A QM/MM Study of Biomimetic Catalysis of Diels-Adler reactions Using Cyclodextrins

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Abstract:

We conducted computational research to investigate the mechanism by which cyclodextrins (CDs) catalyze Diels-Alder reaction between 9-anthracenemethanol and N-cyclohexylmaleimide. Hydrogen bonds between N-cyclohexylmaleimide and the hydroxyl groups of cyclodextrins were initially thought to play an important role in the catalysis [Chaudhuri, S. *et al. Tetrahedron Letters*, 2015, 56, 1619-1623.] Our calculations show that such hydrogen bonds, if exist, could lower the activation energy barrier for the transition state of 9-anthracenemethanol and N-cyclohexylmaleimide to some extent. However, they are not stable enough to promote the reaction. The binding of 9-anthracenemethanol and N-cyclohexylmaleimide to cyclodextrins is found to be the key to the catalysis. Cyclodextrins act as a container to hold the two reactants in the cavity, pre-organizes them for the reactions, and thus reduces the entropy penalty to the activation free energy. Dimethyl-β-CD is found to be a better catalyst for this specific reaction than β-CD because it outperforms β-CD in almost every step of catalysis. It binds N-cyclohexylmaleimide more tightly, holds both 9-anthracenemethanol and N-cyclohexylmaleimide for much longer time in its binding site, and pays smaller entropy penalty to the activation free energy of the transition state. This computational work sheds light on the mechanism of the catalytic reaction by cyclodextrins, and introduces new perspectives to the supramolecular catalysis.

Keywords: Diels-Alder reaction, cyclodextrin, catalyst, hydrogen-bonding, entropy, mechanism

1. Introduction

Supramolecular catalysts offer potential advantages over enzymes, including greater physical and chemical stability, lower molecular weight, and a far more varied selection of chemistries for the creation of structure and functionality. Cyclodextrins were the first hosts used to reproduce the hydrophobic pocket of enzymes [1-9]. One early reaction involving cyclodextrin was the chlorination of anisole complexed in α-cyclodextrin [5]. Other instances of the use of cyclodextrin have since been reported [10,11]. For instance, β-cyclodextrin catalyzes the Diels-Alder reaction of acrylonitrile and cyclopentadiene [6,7].

The Diels-Alder reaction is an important carbon-carbon bond formation reaction in organic synthesis. It forms two carbon-carbon bonds and up to four new stereo centers in one step. For typical Diels-Alder reactions between diene and dienophile, frontier molecular orbital theory states that the interaction of the highest occupied molecular orbital (HOMO) of the diene with the lowest unoccupied molecular orbital (LUMO) of the dienophile is the dominant interaction in the transition state [12]. The rate of the Diels-Alder reaction could be accelerated by narrowing the energy gap between the HOMO and LUMO [13,14].

Recently cyclodextrins were reported to promote Diels-Alder reactions of 9-anthracenemethanol with a variety of N-substituted maleimides under mild reaction conditions [15]. Chaudhuri, S. *et. al* proposed a mechanism that the cyclodextrins bind the hydrophobic substituents on the maleimides (2a – 2d) and activate the dienophile by electronic modulation of the maleimide double bond through hydrogen bonds with cyclodextrins. In addition, Methyl-β-cyclodextrin was found significantly more efficient than β-cyclodextrin at promoting the reaction of N-cyclohexylmaleimide. The authors further suggested that this is likely because methyl-β-cyclodextrin is both more flexible and has a more non-polar cavity than β-cyclodextrin [15]. However, if the reaction is promoted by the hydrogen bonds between the maleimides and cyclodextrins, then β-cyclodextrin should perform at least as well as methyl-β-cyclodextrin because it has more hydroxyl groups to participate the hydrogen bonding. It is also unclear how the flexibility and hydrophobicity of methyl-β-cyclodextrin would help the catalysis. In this paper we present our computational work on the Diels-Alder reactions with cyclodextrins as catalysts, describe a new mechanism as well as the evidences to explain why methyl-β-cyclodextrin outperforms β-cyclodextrin to promote the reactions.

2. Methods

In this work we studied the Diels-Alder reaction of 9-anthracenemethanol (1) with N-cyclohexyl maleimide (2a) (Figure 1) with several computational methods. The catalysts used in our calculations are β-cyclodextrin and methyl-β-cyclodextrin. Each α-D-glucopyranoside on cyclodextrins has one primary hydroxyl group and 2 secondary hydroxyl groups (Figure 2). All the commercially available methylated β-cyclodextrins are mixtures of various isomers and homologues except trimethyl β-cyclodextrin. Since the degree of substitution of methyl-β-

cyclodextrin is 1.8 in the work of Chaudhuri, S. *et. al*, and the primary hydroxyl group is more active than secondary hydroxyl groups in methylation, we assume the major component of methyl-β-cyclodextrin is 2,6-O-dimethyl-β-cyclodextrin. In this work, we investigated the interactions of the two reactants (1 and 2a) in the Diels-Alder reaction with the catalysts β-cyclodextrin (β-CD) and 2,6-O-dimethyl-β-cyclodextrin (dimethyl-β-CD) by the computational methods briefly described as below.

2.1 Free energy calculations with the VM2 method

Reactants bind to cyclodextrins before the catalyzed reactions would happen. Since the cavity of the studied cyclodextrins is only large enough to accommodate one reactant, we calculated the binding free energies of 1 or 2a to β-CD or dimethyl-β-CD by the VM2 method [16] in order to find out which reactant binds first. The initial conformations of the complexes for the VM2 calculations were obtained by an in-house docking script. Force field q4md [17] and General Amber Force Field (GAFF) [18-20] were applied to cyclodextrins and the two reactants, respectively.

The VM2 method provides binding affinities by computing the standard chemical potentials of the free receptor, the free ligand, and their complexes and taking the differences to obtain the standard free energy of binding. The standard chemical potential of each molecular species is obtained as a sum of the contributions from the low-energy conformations of the species. These conformations are identified with the Tork conformational search algorithm [21], and a symmetry-corrected method ensures that no conformation is double-counted in the free energy sums [22]. The contribution of each unique energy well to the free energy is computed with an augmented form of the harmonic approximation, the Harmonic Approximation/Mode Scanning (HA/MS) method [23]. The ligand, the receptor, and their complex are treated as fully flexible during these calculations.

2.2 Unbiased molecular dynamics (MD) simulations

The initial conformations of the complexes of cyclodextrins and compound 2a for the MD simulations were the lowest energy conformations from the VM2 runs. For the complexes of cyclodextrins with both reactants, the initial conformations were obtained by the following method. The reaction product was added in place of 2a in the initial conformations of the complexes of cyclodextrins and 2a. Then the two single bonds connecting 1 and 2a in the product were removed and the whole system was energy minimized.

The Amber 14 package with an efficient GPU implementation [24-26] was employed for the MD simulations of dynamic processes in the binding between cyclodextrins and reactants. Force field q4md and General Amber Force Field (GAFF) [18-20] were applied to cyclodextrins and two reactants, respectively. Minimization on the hydrogen atoms and the entire complex was applied for 500 and 5000 steps, respectively. After being solvated with a rectangular TIP3P water box [27], the edge of the box is at least 12 Å away from the solutes. The system went through a 1000-

step water and 5000-step system minimization to correct any inconsistencies. Next, we relaxed the system by slowly heating it during an equilibrium course of 10 ps at 200, 250 and 298 K. We performed production run in an isothermic-isobaric (NPT) ensemble with a 2-fs time step. The Langevin thermostat [28,29], with a damping constant of 2 ps^{-1}, was used to maintain a temperature of 298 K. The long-range electrostatic interactions were computed by the particle mesh Ewald method [30] beyond 8 Å distance. We collected the resulting trajectories every 2 ps. Finally, the SHAKE algorithm [31] was used to constrain water hydrogen atoms during the MD simulations. We performed 300 ns of MD production runs on each complex by using CPU parallel processing and local GPU machines. Finally, the trajectories were collected and analyzed at intervals of 20 ps.

In this work a hydrogen bond (X-H…Y) is considered formed if the distance between H and Y is smaller than 2.0 Å and the complimentary angle of X-H…Y is smaller than 90º (Figure SI-1). We used an in-house script to post-process the trajectories for direct hydrogen bonds between 2a and cyclodextrins. The occurrence percentage of a hydrogen bond is calculated as the number of the frames where the hydrogen bond is found divided by the total frames (3000).

2.3 QM calculations with the pm3 method

As an initial effort towards understanding the effects of cyclodextrins in catalyzing the Diels-Alder reaction, a semi-empirical PM3 method is used. Despite its limitations, PM3 method characterizes correctly the bond breaking and formation of Diels-Alder reaction and is a practical method for large systems as in this work. Reaction paths and transition states (TSs) with and without β-CD and dimethyl-β-CD catalysts were calculated using Gaussian 09W package [32, 33]. The activation free energies were obtained by computing the difference between the free energies of the reactants and the transition state.

The initial guesses for transition state searches were obtained by Bond Length Scanning. We started with the initial conformations of complexes of cyclodextrins with both reactants. For each complex we used two distinct initial conformations, one with hydrogen bonds between both of the carbonyl groups on 2a and cyclodextrins; and the other without any hydrogen bonds. These conformations were extracted from the trajectories of the MD runs. We created pseudo bonds to connect 1 and 2a, changed the bond length from 3.0 Å to 1.5 Å with a decrement of 0.1 Å. For each bond length we fixed the pseudo bonds and ran optimization for all other atomic coordinates with the pm3 method. Bond Length Scanning was implemented on the reactants alone, reactants with β-CD, and reactants with dimethyl-β-CD. A full TS optimization was then carried out using the selected initial guesses. After the transition states were identified, the Intrinsic Reaction Coordinate (IRC) was calculated for the above three systems.

3. Results and Discussion

3.1 Free Energy calculation results

Table 1 lists the binding free energies and breakdowns between reactants and cyclodextrins. Compound 2a has a binding affinity of -6.578 kcal/mol with β-CD, stronger than that with dimethyl-β-CD by 0.4 kcal/mol. However, this advantage mainly comes from the lower entropy penalty with β-CD. Dimethyl-β-CD provides stronger enthalpy contribution than β-CD by 1.1 kcal/mol. Binding between compound 1 and cyclodextrins is weaker than that of 2a by more than 2 kcal/mol. The binding free energy of 1 and β-cd is merely -2.708 kcal/mol. The result suggests that 2a outperforms 1 and binds to cyclodextrins first. The main driving force for the binding is van der Waals interaction. This is consistent with the binding modes of both reactants in their lowest energy conformations (Figure SI-2). The cyclohexyl group of 2a snugly sits right in the hydrophobic cavity of cyclodextrins and the maleimide moiety stays at the wide rim side (the side with secondary hydroxyl groups) of cyclodextrins, while the anthracene rings stick into the cavity and keep vertical to the macrocycles of cyclodextrins. The principal axes of the reactants are aligned well with those of cyclodextrins to make tight contacts with each other. The van der Waals energy term is similar for all complexes. Surprisingly, no hydrogen bonds were observed between 2a and cyclodextrins in all of the conformations. In the complex with 2a, the secondary hydroxyl groups on β-CD still keep the perfect intra-molecular hydrogen bonding network. The poor solubility of β-CD is believed to be attributed to this stable hydrogen bonding network and methylation is employed to break this network to increase the solubility [34]. However, the hydroxyl groups on dimethyl-β-CD are not able to interact with the carbonyl group on 2a either. Due to the lack of the favorable hydrogen bonding interactions the overall electrostatic contribution ($\Delta E_{Coulomb} + \Delta E_{PB}$) is positive for the binding between the reactants and cyclodextrins.

In sharp contrast to the hypothesis that hydrogen bonds between the carbonyl groups on 2a and cyclodextrins play the key role in the catalysis reaction between compound 1 and maleimide derivatives including 2a [15], VM2 results do not favor hydrogen bonding. Given that the VM2 method uses implicit solvent model and 2a seems to bind a little too deep into the cavity of cyclodextrins to make any hydrogen bonds, it is worth to check the binding of 2a and cyclodextrins with explicit solvent model. We thus ran 300 ns all-atom unbiased MD simulations on the complexes of cyclodextrins with 2a as well as the complexes of cyclodextrins with both reactants.

3.2 MD simulation results

We calculated the binding energies for the complexes of 2a and cyclodextrins with the MMPB/SA method based on the trajectories from the MD runs (Table 2). The MMPB/SA energies are consistent with the VM2 results in that dimethyl-β-CD has stronger enthalpy contribution to the binding with 2a than β-CD, that the dominant contributor is van der Waals interaction, and that the overall electrostatic interaction is positive. MD provides more diversified conformations. We calculated the distances between the centers of 2a as well as its cyclohexyl ring and urea moiety and the center of cyclodextrins. Table 3 presents the averages

and deviations of these distances during the 300 ns MD runs. The numbers also represent the positions of the centers of 2a and its moieties with respect to the center of cyclodextrins which marks zero. A positive value means 2a or the moieties gets closer to the wide rim, i.e., shallower binding, and a negative value means they get closer to the narrow rim, i.e., deeper binding. It appears that 2a binds much shallower in the cavity when compared with what VM2 results show. And 2a binds shallower to dimethyl-β-CD than to β-CD with the both methods. The MD method provides reasonable binding modes for 2a. Its cyclohexyl group is very close to the hydrophobic center of cyclodextrins, and promotes van der Waals interactions. Shallow binding allows the 5-membered maleimide ring to get closer to the wide rim and thus makes more room to facilitate the binding of compound 1 to the complexes of 2a and cyclodextrins. Shallow binding also gets the carbonyl groups of 2a closer to the secondary hydroxyl groups on cyclodextrins to possibly form hydrogen bonds with them.

The trajectories from the MD runs provide the important information about the occurrence percentage of the hydrogen bonds between both carbonyl groups on 2a and cyclodextrins. For dimethyl-β-CD, the percentage is negligibly 0.06%; for β-CD it is 3.23%. This indicates that these hydrogen bonds are not stable at all. This result echoes what VM2 results show, i.e., no such hydrogen bonds are observed. These hydrogen bonds between both carbonyl groups on 2a and cyclodextrins have to exist long enough to promote the Diels-Alder reaction. Furthermore, if the hydrogen bonding mechanism stands, β-CD should work better as a catalyst than dimethyl-β-CD because its hydrogen bonds last longer (3.23% vs. 0.06%), which conflicts with the experimental result showing the opposite ranking. Therefore, it is likely that cyclodextrins catalyze the Diels-Alder reactions between 9-anthracenemethanol and N-substituted maleimides by a different mechanism other than the hydrogen bonding one.

MMPB/SA energies (Table 2) show that the binding of both 1 and 2a together to cyclodextrins has more favorable energy as compared with the binding of 2a only, indicating that after 2a binds to the cavity of cyclodextrins, 1 would also spontaneously bind to the complex. Moreover, binding of 1 to β-CD and 2a gains -1.5 kcal/mol more energy while binding of 1 to dimethyl-β-CD and 2a picks up -3.6 kcal/mol more energy, as shown in Table 2. It suggests that binding of both 1 and 2a to dimethyl-β-CD is stronger than binding to β-CD. We further investigated the binding modes of 1 with 2a and cyclodextrins. The binding modes fall into 4 major groups according to the RMSD with respect to the initial conformation: (1) when RMSD $\leq$ 3.0 Å, 1 stays in the binding site of cyclodextrins and interacts with 2a; (2) when 3.0 Å < RMSD $\leqslant$ 5.0 Å, 1 stays in the binding site of cyclodextrins and but doesn't interact with 2a; (3) when 5.0 Å < RMSD $\leqslant$ 10.0 Å, 1 stays outside of the binding site and sticks to cyclodextrins; (4) when RMSD > 10.0 Å, 1 stays in solution. Figure 3 shows the RMSD of compound 1 in the complexes with cyclodextrins. Among the frames extracted from the 300 ns MD runs, for dimethyl-β-CD, compound 1 was found to be in the binding site in 34.87% frames, and in 24.43% frames 1 interacts with 2a. 1 totally moves to solution in 20.27% frames. This indicates that there is large chance for 1 to stay near 2a and interact with it in the presence of dimethyl-β-CD. Figure 4

shows the typical pose of 1 when interacting with 2a and dimethyl-β-CD. One end of its anthracene ring and the maleimide ring of 2a forms π-π stacking, and the other end contacts with the methyl-oxyl group on dimethyl-β-CD. In contrast, compound 1 seems much more mobile with 2a and β-CD. It was found in the binding site in 8.13% frames, and in only 0.8% frames 1 interacts with 2a. 1 totally moves away in 77.53% frames. So it appears that dimethyl-β-CD holds 1 in the binding site for markedly longer time, which may account for its stronger catalysis capability than β-CD. It is worth noting that compound 1 leaves the binding site of dimethyl-β-CD and enters solution at the very beginning of the MD run, but is able to come back to the binding site quickly. It moves back and forth between the binding site and solution several times during the 300 ns MD run, and the time it interacting with compound 2a lasts from 5 ns to 60 ns.

3.3 QM calculation results

The MD simulations provide a valuable clue that cyclodextrins catalyze the Diels-Alder reactions by a mechanism other than hydrogen bonding. To gain better understand of the reaction mechanisms, we thus performed QM calculations to locate the TSs and the corresponding IRCs with and without β-CD and dimethyl-β-CD. For simplicity, we refer to the TS without catalyst as the TS alone case. Due to the size of the cyclodextrin systems a semi-empirical method pm3 was employed in the calculations to obtain a qualitative understanding of the catalytic mechanism. Also, practice shows that for systems understudy it is difficult to locate the TS by directly putting the reactants together. The Bond Length Scanning method described in the Method section was used to find "good" initial guesses for the transition state searches. Furthermore, since cyclodextrins are flexible and have a lot of conformations, we ran the scanning calculations with a couple of different starting conformations: one with the hydrogen bonds between the two carbonyl groups of 2a and cyclodextrins, and the other without the hydrogen bonds. Both starting conformations result in highly similar energy-bond length curves and energy barriers for both β-CD and dimethyl-β-CD. This result further confirms that hydrogen bonds don't play an important role in the catalysis of this specific Diels-Alder reaction. The Bond Length Scanning result can be found in Figure 5. For simplicity only the result from the starting conformation without hydrogen bonds for β-CD and dimethyl-β-CD is presented. The curves are normalized to set the reactants energies at zero point such that the curves can be compared directly. In general, they give typical curves for the energy changes in reaction paths. Staring from 3.0 Å, the energy gradually rises as the bond length gets shorter. It reaches a maximum at around 2.2 Å and then rapidly drops as the value approaches 1.5 Å which is roughly the length of the covalent bonds connecting 1 and 2a. Bond Length Scanning, though provide useful information regarding the reaction, may lead to a path that deviates from the minimum energy path significantly, which makes the analysis of reaction mechanism difficult. For example it is hard to tell if the flatten top of the energy curve for dimethyl- β-CD is just a result of some higher energy reaction paths from the TS. Therefore, IRC calculations are performed and the results are shown in Figure 5 as well. The flattened top is not observed on the curves by IRC, and except the forward reaction energy

barriers all three curves look quite similar. Therefore, the flattened top obtained by the Bond Length Scanning method is just one of the higher energy paths.

The energy barriers are roughly 40.9, 30.7 and 25.7 kcal/mol for TS alone, TS with β-CD, and TS with dimethyl-β-CD, respectively. These values indicate that both β-CD and dimethyl-β-CD can lower the energy barriers and accelerate the reactions, and their rankings are in agreement with what was observed in the experiment by Chaudhuri, S. *et. al*.

The activation free energy was calculated between reactants and the transition state for TS alone, TS with β-CD, and TS with dimethyl-β-CD. For TS alone, the reactants are the free state of compounds 1 and 2a. For TS and cyclodextrins, the reactants are defined as the bound state of cyclodextrins, 1 and 2a. The result can be found in Table 4. Two sets of calculations were implemented for the cyclodextrin complexes, corresponding to the two starting conformations as aforementioned. The first set was resulted from the conformations with the hydrogen bonds between TS and cyclodextrins, and the second set from the one without the hydrogen bonds. The activation free energy for TS alone is as high as 49.04 kcal/mol, which is in the range of experimental activation free energies for typical Diels-Alder reactions [35, 36]. Cyclodextrins lower the energy barriers significantly and dimethyl-β-CD performs better than β-CD, in agreement with the experimental observation [15].

The calculated activation free energies can be decomposed into enthalpy and entropy terms. The first sets of both β-CD and dimethyl-β-CD complexes have lower enthalpy term than the second set, suggesting that the hydrogen bonds, if exist, may help to stabilize the transition state. It is the low occurrence percentage of the hydrogen bonds that makes their contribution to the activation free energy small. Both sets of dimethyl-β-CD complexes have lower enthalpy term than those of β-CD. Given that dimethyl-β-CD has a large hydrophobic cavity and more contacts with TS, it appears that van der Waals interactions have a favorable contribution to lowering the energy barrier. Most importantly, the entropy term is the dominant factor in differentiating the activation energies. It drops from -17.3 kcal/mol for TS alone case, to -5.0 ~ -5.5 kcal/mol for TΔS with β-CD, and to -1.0 ~ -1.5 kcal/mol for TΔS with dimethyl-β-CD. Therefore, the binding of compounds 1 and 2a to cyclodextrins acts as pre-organization and remarkably reduces the entropy penalty to the activation free energy for the transition state of 1 and 2a. The entropy penalty for TΔS with dimethyl-β-CD is smaller than that of TΔS with β-CD, probably because binding of 1 and 2a to dimethyl-β-CD is stronger and the binding poses are more stable (see section 3.2). This result provides us the insights into the origin of the catalyzing power of cyclodextrins to Diels-Alders reactions and reveals the myth of why dimethyl-β-CD outperforms β-CD.

As discussed in the above, PM3 results are in qualitative agreement with experiment on active energies of the Diels-Alder reactions and the relative catalytic activities for the systems understudy. To further validate PM3 in predicting the cyclodextrin catalyzed Diels-Alder

reactions at the quantitative level and to further understand details of the catalytic mechanisms would require higher level *ab initio* calculations. Work in this direction is being conducted.

4. Conclusion

Dimethyl-β-CD was found to be able to catalyze Diels-Alder reactions of 9-anthracenemethanol with a variety of N-substituted maleimides under mild reaction conditions. However, the mechanism was unclear. We conducted this computational research for a possible explanation.

Hydrogen binding between the carbonyl groups on maleimides and the secondary hydroxyl groups of cyclodextrins was initially sought after as the major contributor to the catalysis. However, to our surprise the results from both the VM2 free energy calculations and the MD simulations show that such hydrogen bonds are unstable in the complexes of cyclodextrins with compounds 1 and 2a. No such hydrogen bonds are found in the conformations obtained from the VM2 calculations. In the trajectories from the MD runs, occurrence percentage of the hydrogen bonds between both carbonyl groups on 2a and cyclodextrins is 0.06% for dimethyl-β-CD and 3.23% for β-CD. The low occurrence doesn't support the mechanism with the hydrogen bonding. These hydrogen bonds, if exist, do help to lower the activation free energy to some extent, as evidenced by the QM calculations. However, both MD and PM3 support the observation of dominant entropic effect in cyclodextrin catalyzed Diels-Alder reaction.

Our calculations revealed valuable information which could lead to a new mechanism to explain the catalysis. Compound 2a has much stronger binding free energy than compound 1 in the binding to cyclodextrins, based on the results from both the VM2 and MD calculations. So compound 2a binds to cyclodextrins as the first step of catalysis. The binding of 2a to dimethyl-β-CD is driven by stronger enthalpy than the binding of 2a to β-CD. Then compound 1 approaches and interact with the complex of 2a and cyclodextrins. The MD result shows that compound 1 interacts with the complex of 2a and dimethyl-β-CD for significantly longer time than with the complex of 2a and β-CD. It interacts with 2a by π-π stacking and with methyloxy groups of dimethyl-β-CD by van der Waals interactions. In this step the binding of compound 1 is weak but still energy favorable according to the MMPB/SA result. Dimethyl-β-CD and β-CD thus serve as a container holding the two reactants to facilitate the reaction. The binding of both 1 and 2a to cyclodextrins appears to be the key to the catalysis of the reaction between these two compounds. It acts as pre-organization for the reaction, thus drastically lowers the entropy penalty in the activation free energy. Dimethyl-β-CD outperforms β-CD in almost every step of catalysis. It binds 2a more tightly, holds both 1 and 2a for much longer time in its cavity, and it pays smaller entropy penalty to the activation free energy of the transition state of 1 and 2a.

This computational work qualitatively explains the mechanism of the catalytic reaction by cyclodextrins. More extensive research is under way, which includes comparison and analysis of

the reactions between cyclodextrins and other N-substituted maleimides, and the work for quantification of the reaction energy profiles using high level ab initio methods.

References:

1. Marchetti, L.; Levine, M. Biomimetic Catalysis, *ACS Catalysis*, 2011, 1, 1090-1118.
2. Chaudhuri, S.; Phelan, T.; Levine, M. Cyclodextrin-Promoted Diels-Alder Reactions of a Polycyclic Aromatic Hydrocarbon under Mild Reaction Conditions, *Tetrahedron Letters*, 2015, 56, 1619-1623.
3. Tabushi, I. Cyclodextrin Catalysis as a Model for Enzyme Action, *Accounts of Chemical Research*, 1982, 15, 66-72.
4. Hapiot, F.; Bricout, H.; Menuel, S.; Tilloy, S.; Monflier, E. Recent Breakthroughs in Aqueous Cyclodextrin-Assisted Supramolecular Catalysis. *Catalysis Science & Technology* 2014, 4, 1899-1908.
5. Breslow, R.; Kohn, H.; Siegel, B. *Tetrahedron Letters*, 1976, 17, 1645–1646.
6. Rideout, D.C.; Breslow, R. Hydrophobic Acceleration of Diels-Alder Reactions, *Journal of the American Chemical Society*, 1980, 102, 7816–7817.
7. Schneider, H.J.; Sangwan, N.K. Diels-Alder Reactions in Hydrophobic Cavities: a Quantitative Correlation with Solvophobicity and Rate Enhancements by Macrocycles, *Journal of the Chemical Society, Chemical Communications*, 1986, 1787-1789
8. Breslow, R. and Dong, S.D. Biomimetic Reactions Catalyzed by Cyclodextrins and Their Derivatives, *Chemical Review*, 1998, 98, 1997–2011.
9. Breslow, R. Biomimetic Chemistry and Artificial Enzymes: Catalysis by Design, *Accounts of Chemical Research*, 1995, 28, 146–153.
10. Szejtli, J. Cyclodextrins and Their Inclusion Complexes: Akademiai Kiado: Hungary, 1982.
11. Dodziu, K. H. Cyclodextrins and Their Complexes: Chemistry, Analytical Methods, Applications. Wiley-VCH: Weinheim, 2006.
12. Boger, D.L., in Modern Organic Synthesis: Lecture Notes, The Scripps Research Institute Press, San Diego, CA, 1999, 213–272.
13. Siegel, J.B.; Zanghellini, A.; Lovick, H.M.; Kiss, G.; Lambert, A.R.; St. Clair, J.L.; Gallaher, J.L.; Hilvert, D.; Gelb, M.H.; Stoddard, B.L. Computational Design of an Enzyme Catalyst for a Stereoselective Bimolecular Diels-Alder Reaction. *Science*. 2010, 239, 309–313.
14. Gouverneur, V.E.; Houk, K.N.; de Pascual-Teresa, B.; Beno, B.; Janda, K.D.; Lerner, R.A. Control of the exo and endo Pathways of the Diels-Alder Reaction by Antibody Catalysis, *Science*, 1993, 262, 204-208.
15. Chaudhuri, S.; Phelan, T.; Levine, M. Cyclodextrin-Promoted Diels-Alder Reactions of a Polycyclic Aromatic Hydrocarbon under Mild Reaction Conditions, *Tetrahedron Letters*, 2015, 56, 1619-1623.
16. Chen, W.; Gilson, M.K.; Webb, S.P.; Potter, M.J. Modeling Protein-Ligand Binding by Mining Minima. *Journal of chemical theory and computation*, 2010, 6(11), 3540-3557.
17. Cézard, C.; Trivelli, X.; Aubry, F.; Djedaïni-Pilard, F.; Dupradeau, F.Y. Molecular dynamics studies of native and substituted cyclodextrins in different media: 1. Charge derivation and force field performances. *Physical Chemistry Chemical Physics*, 2011, 13(33), 15103-15121.
18. Hornak, V.; Abel, R.; Okur, A.; Strockbine, B.; Roitberg, A.; et al. Comparison of multiple

amber force fields and development of improved protein backbone parameters. *Proteins: Struct, Funct, Bioinf*, 2006, 65, 712-725.

19. Wang, J.M.; Wolf, R.M.; Caldwell, J.W.; Kollman, P.A.; Case, D.A. Development and testing of a general amber force field. *J Comput Chem*, 2004, 25, 1157-1174.
20. Ozpinar, G.A.; Peukert, W.; Clark, T. An improved generalized AMBER force field (GAFF) for urea. *J Mol Model*, 2010, 16, 1427-1440.
21. Chang, C.E.; Gilson, M.K. Tork: Conformational Analysis Method for Molecules and Complexes, *Journal of Computational Chemistry*, 2003, 24, 1987– 1998.
22. Chen, W.; Huang, J.; Gilson, M.K. Identification of Symmetries in Molecules and Complexes. *Journal of Chemical Information and Computer Sciences*, 2004, 44, 1301–1313.
23. Chang, C.E.; Potter, M.J.; Gilson, M.K. Calculation of Molecular Configuration Integrals. *The Journal of Physical Chemistry B*, 2003, 107, 1048–1055.
24. Amber 14 by D. A. Case, V. Babin, J. T. Berryman, et al. University of California, San Francisco. 2014.
25. Case, D.A.; Cheatham, T.E.; Darden, T.; Gohlke, H.; Luo, R.; et al. The Amber biomolecular simulation programs. *J Comput Chem*, 2005, 26, 1668-1688.
26. Goetz, A.W.; Williamson, M.J.; Xu, D.; Poole, D.; Le, Grand S.; et al. Routine microsecond molecular dynamics simulations with AMBER on GPUs. 1. Generalized Born. *J Chem Theory Comput*, 2012, 8, 1542-1555.
27. Jorgensen, W.L.; Chandrasekhar, J.; Madura, J.D.; Impey, R.W.; Klein, M.L. Comparison of simple potential functions for simulating liquid water. *J Chem Phys*, 1983, 79, 926-935.
28. Doll, J.D.; Dion, D.R. Generalized Langevin Equation Approach For Atom-Solid-Surface Scattering - Numerical Techniques For Gaussian Generalized Langevin Dynamics. *Journal of Chemical Physics*, 1976, 65, 3762-3766.
29. Adelman, S.A. Generalized Langevin Theory For Many-Body Problems In Chemical-Dynamics - General Formulation And The Equivalent Harmonic Chain Representation. *Journal of Chemical Physics*, 1979, 71, 4471-4486.
30. Essmann, U.; Perera, L.; Berkowitz, M.L.; Darden, T.; Lee, H.; et al. A Smooth particle mesh Ewald method. *J Chem Phys*, 1995, 103, 8577-8593.
31. Ryckaert, J.P.; Ciccotti, G.; Berendsen, H.J.C. Numerical-interaction of cartesian equations of motion of a system with constraints - molecular-dynamics of N-alkanes. *J Comput Phys*, 1977, 23, 327-341.
32. GaussView, Version 5; Semichem Inc.: Shawnee Mission, KS, USA, 2009.
33. Gaussian 09, Revision E.01, Gaussian, Inc., Wallingford CT, 2009.
34. Cui, Y.; Wang, C.; Mao, J.; Yu, Y. A facile and practical approach to randomly methylated β-cyclodextrin. *J. Chem. Technol. Biotechnol*., 2010, 85: 248–251.
35. Rowley, D.; Steiner, H. Kinetics of diene reactions at high temperatures. *Discuss. Faraday*

Soc., 1951, 10, 198-213.

36. Loncharich, R.J.; Brown, F.K.; Houk, K.N. Transition structures of the Diels-Alder reaction of butadiene with acrolein. *The Journal of Organic Chemistry*, 1989, 54(5), 1129-1134.
37. Humphrey, W.; Dalke, A.; Schulten, K. VMD: Visual molecular dynamics. *Journal of Molecular Graphics & Modelling* 1996, 14, 33-38.

	ΔG_{calc}	$\Delta E_{Valence}$	$\Delta E_{Coulomb}$	ΔE_{PB}	ΔE_{NP}	ΔE_{VDW}	ΔH	$T\Delta S$
β-CD and 1	-2.708	1.959	-8.041	15.693	-2.855	-25.271	-18.515	-15.807
dimethyl-β-CD and 1	-4.085	3.009	-8.497	14.839	-2.908	-26.058	-19.615	-15.530
β-CD and 2a	-6.578	0.391	-5.980	13.230	-2.756	-25.115	-20.230	-13.652
dimethyl-β-CD and 2a	-6.173	2.570	-11.253	15.276	-2.761	-25.218	-21.386	-15.213

Table 1. Calculated free energies and breakdowns by the VM2 method for the complexes of reactants and cyclodextrins. Unit in kcal/mol.

	$\Delta E_{Coulomb}$	ΔE_{PB}	ΔE_{NP}	ΔE_{VDW}	$\Delta H_{MMPB/SA}$
β-CD with 2a	-7.240	17.231	-2.189	-23.074	-15.272
dimethyl-β-CD with 2a	-3.379	13.350	-2.179	-24.514	-16.722
β-CD with 1 and 2a	-15.997	27.791	-2.657	-25.883	-16.746
dimethyl-β-CD with 1 and 2a	-5.508	19.171	-2.964	-31.089	-20.390

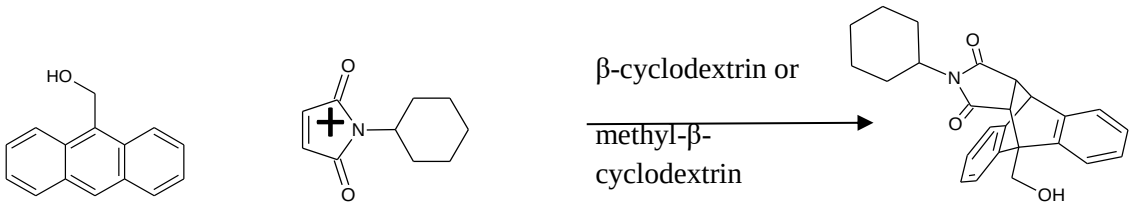
Table 2. The MMPB/SA energies and breakdowns for the complexes of reactants and cyclodextrins. Unit in kcal/mol.

	MD		VM2	
β-CD	2a	1.437 ± 0.701	2a	0.381 ± 0.112
	cyclohexyl	-0.033 ± 0.870	cyclohexyl	-1.388 ± 0.154
	urea moiety	3.351 ± 0.678	urea moiety	2.136 ± 0.107
dimethyl-β-CD	2a	2.048 ± 0.731	2a	1.423 ± 0.126
	cyclohexyl	0.674 ± 0.873	cyclohexyl	-0.104 ± 0.167
	urea moiety	3.946 ± 0.701	urea moiety	3.373 ± 0.119

Table 3. The average distances between centers of 2a or its moieties and the center of cyclodextrins in the course of 300 ns MD runs. The corresponding values from the conformations of the VM2 calculations are also listed for comparison. Unit in Å. Please refer to the text for the meaning of positive and negative values.

	ΔG	**ΔH**	**TΔS**
TS alone	49.040	31.759	-17.281
TS with β-CD, set 1	36.465	30.963	-5.502
TS with β-CD, set 2	38.321	33.324	-4.997
TS with dimethyl-β-CD, set 1	29.464	27.904	-1.560
TS with dimethyl-β-CD, set 2	29.171	28.131	-1.040

Table 4. The activation free energies, enthalpies and entropies for TS alone, TS with β-CD, and TS with dimethyl-β-CD. Two transition state settings were used for β-CD and dimethyl-β-CD. In set 1 there are hydrogen bonds between TS and cyclodextrins and in set 2 no such hydrogen bonds are present. Unit in kcal/mol.



1 2a

Figure 1. The Diels-Alder reaction of 9-anthracenemethanol (1) with N-cyclohexyl maleimide (2a) with β-cyclodextrin or methyl-β-cyclodextrin as catalyst.

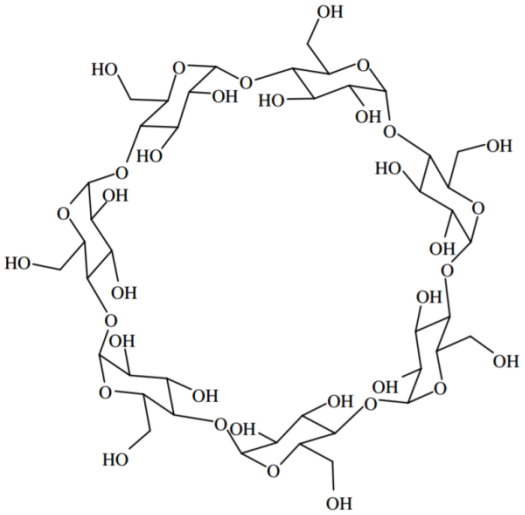


Figure 2. Molecular structure of β-cyclodextrin.

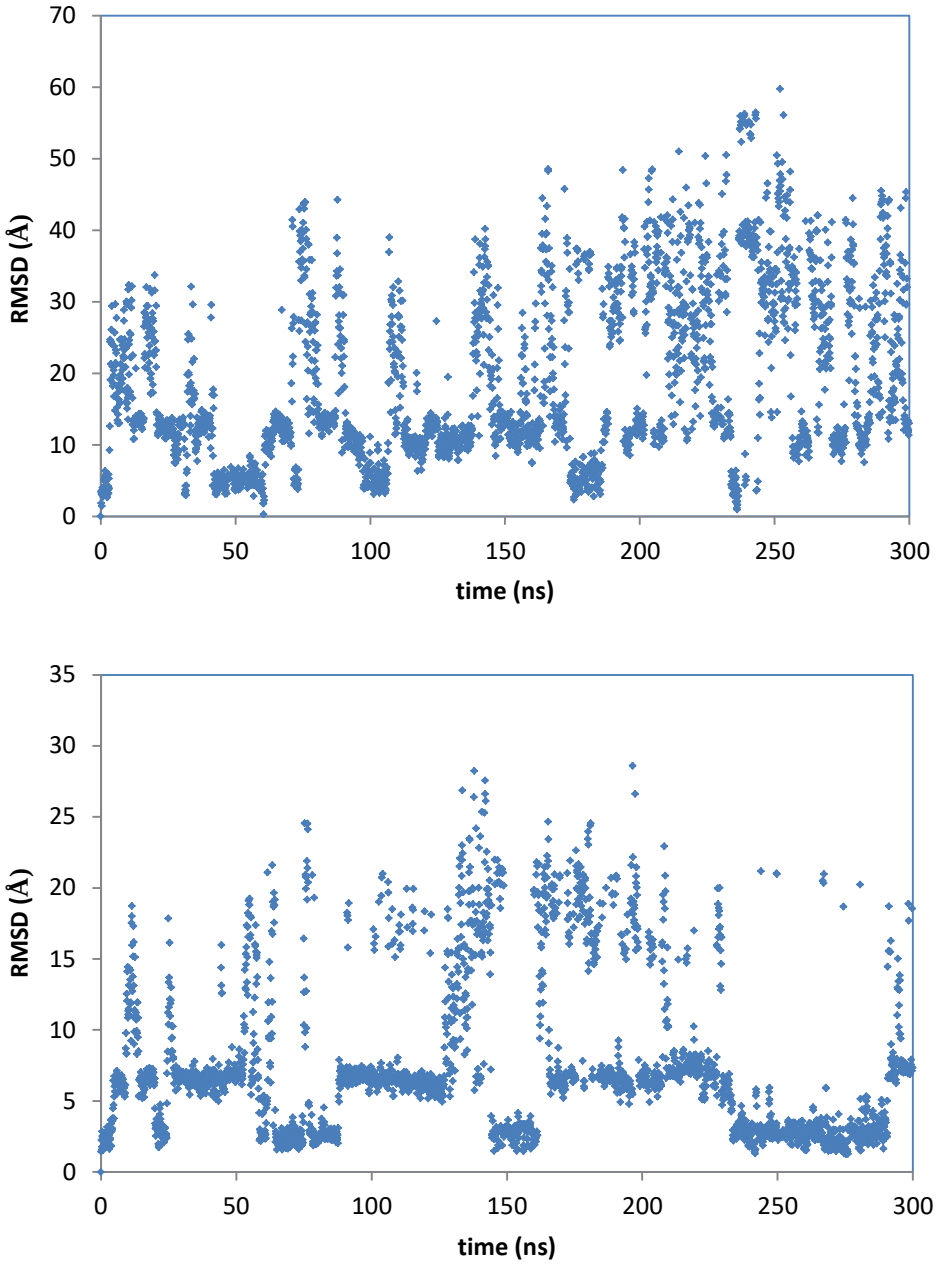


Figure 3. RMSD of compound 1 with respect to the initial conformation in the 300 ns MD runs. Left: complex of β-cd with 1 and 2a; right: complex of dimethyl-β-cd with 1 and 2a.

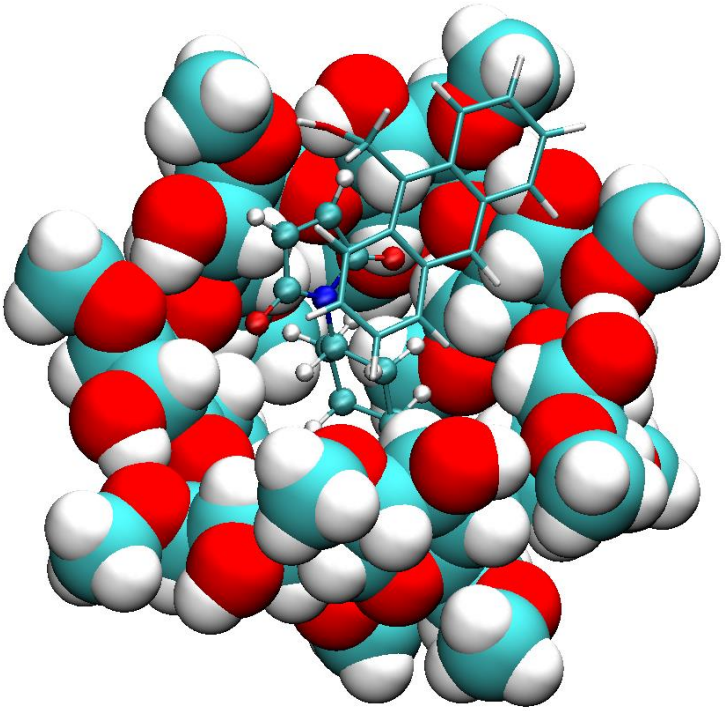


Figure 4. Binding mode of compound 1 with 2a and dimethyl-β-CD. Compound 1 is rendered in licorice, 2a in CPK and dimethyl-β-CD in VDW. The picture was generated with VMD [37].

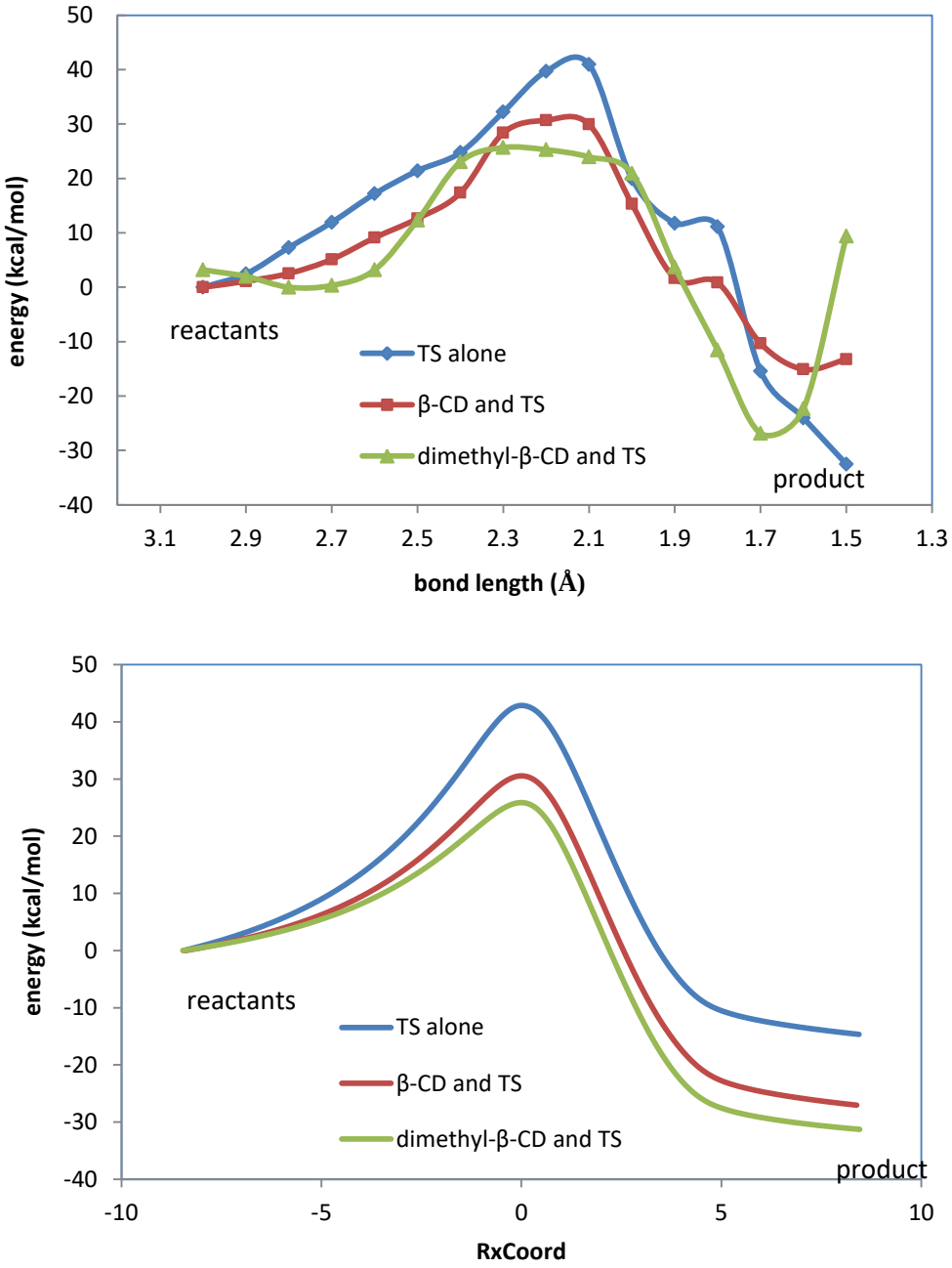


Figure 5. Top: energy changes with the length of the bonds connecting 1 and 2a to form the product by the Bond Length Scanning method. Bottom: Reaction paths obtained by IRC. In both plots the curves are normalized to set the reactants energies at zero point.

Supplement materials:

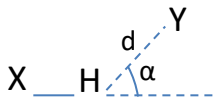


Figure SI-1. Definition of hydrogen bonds. X and Y stand for the donor and the acceptor respectively. d is the distance between the acceptor Y and the hydrogen, and α is the complimentary angle of X-H…Y. A hydrogen bond is formed if d is smaller than 2.0 Å and α is smaller than 90^{o} .

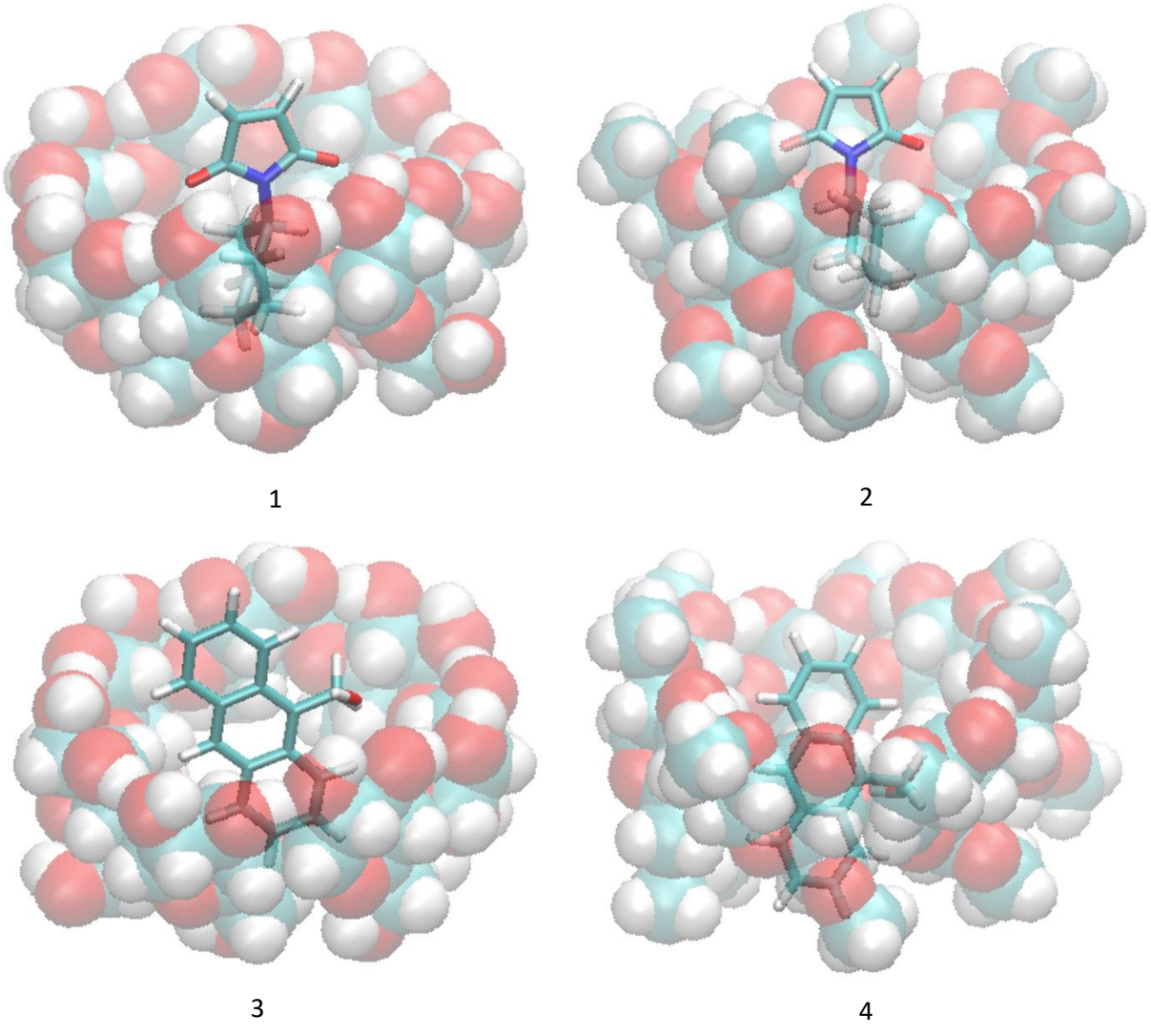


Figure SI-2. Binding modes of compounds 1 and 2a to cyclodextrins by VM2. (1) 2a and β-CD; (2) 2a and dimethyl-β-CD; (3) 1 and β-CD; (4) 1 and dimethyl-β-CD.