alkyne inside the macrocycle cucurbit[6]uril, in order to elucidate the catalytic function of a highly efficient supramolecular catalyst.

Supramolecular chemistry is an area of great research interest, and one of its most exciting and difficult challenges is supramolecular catalysis. The seemingly simple idea is to design molecular aggregates with the ability to selectively bind substrates and turn them into products in an efficient and selective way. Although catalytic turnover has been achieved in a number of cases,[1–4] we are still a long way from the extreme efficiency displayed by enzymes. A detailed mechanistic understanding of the catalytic mechanisms involved would be desirable. In this communication we present a density functional theory study on one of the most efficient supramolecular catalysts, with the aim to explain the catalytic effect on a molecular level, while at the same time demonstrating the usefulness of computational chemistry in this fascinating area of research.

In the seminal work by Mock *et al.*[5,6] the catalysis of a 1,3-dipolar cycloaddition between an azide and an acetylene by the reaction vessel cucurbit[6]uril[7] (CB[6], see Fig. 1) was presented. CB[*n*] is a pumpkin-shaped family of macrocycles that has found various applications in catalysis[8–10] and molecular recognition.[11] The Huisgen 1,3-dipolar cycloaddition reaction[12] is today considered to be among the best in 'click-chemistry' reactions[13] and Mock's work has served as a chemical precedent for the *in situ* click chemistry used for target-guided synthesis of enzyme inhibitors.[13,14] Mock *et al.* studied the reaction between **1** and **2** (Scheme 1), a slow reaction producing the two regioisomers **5** and **6**. With the addition of catalytic amounts of CB[6] the reaction is accelerated by a factor of 5.5×10^4 and regiospecific, forming **5** as the only product. In their detailed kinetic study[6] they postulated two factors explaining the rate enhancement, which they labeled as (i) *overcoming of entropic constraints* and (ii) *strain activation of bound substrates*. These concepts, which can be loosely connected to entropic and enthalpic contributions to free energy, are intuitively simple, but difficult to quantify experimentally in these complex mixtures. Because of this, ulterior work in the area has focused on concepts like effective molarity,[15] the ratio between bi- and unimolecular rate constants. Computational chemistry, with its different approach, can be a good complementary tool for the analysis of these problems.

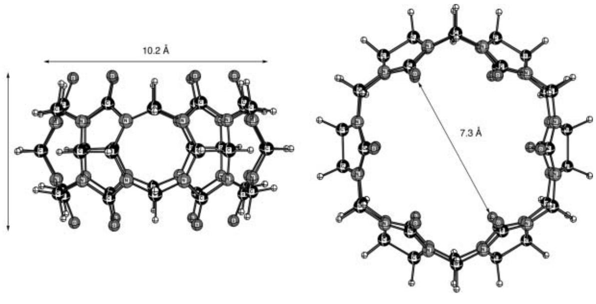

Fig. 1 Cucurbit[6]uril.

The method of choice‡ for the present study has been DFT because it provides an accurate, although computationally demanding, description of this type of systems. In Table 1 we present the calculated energetics for the 1,3-dipolar cycloaddition between **1** and **2**. The values indicate the reaction to be very slow in gas phase and slow in solution. The two routes, A and B, have similar barriers in solution that should lead to formation of both **5** and **6**, in a proportion of approximately 2 : 1 at 298 K. Solvent effects have a large influence on the barriers; which is due to two positively charged fragments being brought together. This was further confirmed by additional calculations on the neutral counterparts of **1** and **2**. The model reaction between NH_2CH_2CCH and $NH_2CH_2CH_2N_3$ has a free energy of activation of 29.5 kcal mol^{-1} in gas phase, only 1.5 kcal mol^{-1} lower than the value for the reaction between **1** and **2** in solution. This indicates that the repulsion between the two positively charged reactants is cancelled by the effect of the solvent.

In the first step of the CB[6] catalysed reaction a ternary complex (**7**) between **1**, **2** and CB[6] is formed (Scheme 2). The reactants are aligned as to react *via* route A. The ammonium groups of **1** and **2** bind to the carbonyl oxygen rims of CB[6] through two hydrogen bonds each, while the alkyne group of **1** and the azide group of **2** extend into the hydrophobic cavity of CB[6] (see Fig. 2). The reaction proceeds through the transition state for the addition step (**8TS**) to the product complex (**9**), where the product of the cycloaddition stays within CB[6]. The last step of the reaction is the release of the product from CB[6]. Attempts to follow route B in CB[6] failed because CB[6] is too small to accommodate the stationary points of route B.

The energetics of the catalysed reaction are collected in Table 2. We have assumed that the transition states for binding of reactants and release of products have energies similar to the separated species, that is, that these processes of binding and release are essentially controlled by thermodynamics. The size of the system precluded the calculation of gas phase free energy corrections, but

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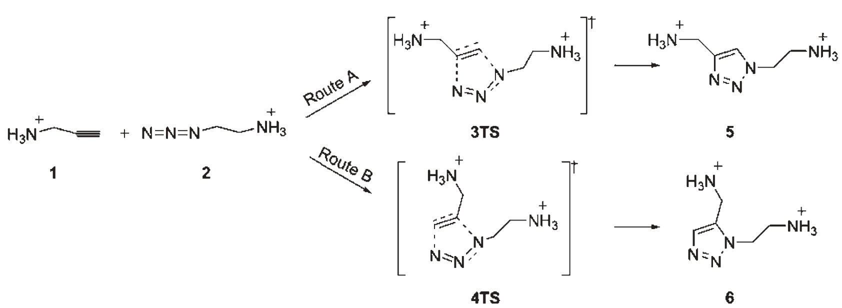
† Electronic supplementary information (ESI) available: All absolute energies for the optimised stationary points together with their cartesian coordinates. See DOI: 10.1039/b613434c



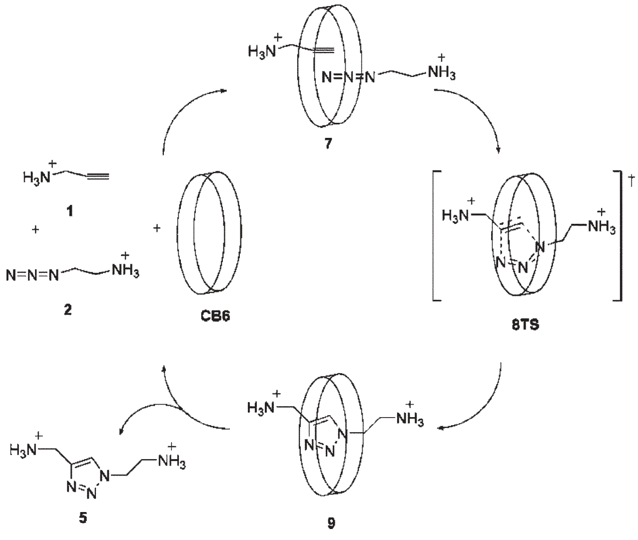
Scheme 1 1,3-dipolar cycloaddition.

Table 1 The uncatalysed reaction, all values in kcal mol$^{-1\,a}$

	ΔE	ΔH°_g	ΔG°_g	ΔG°_{sol}
1 + 2	0.0	0.0	0.0	0.0
3TS	53.7	54.1	67.2	31.0
4TS	62.0	62.4	75.4	31.4
5	−31.6	−27.7	−12.6	−57.0
6	−9.3	−5.7	8.8	−52.9

[a] The definition for the energetics (relative to the free reactants **1** and **2**) are: ΔE, the potential (B3LYP) energy. $\Delta H^\circ_g = \Delta E + \Delta\Delta H_g$, where $\Delta\Delta H_g$ is the enthalpy correction. $\Delta G^\circ_g = \Delta E + \Delta\Delta G_g$, where $\Delta\Delta G_g$ is the free energy correction. $\Delta\Delta H_g$ and $\Delta\Delta G_g$ are calculated at 298.15 K and 1 atm. $\Delta G^\circ_{sol} = \Delta G^\circ_g + \Delta\Delta G_{sol} + \Delta\Delta G\,(1\text{ atm} \rightarrow 1\text{ M})$. $\Delta\Delta G_{sol}$ = Solvation free energy correction. $\Delta\Delta G\,(1\text{ atm} \rightarrow 1\text{ M})$ is the correction factor for changing the standard state from 1 atm to 1 M (2.02 kcal mol^{-1} per molecule). The ΔG°_{sol} values correspond to a standard state of 1 M solution in a solvent that has the same properties as pure water

the results are still informative. As in the uncatalysed reaction the addition of solvent to the calculations has a large effect on the relative energies, and only the values in solution are discussed here. The reaction complex **7** is 24.9 kcal mol^{-1} below the free reactants. This particular value may be modified by the presence of counterions, but these are unlikely to affect the energetics of the key subsequent step, because the counterions will have to stay out of the supramolecule. The barrier for the addition step (from **7** to **8TS**) is 17.9 kcal mol^{-1}, and the product complex **9** is 23.0 kcal mol^{-1} below free product (**5** and CB[6]). According to these calculations, the rate-limiting step in the catalytic cycle is the product release from CB[6], in agreement with the experimental observation. The computed value for this step (23.0 kcal mol^{-1}) is close to the experimental one (23.8 kcal mol^{-1}). This close agreement may be accidental due to an eventual cancellation of errors, but is encouraging.



Scheme 2 The CB[6] catalysed reaction.

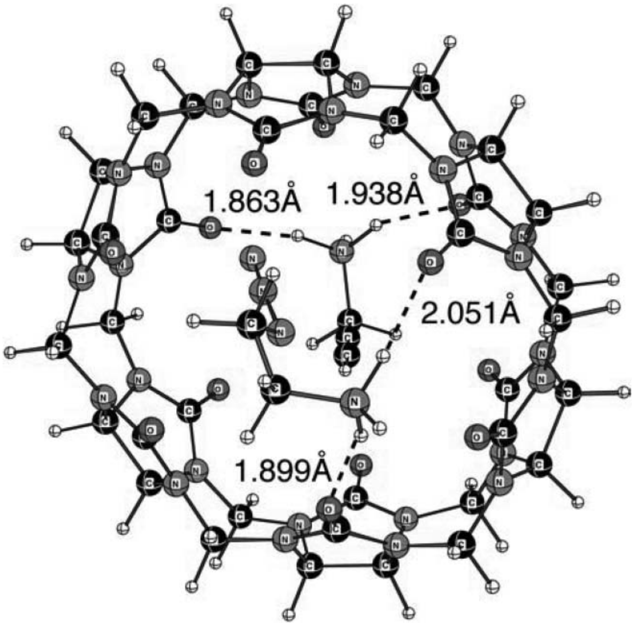


Fig. 2 The reaction complex **7**.

The key to the catalytic acceleration is that the formation of the stable reaction complex **7** transforms the bimolecular 1,3-dipolar cycloaddition into a unimolecular process. The eventual entropy cost to bring together the three fragments composing **7**, that is **1**, **2** and CB[6], is more than outweighed by the favorable electrostatic

Table 2 The catalysed reaction, all values in kcal mol$^{-1\,a}$

	ΔE	$\Delta G^{\circ *}_{sol}$
1 + **2** + CB[6]	0.0	0.0
7	−111.5	−24.9
8TS	−90.0	−7.0
9	−181.7	−97.0
5 + CB[6]	−31.6	−74.0

[a] The definition for the energetics (relative to the free reactants **1**, **2** and CB[6]) are: ΔE, the potential (B3LYP) energy. $\Delta G^{\circ *}_{sol} = \Delta E + \Delta\Delta G_{sol}$.

stabilization of 24.9 kcal mol^{-1} associated with its formation. The barrier for the addition step, from **7** to **8TS**, is thus mainly enthalpic. Things are very different for the uncatalysed reaction, where the addition step has a substantial entropic contribution ($-T\Delta S$ = 13.1 and 13.0 kcal mol^{-1} for routes A and B, respectively). CB[6] effectively avoids this 'direct' step by first forming **7**; hence, the main catalytic effect of CB[6] is the elimination of the large cost in entropy of the uncatalysed reaction. We think that this contribution can be assimilated to the *overcoming of entropic constraints* discussed by Mock.

In order to evaluate the 'extra' catalytic effect of *strain activation of bound substrates* suggested by Mock, we performed a series of single point calculations on the stationary points of the CB[6] catalysed reaction. We first removed CB[6] from the stationary points and calculated the energy for the addition step with frozen geometries; this removes the electronic effect of CB[6]. The barrier was found to be 20.7 kcal mol^{-1} in the gas phase, a value 0.8 kcal mol^{-1} lower than with CB[6]! In another series of calculations we removed the reactants, TS structure and product complex from CB[6] to estimate the deformation of CB[6] in the reaction compared to empty CB[6]. The results showed that **8TS** has the least deviation from the structure of empty CB[6] and is approximately 1 kcal mol^{-1} more stable than CB[6]'s structure in the reactant and product complex. The TS stabilization (or destabilization!) is very small, and must play a minor role in the catalytic acceleration.

Our calculations reproduce the experimental observation that the 1,3-dipolar cycloaddition between molecules **1** and **2** is a slow reaction in solution with low regioselectivity; and that the addition of the reaction vessel cucurbit[6]uril accelerates the reaction and makes it regiospecific. Analysis of the results shows that the main catalytic effect of CB[6] is the elimination of the entropy cost of bringing the two reactants together, through the formation of a stable ternary complex between the reactants and CB[6], turning the addition reaction unimolecular. We found no evidence for transition state stabilization by the CB[6] system.

The fact that the supramolecule presents a similar interaction with the different encapsulated units, regardless of their nature as reactants or transition state, represents a substantial qualitative difference with the usually postulated mechanism of enzymes.[16] If this behavior is general, it would explain why supramolecular catalysts are still so far from enzymatic efficiency. The identification of the nature of the interaction has furthermore significant implications on catalyst design. For example, in the process studied here, there is some margin for improvement in facilitating the product release, but the optimization of interaction between the supramolecule and the transition state would require a fundamental modification of the chemical system.

In conclusion, we think this work proves that computational chemistry is useful for the reproduction and analysis of supramolecular catalysis, and can be a valuable tool for the design of more efficient systems. We are currently working in our Laboratory on the study of related systems.

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Notes and references

‡ All stationary points, transition states and minima were fully optimised at the B3LYP/6-31G(d) level of theory.[17,18] The stationary points for the uncatalysed reaction were characterized by vibrational frequency analysis at the same level of theory. Solvation effects were calculated using the Poisson–Boltzmann method as implemented in Jaguar 5.5[19] with default settings and the dielectric constant of water. All quantum chemistry calculations were performed with the Jaguar 5.5 program.[19]

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