



In silico studies to probe the catalytic role of cucurbit[*n*]uril on [4+2] cycloaddition reaction between cyclopentadiene and methyl acrylate



Debashis Sahu, Bishwajit Ganguly*

Computation and Simulation Unit (Analytical Discipline and Centralized Instrument Facility), CSIR-Central Salt and Marine Chemicals Research Institute, Bhavnagar, Gujarat 364002, India

Academy of Scientific and Innovative Research, CSIR-Central Salt and Marine Chemicals Research Institute, Bhavnagar, Gujarat 364002, India

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ABSTRACT

The catalytic role of cucurbit[*n*]urils on the reactivity and stereoselectivity of the [4+2] cycloaddition reaction between cyclopentadiene and methyl acrylate has been examined with density functional calculations.

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The Diels–Alder (DA) reaction is one of the most valuable reactions in preparative organic synthesis involving a conjugated diene and a dienophile.¹ It has been used for the diastereo- and regioselective generation of six-membered rings with upto four stereogenic centers in a single step.² DA reactions are extensively used for the production of different kinds of products like pharmaceutical drugs, agrochemical compounds, flavors, and fragrances in industries.² Kleemann et al. reported that more than 2400 active pharmaceutical drugs have been marketed that include a DA cycloaddition in their synthetic sequence.^{2,3} Solvents⁴ and catalysts⁵ have an important role to control the product yield as well as the selectivity for such cycloaddition reactions.

The reaction between cyclopentadiene (Cp) and methyl acrylate (MA) is one of the well studied cycloaddition reactions in this class, which has been extensively studied to get a better insight of the role of the different solvent media (like methanol, ethanol, and ionic liquids) and the influence of different Lewis acid based catalysts (BH₃, clay, salt solution of LiCl₄/LiClO₄, and guanidinium sulfate) to the reaction rate as well as the selectivity of the products.^{6–9} The *endo* selectivity is observed for this reaction in the common organic solvents like methanol, ethanol, acetone, acetonitrile, pyridine etc at different temperatures.¹⁰ The *exo/endo* ratio varied with temperature and the use of different solvent medium. The hydrogen bond donation ability of the solvent media has an important role

in the selectivity as well as the rate of the reactions.¹¹ Initially the observed *endo*-selectivity was rationalized with secondary orbital interactions.^{12,13} However, the recent studies have shown that electrostatic interactions, steric interactions, hydrogen bonding, and solvent effects can also explain the stereoselectivities of DA reactions.^{14–16} We have examined this reaction in the supramolecular polycyclic hosts molecules like cucurbit[6]uril and cucurbit[7]uril in methanol to investigate the role of such hosts in DA reaction.

In the new millennium, cucurbiturils (CBs) have become an adaptable and extremely attractive class of supramolecular synthetic receptors^{17,18} with various molecular applications.¹⁹ These synthetic macropolycyclic receptors have superb capability to bind a variety of organic, inorganic, and biological molecules and ions in the aqueous phase as well as in the solid state.^{20,21}

The pumpkin shape cucurbit[*n*]urils (CB[*n*], *n* = 5–8, 10) are a family of synthetic supramolecular host molecules which are cyclic oligomers of *n* glycoluril units linked by 2*n* methylene groups²² making two portals that are the carbonylated hydrophilic portion and a hydrophobic cavity (nanocavity).²³ These two portals permit CBs to bind to both the polar and the nonpolar organic molecules.²³ CBs contain a cavity comparable to that of cyclodextrins,²⁴ which are made of *D*-glucopyranosyl units.²³ The primary differences between CBs and cyclodextrins are in their host–guest interactions due to the different functional groups decorating the cavity entrances.²⁵ From CB[5] to CB[10], the cavity size as well as the outer diameter gradually increase.²⁵

* Corresponding author. Tel.: +91 278 256 7760; fax: +91 278 256 7562.

E-mail address: ganguly@csmcri.org (B. Ganguly).

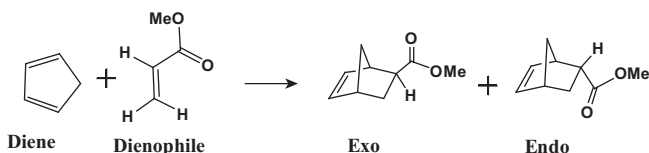
Recently, CB homologs and its derivatives offer novel scopes in many areas of supramolecular chemistry including recognition,^{26–28} catalysis,^{23,29–32} sensor,³³ transport,³⁴ drug/gene delivery,^{21,22} artificial ion channels,³⁵ and nanomaterials.³⁶ The uses of CB[n]urils are also important in the green chemistry.³⁷ The highly potent greenhouse gases SF₆ and CO₂ (long-lived in the atmosphere) that contribute to climate change, can be trapped by CB[n]uril.^{38,39}

Mock et al. reported the catalysis of a 1,3-dipolar cycloaddition between an azide and an acetylene by the reaction vessel CB[6] where the 1,4-disubstituted product dominates over the 1,5-disubstituted product in a regiospecific way.^{29,40} The influence of CB[n]urils on the polar cycloaddition reaction was examined by computational studies.⁴¹ The catalysis of the DA reactions between Cp with butenone inside the hydrophobic cavity of cyclodextrin is reported in the literature.⁴²

The host–guest template effect of macrocyclic receptors, CB[n] family offer an interesting alternative for controlling reactions that require higher order by forming the stable host–guest inclusion complexes in their nano-cavity. Inspired by such experiments, we have computationally investigated the [4+2]-DA reaction between Cp and MA inside the cavities of two different sized CBs, CB[6], and CB[7]. It is expected that CB[n]urils can bring the two reactant molecules (diene and dienophile) into close proximity with desired orientations and facilitate the [4+2] cycloaddition reaction in their cavities. The schematic presentation of the cycloaddition reaction in the absence of CB[n]uril is given in the Scheme 1.

First the cycloaddition reaction was performed in the absence of CB[n]uril and then the same reaction was carried out in the presence of the supramolecular host CB[n]uril. Full geometrical optimizations have been carried out in the gas phase employing the M05-2X level with standard 6–31G(d) basis set. Frequency calculations were performed at the same level of theory, to confirm that each stationary point is a local minimum (with zero imaginary frequency) or transition state (with one imaginary frequency). The M05-2X level^{43–45} of theory has been considered as an excellent DFT functional and also shows good robustness in different studies.^{44,46–49} To account for the solvation effects, the universal solvation model, SMD,^{50,51} by Truhlar and co-workers was employed with the dielectric constant corresponding to methanol ($\epsilon = 32.613$). The reactant complex (RC) and the transition state (TS) geometries were placed at the mid-position of the supramolecular host CB[n]uril for the calculations. To examine the variation of energies with the location of RC and TS inside the cavity, additional calculations have been performed. The reactants were shifted from the mid-position to the periphery of the host CB[n]uril. The optimized geometries were found to move much inside the cavity and a very similar situation to the previous geometries as obtained from mid-position calculations was seen. All the calculations have been performed with GAUSSIAN 09 suite of program.⁵²

We have examined the *exo*- and *endo*-TSs corresponding to the *exo* and *endo* diastereomers in the absence of the supramolecular synthetic host molecules. The experimental free energy of activation reported for the cycloaddition reaction between Cp and MA is 22.4 kcal/mol in a mixture of methanol/water (50/50) at 298.15 K,⁵³ which is in good agreement with the M05-2X calculated results (Table 1). The free energy of activations calculated with M05-2X/6–31G(d) level of theory in methanol showed larger



Scheme 1. [4+2] Cycloaddition reactions between Cp (diene) and MA (dienophile) in the absence of CB[n]uril.

Table 1

M05-2X/6–31G(d) calculated electronic activation energy (ΔE^\ddagger) and free energy of activation (ΔG^\ddagger) for the reactions between Cp and MA in methanol medium in the absence of host

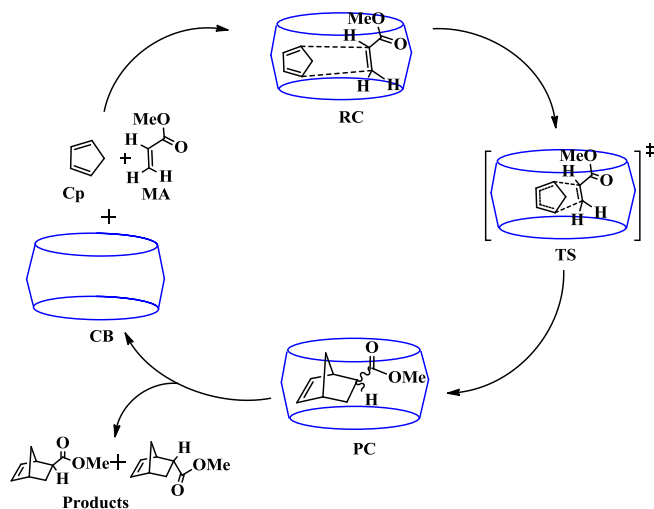
	ΔE^\ddagger	ΔG^\ddagger
Cp+MA	0.0	0.0
<i>exo</i> -TS	7.6	20.8
<i>endo</i> -TS	6.1	19.1
<i>exo</i> -Pdt	–33.9	–17.2
<i>endo</i> -Pdt	–34.1	–17.5

All energies are in kcal/mol.

preference for the *endo*-TS (19.1 kcal/mol) compared to the *exo*-TS (20.8 kcal/mol) of Cp and MA, which is in agreement with the experimental observations.⁵³ The electronic activation energies also corroborate the formation of the *endo*-product over the *exo*-product (Table 1).

The interaction of Cp and MA for the cycloaddition reactions is shown in Scheme 2. In the first step, the reactants form a ternary reactant complex (RC) between Cp and MA inside the cavity of CBs. The RC moves to the transition state (TS), which leads to the formation of product complex (PC) inside the cavity of CBs. Finally the product is released from the CB in the final step.

Accordingly, the cycloaddition reaction of Cp and MA has been performed in the cavities of CB[6] and CB[7] in methanol to understand the catalytic role of the host molecules. The reactant complex (RC) of Cp and MA has been calculated inside the cavity of CB[6] and CB[7], while docking them in the middle of the host molecules (see Supplementary data, Fig. S1). Further, the transition states have been located inside CB[6] and CB[7] host molecules. The M05-2X/6–31G(d) calculated results suggest that the RCs inside the CB[6] cavity is higher in energy than the free reactant molecules. The relative free energy values for the *exo*-RC is 30.0 kcal/mol, whereas, the corresponding value for the *endo*-RC is 25.8 kcal/mol, respectively. The *exo*- and *endo*-TSs located for Cp and MA within the cavity of CB[6] were found to be 7.7 and 5.3 kcal/mol higher in energy than the corresponding complex (RC) (Table 2). However, the situation is different for the cycloaddition reaction between Cp and MA within the cavity of CB[7]. The calculated free energy values (RCs) were found to be lower than the free reactants (Table 2). The free energy activation barrier calculated for the preferred *endo*-product with M05-2X/6–31G(d) level was found to be 14.9 kcal/mol with respect to the *endo*-RC, which is much lower than the free energy activation barrier



Scheme 2. The CB catalyzed [4+2] cycloaddition reaction.

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