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Using non-covalent interactions to direct regioselective 2+2 photocycloaddition within macrocyclic cavitand

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ABSTRACT

The relative orientation of guests within ternary inclusion complexes is governed by the host-guest and guest-guest supramolecular interactions. Selectivity in 2+2 photocycloaddition between two alkenes included within macrocyclic cavitand (γ-cyclodextrin) can be controlled using non-covalent interactions. In this manuscript we report caviand-mediated control of regioselectivity between alkyl cinnamates using non-covalent interactions. Using this method, we have shown that regioselectivity can be switched completely from a head-to-head dimer to head-to-tail dimer. The reactions were also stereoselective in most cases. Stoichiometry experiments were performed to explore relative stabilities of the complexes, which indicate that the ternary complex is more stable than others. Selectivity in the photocycloaddition reaction was also applied retrospectively to deduce intermolecular orientations. Time-dependent conversion study indicate that the observed reactivity of the alkenes is representative of the intermolecular orientations in the bulk of the complex medium. Experimental observations and computational studies were used to qualitatively understand the complex structures, and relative magnitudes of the weak interactions. The reactions of complexes were studied in slurry form, and extent of reaction control suggests a solid-state like behavior.

INTRODUCTION

Photocycloaddition is a well-studied bimolecular photoreaction.[1] Application of this reaction in the fields of materials science,[2-4] organic synthesis,[5-7] and optical data storage,[8-10] makes it a highly useful reactions. Photocycloaddition between the nucleic bases is an important reaction relevant to cell biology.[11-13] Moreover, stereospecific cyclobutane cores are found in a number of natural compounds with biological and medicinal significance.[14] Given its importance, controlling reaction efficiency and selectivity will have practical value. The 2+2 photocycloaddition of alkene can give rise to four different isomeric dimers (scheme 1),[15-17] As a simple addition reaction between π-bonded carbons, the shape of the isomer is structurally close to the arrangement of the alkenes prior to reaction, a term referred to as 'molecular memory'.[18-21] This has proved to be a valuable tool in the hands of supramolecular chemists for deducing effects of weak interactions in molecular self-assembly. Photoactive alkenes with weakly interacting groups were allowed to self-assemble, whose photoreactivity and chemo- and/or stereoselectivities were used to predict influence of weak interactions. Starting with Schmidt's topochemical studies of cinnamic acids, several examples are known, where the effects of weak interaction such as π-π,[22] CH-π,[23, 24] charge-transfer,[18, 25, 26] weak hydrogen bonding,[27] and halo-halo,[18, 28] have been studied through their manifested reaction selectivities. While this approach has been predominantly studied in the crystalline-state, it has also been implemented using host-guest chemistry. The proximity between guest molecules entrapped within the limited spaces of cavitands (host) facilitate intermolecular interactions. Host-guest chemists have used such reaction selectivity to study directing effects of weak interactions in the complexes.[29-35] In this manuscript we report the directing influences and relative magnitudes of steric, π-π, and halo..halo interactions deduced through photochemical reactivity of γ-cyclodextrin (γ–CD) complexes of alkyl cinnamates.

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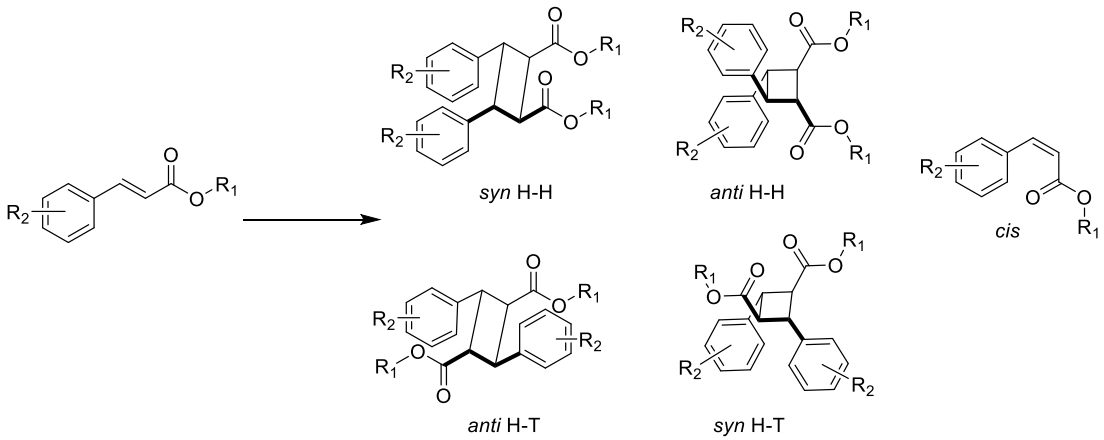

Scheme 1. Photoproducts resulting from the excited state reactivity of alkyl cinnamates.

Cavitand-mediated photodimerization of alkenes has been known since the early 1980s when Tanaka et al reported the influence of β-cyclodextrin on the photodimerization of coumarins.[36] Leading supramolecular chemistry groups have utilized this strategy to control the stereo- and regioselectivities of bimolecular photoreactions.[37-39] In this manuscript we report our ability to control the regiochemistry (predominantly) of photocycloaddition reaction with weak interactions through cavitand-mediation approach. The effectiveness of this method is demonstrated through the complete switch in regioselectivity in some cases. In 2006 Ramamurthy et al (along with one of the authors of this manuscript) reported the photoreaction of *trans*-cinnamic acids (CA) complexed within γ-cyclodextrin (γ-CD). The reaction yielded the most compact *syn* Head-to-Head (*syn* H-H) dimer[30] with excellent selectivities and high yields. Considering the efficiency of this method, we envisioned that the cavitand-mediated photodimerization can be further broadened to produce desired regioisomer. We reasoned that substituting the carboxylic acid protons with alkyl group should disfavor the *syn* H-H arrangement, as the two alkyl groups would deter each other sterically. This should favor the other compact, *anti* Head-to-Tail (*anti* H-H) dimer (figure 1). The work reported herein is part of our ongoing effort[35] to generalize the cavitand-mediated photodimerization approach for directing reaction specificity to produce broad array of cyclobutanes. Our strategy towards this goal involves modifying the intermolecular interactions between reacting alkenes, which will lead to a different pre-orientation, and thus a different isomer. γ-CD-complexes of the alkenes reported in this were irradiated as slurry, while earlier works were either performed in solid-state or aqueous solution. Thus, this work is useful in understanding the stability of complex in slurry form. Cyclodextrins are used in drug formulations as drug delivery agents. Hence, studying characteristics of complexes in slurry form will be useful in this regard. We have also performed some comparative studies with another macrocyclic host 2-hydroxy propyl γ-cyclodextrin (HP-γ-CD) to better understand supramolecular forces governing the relative orientation of guests within cavitands.

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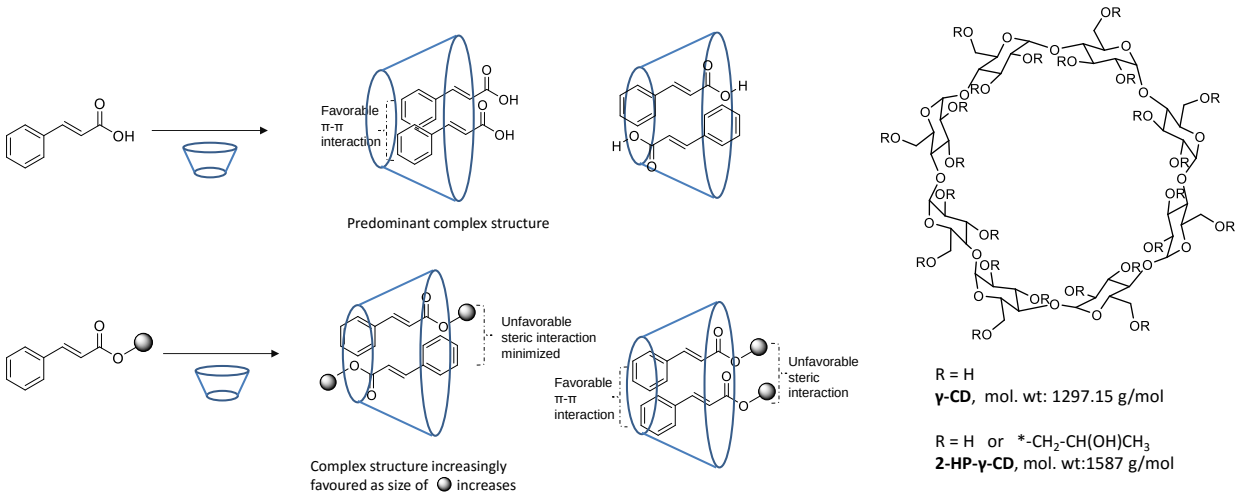

Figure 1. Graphical representation of the supramolecular approach used to switch the relative orientation of alkenes within the cavitand to direct regioselectivity.

EXPERIMENTAL

γ-Cyclodextrin was purchased from CDT, Inc. and used as received. 2-hydroxypropyl-γ-cyclodextrin was purchased from Research Biochemicals International. The cinnamic acids, solvents, and drying agents were purchased from commercial sources (Sigma Aldrich, Fischer Scientific, VWR, and MP Biomedicals LLC) and used as received.

Preparation of esters: Cinnamic acids purchased from commercial vendors were converted to the respective acid chlorides by refluxing in excess thionyl chloride. The excess thionyl chloride was removed under vacuum and the dry product was refluxed in excess alcohol. The reaction mixture was washed with water, and aq. sodium carbonate to remove water-soluble components, and extracted with dichloromethane. Unreacted acid/acid chloride were simply removed in the base wash. The organic layer was stripped off the solvent using a rotavap, dried under high vacuum for several hours, and analyzed using ^{1}H NMR. Esters prepared this way yielded products in almost 100% purity, and were obtained as viscous neat substances. The vacuum dried products were used to prepare standard solutions in volumetric flasks in dichloromethane. Aliquots of the solutions for required quantities were measured out into 20 mL scintillation vials, dried using nitrogen stream to remove the solvent, and mixed with 0.5 (or 1) equivalents of host for complexation.

Complexes and irradiation: Host-guest complexes were prepared by mixing half equivalents of γ-CD with the nitrogen stream-dried ester with 5 mL of water. The mixtures were sonicated for 2 hrs, followed by 5 hrs of stirring. A white precipitate formed during sonication indicating complexation. Resulting insoluble white precipitates were irradiated as it is in slurry form. Irradiations were performed with a medium pressure mercury vapor lamp immersed in a water-cooled Pyrex jacket. Following irradiation, the inclusion complexes were dissociated through biphasic extraction with water and ethyl acetate. The organic layer was separated, and residual water was removed using anhydrous Na_2SO_4. The solvent was rotary evaporated, and the final sample dried under high-vacuum. The dried samples were then subject to ^{1}H NMR (300 MHz Bruker Avance) analysis in $CDCl_3$. Product proportions were determined from integration of peak areas of characteristics signals. Integrations, and coupling constants were performed using the Bruker Topspin software, and ACD labs freeware respectively. The dimer signals were characterized based on NMR data reported in literature.[16, 18, 29, 40-44] In cases of esters with more than 2-carbon alkoxy groups, the reaction mixtures were too complex for direct NMR analysis. The dimers were base hydrolyzed, and

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acid treated to obtain the dimers in their carboxylic acid forms. The dimers with carboxylic acid units were then compared with the literature-reported chemical shifts.

Computational chemistry calculations were performed using the Gaussian '09 software package.[45, 46] Geometry optimizations and thermochemical calculations of the complexes were performed using the Universal Force Field package in the software (molecular mechanics). Both the geometry optimizations and thermochemical calculations were performed in water as the medium based on the Implicit Polarizable Continuum Model (IPCM).

RESULTS AND DISCUSSION

Host, guests, and complexes: Cyclodextrins are a family of toroid-shaped macrocyclic cavitands composed of oligomeric sugar (glucose) units. They are made from the enzymatic digestion of starch to produce predominantly α-, β-, and γ-cyclodextrins. These cavitands consist of hydroxyl groups on the top and bottom rims rendering them water-soluble, while the interiors are hydrophobic, which can accommodate hydrophobic small molecules within. γ-cyclodextrin consists of eight glucose units and is the larger among the three, capable of including two guests simultaneously. The choice of γ-CD for this study is based on its tendency to form ternary complexes, which will be conducive for the bimolecular photodimerization reaction. The cavitands used in this γ-CD, and its functionalized derivative (2-hydroxypropyl- γ-CD) were purchased from commercial vendors (experimental section). Cinnamic acids are naturally occurring compounds found commonly in plants, and are well-studied photosubstrates in organic photochemistry. Excited state reactivity of cinnamic acids predominantly favors isomerization over photodimerization due to entropic disfavorability for the latter pathway. Some of the stereoisomers of cinnamic acid photodimers (truxillic and truxinic acids) are also found naturally in plants. Efficiency of cinnamic acid photodimerization is improved when two cinnamic acids are placed proximally, such as in solid-state or host-guest complexes. In this paper we have used γ-CD to bring two cinnamic acids/esters together to control dimer stereoselectivity by taking advantage of the steric and electronic interaction between them. Esters used in this study were synthesized by treating the cinnamic acids with thionyl chloride to generate acid chlorides followed by alcohol solvolysis reaction.

Photochemical studies: We started our investigation with the reaction of 1:2 complex of γ-CD cinnamic acid complex. When irradiated as a slurry, the complex yielded predominantly *syn* H-H dimer (83%) and a small amount of *cis*-cinnamic acid (figure 2, and table 1). This is similar to the reaction reported by Ramamurthy's group in 2006, in the solid state.[26] The predominance of dimer in product mixture is attributed to predominance of 1:2 complex, with alkenes in proximity. As in this reaction, the *cis* cinnamic isomer was not formed in any significant amounts in other reactions as well (vide infra).The high degree of reaction control is very similar to that of reactions in solid-state. Among the four possible dimers that could result from this reaction, only *syn* H-H was the major product at near complete conversion. This suggests that the overlapping phenyl ring precursor (*syn* H-H) arrangement is more favourable. Though the compactness of the resulting dimer was originally thought to be the main reason for the selectivity, we speculate that the π-π interaction between the aromatic rings is also a dominant stabilizing factor favouring the precursor *syn* H-H arrangement. Support for this speculation can be derived from related work in literature,[22, 29, 41, 47, 48] where stereoisomers with stacked aromatic rings were major products.

We then proceeded to study alkyl cinnamates. The steric interaction between alkyl groups should disfavor the H-H arrangement, leading to another compact arrangement (head-to-tail) that could fit within the γ-CD cavity. Such a reasoning proved to correct from the product distribution observed in the reaction of 1:2 complex of γ-CD-*trans* methyl cinnamate complex. As shown in figure 2 (second ^{1}H NMR spectrum), we observed the formation of two dimeric products as the major products of the reaction with almost no isomerization. Based on the shape, multiplicity, chemical shifts, and coupling constants, the products were identified to be *syn* H-H and *anti* H-T dimers. The dimers formed in approximately equal proportions with slight excess of the *anti* H-T isomer. Intrigued by these findings, we proceeded to perform a systematic

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study to understand how the characteristics of alkyl substituents influence complex structure, and dimer distribution.

Irradiation of 1:2 complex of *trans*-ethyl cinnamate swayed the selectivity more towards the *anti* H-T dimer (63%), expectedly due to further destabilization of the H-H arrangement induced by the ethyl group. Finally, with isopropyl cinnamate we observed that the reaction yielded the *anti* H-T dimer exclusively. This reaction outcome marked a complete switch in regioselectivity from *syn* H-H to *anti* H-T. Gradual change from formation of predominance of one dimer to the exclusive formation of the other is presented in figure 2.

Table 1. Product distribution resulting from irradiation of *trans* cinnamic acid and alkyl cinnamates complexed to γ-CD.

Cinnamic acid (R_2-Ar)	Alkoxy group (R_1-O)		*% syn* H-H	*% anti* H-T	*% syn* H-T/*anti* H-H	*cis*
H	H	1	83	-	-	17
H	methyl	1a	45	52	-	3
H	Ethyl	1b	34	63	-	3
H	isopropyl	1c	-	97	-	3
H	n-propyl	1d	26	47	10	17
H	n-butyl	1e	16	17	11	56
H	cyclohexyl	1f	-	-	-	100

Percentage of products from reaction mixtures calculated from integration of ^{1}H NMR signals.

Table 1 consolidates the product distribution resulting from irradiation of 1:2 γ-CD complexes of alkyl cinnamates. The isopropyl group conferred high degree of reaction control and selectivity, as *anti* H-T was the only product observed. But, switching the isopropyl group to n-propyl group resulted in some noticeable differences, though *anti* H-T was still the major product. Significant amounts of two other dimers, and *cis* cinnamate were observed in the NMR spectrum. One of those dimers was the *syn* H-H dimer, and based on the signal structure, the other is speculated to be *anti* H-H. However, the identity of the dimer is not crucial due to its lower proportion, and we merely consider the formation of this dimer as an indication of loss of reaction control. This loss of reaction control was even more evident with *n*-butyl cinnamate, where *cis* cinnamate was the major product. The end-point of the trend was found in cyclohexyl cinnamate, for which isomerization product was the only photoproduct, and no dimerization product resulted. We believe that the larger size of the cyclohexyl group prevented the guests from forming a 1:2 complex, and that 1:1 complex is most likely the predominant complex.

Table 2. Product distribution resulting from irradiation of substituted *trans* cinnamic acid and alkyl cinnamates complexed to γ-CD.

Cinnamic acid (R_2-Ar)	Alkoxy group (R_1-O)		*% syn* H-H	*% anti* H-T	*% syn* H-T/*anti* H-H	*% cis*
4-methyl	methyl	2a	43	51	-	6
4-methyl	Ethyl	2b	28	64	-	8
4-methyl	isopropyl	2c	20	77	-	3
3-methoxy	Methyl	3a	61	32	-	7
3-methoxy	Isopropyl	3b	24	58	7	11

Percentage of products from reaction mixtures calculated from integration of ^{1}H NMR signals.

Having studied the influence of size of the alkyl group on product distribution, and its correlation to complex structure, we turned our attention to understanding the influence of substituents on the aromatic side of the guest. Alkyl cinnamates with methyl, methoxy, and halogen substituents on the aromatic ring were studied. Product mixtures from photochemistry of complexes of esters of 4-methyl cinnamic acid[40] (**2**) followed a similar selectivity trend as those for the parent cinnamates, discussed above; amount of *anti* H-T in reaction mixture increased with increasing size of alkoxy group. We noticed that despite the presence of volume-demanding methyl substitution on the aromatic ring, methyl and ethyl esters of the acids (**2a-b, and 1a-b)** yielded similar proportions of the two dimers. It is important to point out here that 4-methyl cinnamic acid yielded *syn* H-H dimer selectively in solid-state.[26] Hence, it is not surprising that the methyl and ethyl esters of **1** and **2** behave similarly. Isopropyl ester of **2** yielded *anti* H-T as the predominant product. However, a 20% of *syn* H-H also resulted in the reaction, which was not observed for **1C**. We

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believe that this is difference is due to the larger size of isopropyl group and the steric conflict it poses is with aromatic methyl group is now significant. This should have reduced the difference in stabilization energies between the H-H and the H-T arrangements. Such an effect would be missing in **1C**, which will lead to a larger difference in energies between the two arrangements. This line of reasoning was justified by similar product distributions for 3-methoxy cinnamates (**3a-b**) wherein the isopropyl ester afforded *anti* H-T as the major product with sizable amount of *syn* H-H. However, a greater loss in reaction control was also recognized due to formation of noticeable amount of a third dimer, and isomerization product.

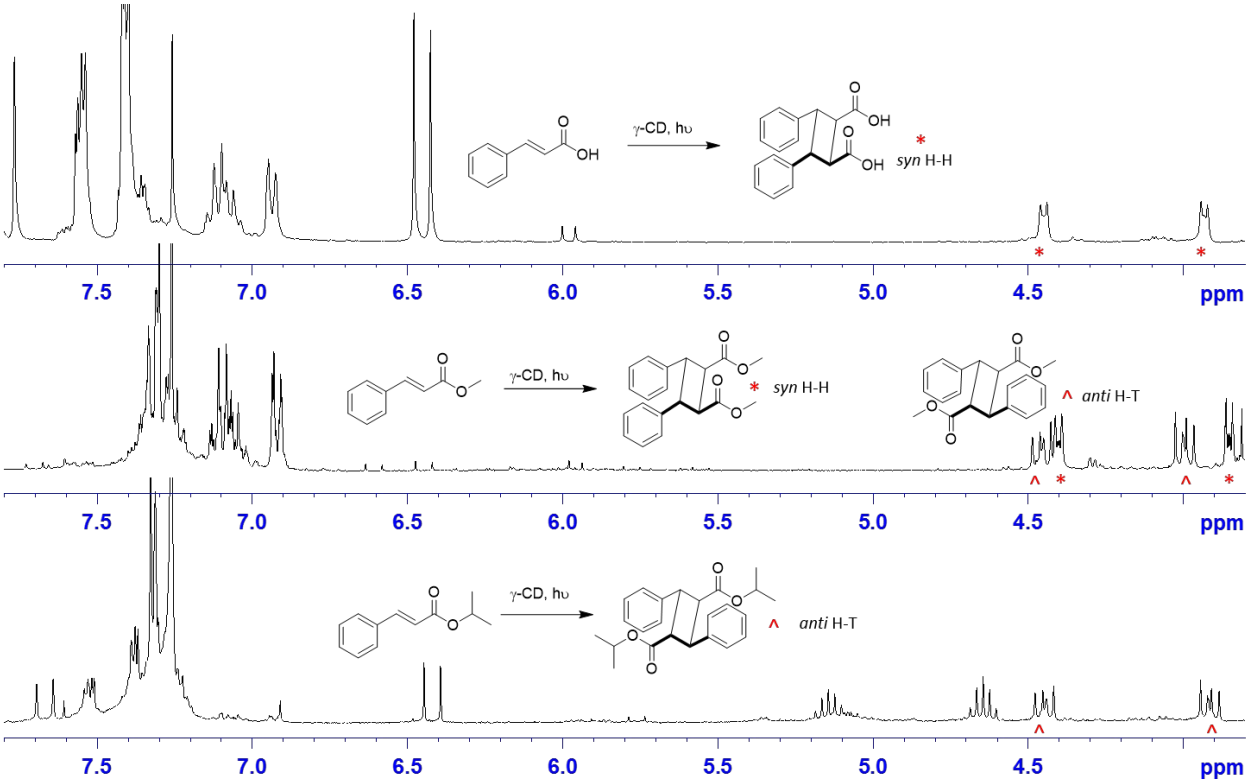

Figure 2: ^{1}H NMR spectra of reaction mixtures that resulted from the irradiation of slurry 1:2 (H:G) γ-CD complexes of cinnamic acid, and its esters. A gradual, but complete, switch from *syn* H-H to the *anti* H-T dimer was achieved through the use of appropriate alkoxy substituent.

Halogen-substituted cinnamates afforded a more different product distribution, and interesting insight into the halogen…halogen interactions. Halogen…halogen interaction[49-52] (C-X…X-C) is an important, yet relatively less-studied, bonding interaction, and is known to be attractive in nature. For example, Cl…Cl attractive forces have been used in crystal engineering to direct molecular packing into arrangements where the chlorines are proximal, or oriented towards to each other.[53-56] Given this background, we expected that chloro cinnamates (**4a-d**) will yield more H-H dimers than the corresponding unsubstituted cinnamates **1a-d**. As predicted, methyl ester complex (**4a**) yielded a much higher percent of *syn* H-H[57] (67%) than **1a** (51%). Correspondingly, a significantly lower percentage of *anti* H-T dimer was seen, along with similar proportion of a third dimer. Based on the chemical shift and peak shape the third dimer was identified to be the *anti* H-H isomer (supporting information, isopropyl ester). The effect of Cl…Cl in favoring H-H arrangement is evident from this first example. We then investigated chloro cinnamates with larger alkoxy groups (**4b-d**). Despite the increase in size of alkoxy group in **4b-d**, *syn* H-H was the major product in chloro cinnamate reactions. This is markedly different from what was observed earlier as the steric conflict between the alkoxy groups favored the H-T dimer more. The combined proportion of the H-H dimers indicate a strong attractive force between the intermolecular chlorine atoms, which is able to overcome the steric conflict between the isopropyl groups. The magnitude of Cl…Cl interaction can be qualitatively understood by comparing the relative proportions of the H-H and the H-T dimers between

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esters with same alkoxy group. While the isopropyl cinnamate yielded 100% H-T dimer, the isopropoxy ester of chloro-substituted cinnamic acid yielded around 70% H-H dimers. One might wonder whether a steric interaction from chlorine substitution on aromatic ring could destabilize the H-T arrangement, leading to higher proportion of H-H dimer. However, **3b** with its bulky methoxy substitution was able to afford no more than 24% *syn* H-H dimer, while the methoxy group is bulkier than a chloro atom. The difference of around 50% of H-H dimers between **4d** and **3b** can be attributed to the Cl…Cl interaction.

Table 3. Product distribution resulting from irradiation of halogen-substituted *trans* cinnamic acid and alkyl cinnamates complexed to γ-CD.

Cinnamic acid (R_2-Ar)	Alkoxy group (R_1-O)		*% syn* H-H	*% anti* H-T	*% syn* H-T/*anti* H-H	*% cis*
2-chloro	Methyl	4a	69	10	9	12
2-chloro	Ethyl	4b	52	12	22	14
2-chloro	*n*-propyl	4c	35	26	25	14
2-chloro	isopropyl	4d	52	29	19	-
3-bromo	Methyl	5a	35	57	-	8
3-bromo	Isopropyl	5b	60	40	-	-
3-fluoro	Isopropyl	6a	-	100	-	-

Percentage of products from reaction mixtures calculated from integration of ^{1}H NMR signals.

The Br…Br and F…F interactions were explored through compounds **5-6**. The esters of bromo cinnammic acids yielded high amounts of *syn* H-H dimers[42] as well (figure 3), though it was slightly lesser in proportion than the corresponding chloro compounds. This observation in combination with the product distribution observed for **4d** reinforces the influence of attractive halo…halo interaction in selectivity. However, no significant amount of the third dimer was seen. Thus, here we see that despite the presence of a bulky alkoxy substitution, the halo…halo attraction is able to direct intermolecular orientation towards the H-H arrangement. On the other hand, isopropyl ester of fluoro cinnamic acid did not yield any H-H dimer[44] at all, and *anti* H-T was the only product. Based on this we believe that the strength of F…F interaction is almost incomparable to that of the larger halogens. The directing effect of the halogen effect is summarized with the NMRs in figure 3. Considering the structure of the complexes (vide infra) and the predcited co-planar relative arrangement of the guests within the cavitand, it is expected that the C-X…X-C contact angle would be around 90°, which is not unusual for halogen…halogen interactions.[18, 49]

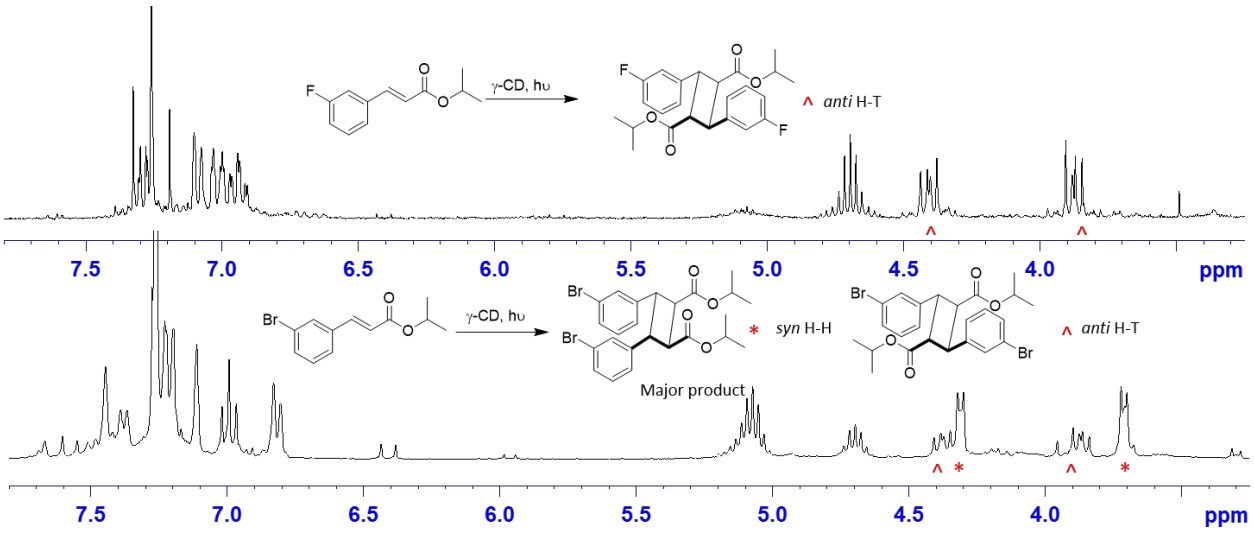

Figure 3. ^{1}H NMR spectra of reaction mixtures that resulted from the irradiation of slurry 1:2 (H:G) γ-CD complexes of isopropyl esters of halo cinnamic acid. The difference in selectivity are attributed to the halogen…halogen interaction (or lack thereof).

Time-dependence and stoichiometry studies: The premise of this project is to deduce complex structure, and relative orientation of the alkenes based on stereochemistry of the dimer. Thus, it is important to ensure that product selectivity observed in the reactions is not due to (a) differential reactivity and/or (b) lack of product representation from non-reacting orientations. Towards this end, we performed time-dependence

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experiments scanning a broad conversion range. We chose to study the methyl cinnamate γ-CD complex (1:2) as a representative example as it is yields both the dimers. A slurry of the complex was split evenly into four equal portions, and irradiated for four different durations: 1, 3, 7, and 9 hours. Any difference in product selectivity between the reactions could indicate differential reactivity. The proportion of *syn* H-H and the *anti* H-T dimers remained almost constant throughout the four reactions (supporting information). The variation in dimer proportion was within 5%, which should be considered the margin of error. Except for the difference in intensity of the *trans* ester signals, the product proportions were essentially constant. Thus, the reaction selectivity is representative of the complex structures in the bulk of the slurry.

It is clear that the large cavity of γ-CD forms the ternary 1:2 complex. However this does not necessarily imply that 1:2 complex is the only stable complex, as we did not have more host to form other complex ratios. Hence, we performed stoichiometry experiment to understand the dynamics between host and guest, variation in complex stoichiometry and structure. Methyl cinnamate and isopropyl ester of 4-methyl cinnammic acid were used as representative examples. As mentioned earlier, irradiation of complex resulting from mixture of 1:2 complex of **1a** yielded roughly equal proportions of *syn* H-H and *anti* H-T dimers. Similarly, the 1:2 complex of **2c** yielded about 80% *anti* H-T and 20% *syn* H-H. We then studied reactions of host-guest ratio was increased to 1:1. Product mixtures resulting from the 1:1 complexes of **1a**, and **2c** were both surprisingly very similar to the product mixtures from the 1:2 complexes. This suggests that in the slurry even when 1 equivalent of the host was present, photodimerization was the major reaction pathway, implying that the 1:2 complex is much more stable than 1:1. This might appear counter intuitive, as the steric interaction from dual occupancy will be destabilizing. But, the predominance of 1:2 complex despite excess γ-CD could be explained based on concept of 'tight fit', wherein a stable complex results between cavitand and guest of complementary sizes, than with a guest of smaller size. Alternatively, one might wonder whether the stability of the 1:2 complex could also be due to the stabilizing π-π (maybe even CH-π) interaction(s). Computational studies we performed (discussed below) correctly predicted that a ternary complex will be more stable than the binary complex. As the computational method we used (MM) does not involve electronic interaction term, and it was able to correctly predict stabilities, we believe that the tight-fit factor is a more plausible explanation.

2-hydroxypropyl-γ-cyclodextrin complexes: One of our approaches for generalizing the cavitand-mediation method to produce stereospecific cyclobutane structures is to explore the influence of cavitand characteristics on reaction selectivity. We intend to study the influence of other cavitands on selectivity. This would include cavitand families such as cucurbiturils, and calixarenes, and their derivatives. As a preliminary effort, we have studied reactions of some cinnamates within 2-hydroxypropyl-γ-cyclodextrin (2HP-γ-CD). 2HP-γ-CD is a functionalized derivative of γ-CD, wherein some of hydroxyl groups are randomly substituted with 1-(2-hydroxy)propyl units. The degree of substitution is approximately five hydroxypropyl units per cavitand. The presence of the hydroxypropyl arm extends the portal height with solubility comparable to that of γ-CD in aqueous medium. Complexes of 2-HP-γ-CD were prepared in an identical manner to that of γ-CD complexes. However, visually, the amount of precipitate resulting from the complexation was significantly lesser.

Irradiation of 2-HP-γ-CD complex of cinnamic acid resulted in high, selective yield of the *syn* H-H dimer, which was similar to that of the parent cavitand (table 4). On the other hand, methyl cinnamate yielded higher amount of *syn* H-H dimer, and isomerization product than the γ-CD complex. A marked difference was observed in case of the isopropyl ester, where the 2-HP-γ-CD complex yielded no dimers at all, and *cis* methyl cinnamate was the only product observed. The presence of bulky alkoxy substitution on the tail-end of guests most likely face a steric interaction from the 2-hydroxypropyl groups in 2-HP-γ-CD, leading to formation of higher proportion of 1:1 complex, which results in isomerization. These reactions suggest that 2-HP-γ-CD is not a conducive host for photodimerization larger guests. The hydroxypropyl arms, even though present in small numbers, are strong enough to prevent formation of higher order complexes.

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Table 4. Product distribution resulting from irradiation of substituted *trans* cinnamic acid and alkyl cinnamates complexed to 2-hydroxypropyl-γ-CD.

Cinnamic acid (R_1-Ar)	Alkoxy group (R_2-O)		% *syn* H-H	% *anti* H-T	% *syn* H-T/*anti* H-H	% *cis*
H	H	1	87	-	-	13
H	Methyl	1a	48	26	-	26
H	Isopropyl	1c	-	-	-	100[a]
		1c	-	-	-	100[b]
3-Methoxy	H	3	92	-	-	8
4-Methyl	Methyl	2a	35	20	-	45
4-Methyl	Isopropyl	2c	-	-	-	100

[a]Complex stoichiometry (1:2, host:guest) [b]complex stoichiometry (1:1, host:guest). Percentage of products from reaction mixtures calculated from integration of ^{1}H NMR signals.

Computational studies: Computational studies were performed to understand the structural characteristics of the complexes involved in this work. Structures of individual molecules, their γ-CD complexes, and their binding energies in polar medium in universal force field (UFF) were calculated in Gaussian '09. We included water as the solvent in our calculation as hydrophobic interaction is the primary force driving complexation. Solvent effects due to aqueous environment was included through the use of implicit polarizable continuum model (IPCM).

$$\Delta E = E_{complex} - (E_{CD} + E_{guest1} + E_{guest2}) \quad \text{(eq. 1)}$$

$$\Delta\Delta E = \Delta E_{complex(syn\ H\text{-}T)} - \Delta E_{complex(anti\ H\text{-}T)} \quad \text{(eq. 2)}$$

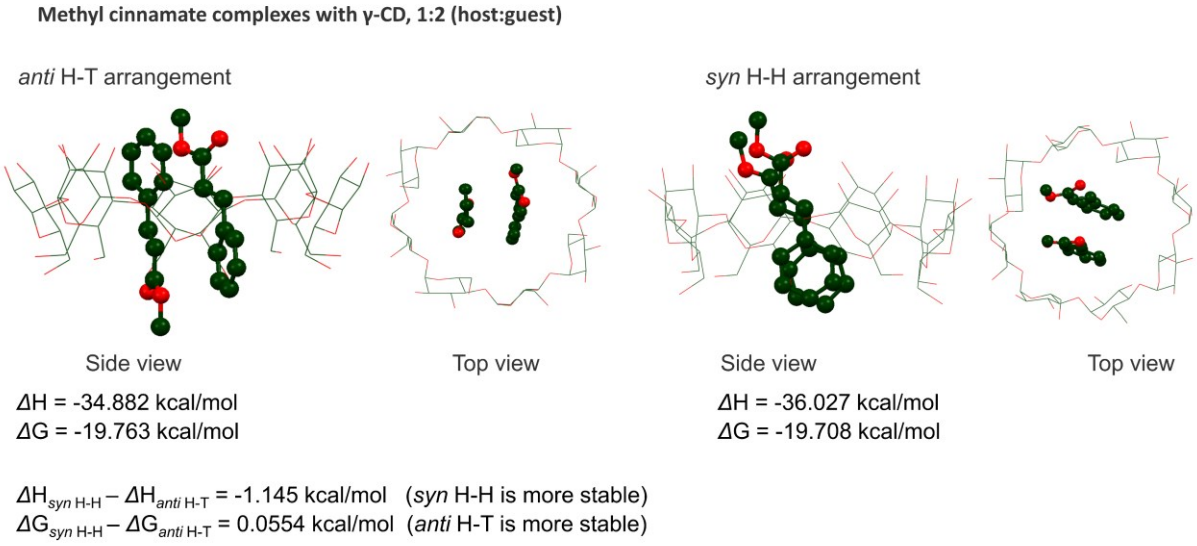

Figure 4. Energy minimized structures (MM-UFF) of 1:2 host-guest complex of methyl cinnamate with γ-CD, and their stabilization energies. Hydrogens are not displayed for sake of clarity. *Note: Two isomeric complex structures of syn H-H arrangement are possible, which arise from carboxylic acids protruding out of the secondary portal or the primary portal. Analysis of the two isomeric structures of cinnamic acid complexes show that the former is more stable (supporting information). In this study we have focused only on syn H-H structures where the carboxylate units protrude through the secondary portal.*

Generally AMBER force field is used to study organic molecules, while UFF is applicable to molecules containing any element in the periodic table. However, UFF treatment of organic molecules,[58] inclusion complexes of organic[59, 60] and metal ion complexes[61, 62] can be found in literature.[63, 64] We intend to study these complexes and future complexes using AMBER force field in future and compare the predictabilities of UFF and AMBER. Relative stabilities of the complexes were deduced through the differences in formation energies of complexes and those of the guests, as expressed in equation 1. Computational analysis of supramolecular assemblies is a relatively recent endeavor among supramolecular chemists. Dodzuik, an expert in the field, argues that stand-alone computational studies of host-guest complexes cannot yield realistic information regarding the complexes,[65] and that reliable

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conclusions can only be elicited with the help of a comprehensive and systematic analysis of a given system. We agree with her conclusions derived based on critical analysis of previously published works, discussed in her book. Thus, instead of exploring the structures from a purely computational standpoint, we believe that computational studies combined with experimental data can useful in providing qualitative information regarding host-guest complexes, and help in visualization of complex structures. Our aim for using computational chemistry in this work was to explore possible correlation between theoretical and experimental findings, and understand relative stabilities of complexes in a qualitative manner.

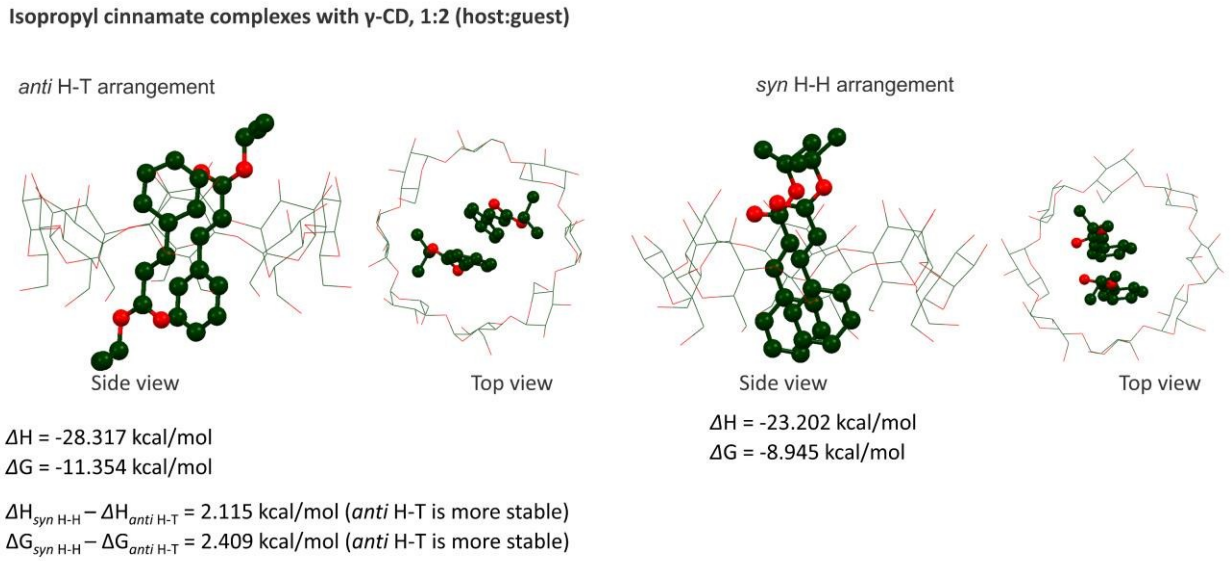

Figure 5. Energy minimized (MM-UFF) structures of 1:1 host-guest complexe methyl cinnamate with γ-CD. Hydrogens omitted for clarity

We primarily studied the structures of complexes with the alkenes in the *syn* H-H and *anti* H-T precursor arrangements, as the corresponding dimers were the major products observed. Moreover, optimization of complexes with other two precursor arrangements resulted in structures in which one of the alkene bonds were much farther away. Geometry optimized structures of the complexes along with their stabilization enthalpies and free energies (standard conditions) are presented in figures 4-7. It should be noted that the numerical values of individual energies are rather less significant, but the difference in stabilization energies between two different complexes can be considered as useful information (eq. 1 and 2). The enthalpic and free energy changes for complexes of **1a** (figure 4) and **1c** (figure 5) with γ-CD for both the *anti* H-T and *syn* H-H arrangement were all negative values, suggesting an enthalpy driven spontaneous process. Comparing the corresponding enthalpic and free energy values between the two complexes (different arrangements) of **1a** indicate that the *syn* H-H arrangement is enthalpically more stable by 1.1447 kcal/mol, while the *anti* H-T is more stable by 0.0554 kcal/mol free energy wise (figure 4). The values for the complexes of isopropyl ester **1C** show that the *anti* H-T dimer is more stable both enthalpy (2.115 kcal/mol) and free energy wise (2.409 kcal/mol) (figure 5). The stabilization of the *anti* H-T, compared to the *syn* H-H arrangement, was significantly greater for the isopropyl ester (-2.409 kcal/mol) than the methyl ester (-0.0554 kcal/mol). This trend in stabilization energy increase concurs with the experimental result where methyl cinnamate yielded roughly equal amounts of the *syn* H-H and *anti* H-T dimers, while the isopropyl ester yielded exclusively the latter.

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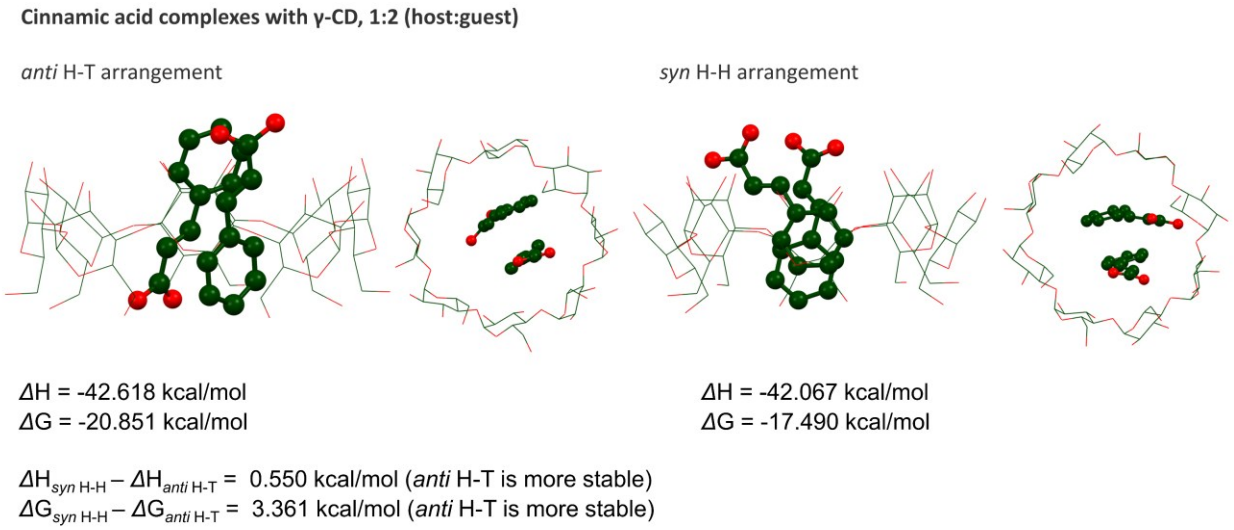

Figure 6. Energy minimized structures (MM-UFF) of 1:2 host-guest complexes of isopropyl cinnamate with γ-CD, and their stabilization energies. Hydrogens are not displayed for sake of clarity.

Computational results for the complexes of parent cinnamic acid **1** (figure 6) predicted that the *anti* H-T arrangement is be more stable than the *syn* H-H by 0.550 kcal/mol (Δ*H*), and 3.361 kcal/mol (Δ*G*). According to this prediction, the *anti* H-T dimer should be the major product, contrary to the *syn* H-H dimer observed experimentally. The contradiction here arises due to the lack of attractive electronic terms (in this case π-π interaction) in molecular mechanics force field definitions, which does not account in such stabilization in *syn* H-H. Thus, the pure MM treatment based on hydrophobic and steric interactions would predict that the H-T arrangement would be more stable due to the missing phenyl-phenyl steric conflict. This, in fact, serves to support the idea that though π-π interaction is a weak attractive force in nature, it can profoundly manifest in chemical reactions when mediated though macrocyclic hosts.

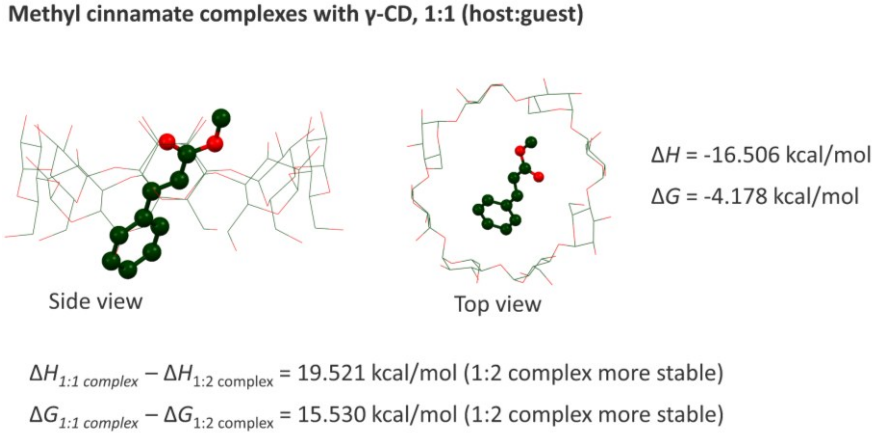

Figure 7. Energy minimized structures (MM-UFF) of 1:2 host-guest complexes cinnamic acid with γ-CD, and their stabilization energies. Hydrogens are not displayed for sake of clarity.

In our computational studies, we also studied the 1:1 complex of methyl cinnamate (figure 7). The enthalpic and free energy stabilizations for the complexes were calculated to be -16.506 kcal/mol and -

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4.178 kcal/mol. Comparing these values with that for the 1:2 complex (-36.027 kcal/mol, and -19.708 kcal/mol, figure 4), it follows that the 1:2 complex is more stable than the 1:1 complex. This is also consistent with the experimental observation that 1:2 complex is preferentially formed over the 1:1 complex, even when equimolar amounts of the host and guest were mixed. Thus, based on the above results, we believe that UFF is able to predict the relative stabilities of complexes.

CONCLUSION

In this work, we have shown regioselectivity of photocycloaddition between cinnamic acids and their esters can be directed through the use of non-covalent interactions. The reactions were also affected in a stereoselective manner. Cinnamic acid yields *syn* Head-to-Head (*syn* H-H) as the only dimeric product when irradiated as a complex in γ-cyclodextrin. Our investigations lead us to believe that π- π interaction is an important factor in its selectivity. The selectivity is completely reversed when isopropyl cinnamate- γ-cyclodextrin complex was irradiated, resulting in the *anti* Head-to-Tail (*anti* H-T) dimer exclusively, as steric interaction between the isopropyl groups favor a H-T arrangement in complex. This complete switch in regioselectivity marks the next step in our effort to generalize the cavitand-mediated photodimerization approach to produce broad array of substituted cyclobutanes. Cinnamic acid esters with smaller than butyl groups bind with the macrocyclic cavitand γ-cyclodextrin to form 1:2 (host:guest), and yield photodimers predominantly. The relative proportion of the *syn* H-H and *anti* H-T dimers is influenced by the size of alkoxy chain, as the latter was favored with larger alkoxy groups. This gradual shift in product distribution can be regarded as tunable control in reaction selectivity. Stoichiometry experiments suggest that 1:2 (host:guest) complex is more stable than the 1:1 complex, perhaps due to the tight-fit factor.

The effect of halogen substituents on the aromatic ring was also studied. Chloro and bromo substituted cinnamate esters yielded significantly higher *syn* H-H in their product mixtures than the other potosubstrates due to the attractive halogen…halogen interaction. Product distributions indicate that the chlorine…chlorine and bromine…bromine interaction is rather strong, and outweighed the destabilization from steric conflict between even isopropoxy groups. Fluorine…Fluorine interaction appears to be very weak in comparison. Computational studies of the complexes were performed to explore its predictive power. Relative stabilities of complexes predicted using Molecular Mechanics Universal Force Field (MM-UFF) analysis of the complexes in an aqueous shell is consistent with structures deduced using photochemical studies. Our future efforts will aim to access the other photodimers (*anti* Head-to-Head and *syn* Head-to-Tail), and non-symmetric cyclobutanes as well with the cavitand photodimerization approach. We believe that this method will also serve as a means to understand the dynamics and relative influences of supramolecular interaction in host-guest complexes.

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Graphical Abstract

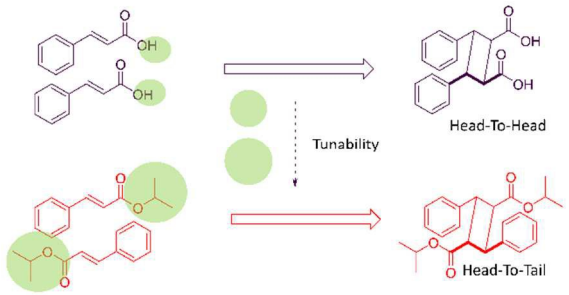

Table of content entry

A cavitand mediation approach involving host-guest and guest-guest interactions has been developed to direct regioselective photocycloaddition of non-symmetric alkenes wherein a complete reversal in selectivity is achievable