ARTICLE

OBC
www.rsc.org/obc

Effect of cyclodextrin complexation in bromine addition to unsymmetrical olefins: evidence for participation of cyclodextrin hydroxyl groups†

Manickam C. Durai Manickam,[a] Subramanian Annalakshmi,[b] Kasi Pitchumani*[b] and Chockalingam Srinivasan[a]

[a] *Department of Materials Science, Madurai Kamaraj University, Madurai, 625 021, INDIA*
[b] *School of Chemistry, Madurai Kamaraj University, Madurai, 625 021, INDIA. E-mail: pit12399@yahoo.com; Fax: 91-0452-2459181; Tel: 91-0452-2458246*

Received 13th December 2004, Accepted 17th January 2005
First published as an Advance Article on the web 14th February 2005

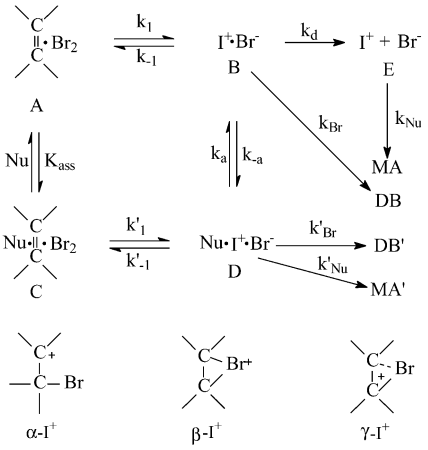
Multiple recognition by cyclodextrin in a bimolecular reaction, namely bromination of styrene, methyl cinnamate, phenylacetylene and allylbenzene, has been studied. Bromohydrin is obtained as a major product along with dibromide in the bromination of styrene and methyl cinnamate. The percentage of bromohydrin decreases as the cavity size increases. With phenylacetylene, bromophenylacetylene and phenacyl bromide are obtained in addition to the dibromides. In the bromination of cyclodextrin complexes of allylbenzene, the product distribution is the same as in solution bromination. The observed results demonstrate the efficiency of cyclodextrin in stabilizing the open carbocationic intermediate and thus provide chemical evidence for the participation of cyclodextrin hydroxyl groups.

Introduction

Cyclodextrins (CDs), cyclic oligosaccharides with a hydrophobic cavity, possess the ability to form host–guest complexes with different guest molecules of appropriate size, resulting in modified reactivities and selectivities.[1] Many synthetic strategies in which CDs have been used as reaction vessels to control photochemical[2] and thermal reactions[3] are reported. In several cases, reactivity inside the CD cavity is distinct from the solution phase due to the restricted motions of the guest molecule and the incoming reagent, which is more pronounced in solid state.[4] Selective and catalytic transformations such as reduction,[5] epoxidation,[6] sulfoxidation[7,8] and halogenation of olefins[9] catalyzed by CDs have been studied.

Electrophilic bromination of olefins by molecular bromine is stereoselective and the nature of the olefin–bromine complex and the intermediates involved have been extensively studied.[10–12] Other notable features[13,14] include dependance of stereochemistry on the solvent and substituents, as well as the chemoselectivity (predominant dibromide or solvent-incorporated adducts). The stereochemical outcome is controlled not only by the bridged or unbridged structure of the cationic intermediate, but also by the association with its nucleophilic partners and its lifetime. Based on extensive product and kinetic evidence, a mechanistic scheme may be visualized (Scheme 1) in which preassociation, free-ion and ion-pair pathways compete. The stereochemical outcome depends on the nucleophilic partners of the product-forming ionic intermediates (which, depending on the double bond substituents, can be open α-I^+, fully bridged β-I^+ or weakly bridged γ-I^+), arising from different ionization routes. The products are the solvent-incorporated or mixed adducts (MA) and the dibromides (DB). They can be obtained from free-ions (E), ion-pairs (B) or ion-dipole sandwiches (D), formed *via* preassociation or ion-pair pathways.

In our earlier study[15] on bromination of *trans*-stilbene in CDs, a significant change in product composition with a consequent loss of stereoselective *trans*-mode of addition was reported. The *meso*/*dl* ratio is less than one in the bromination of 1 : 1 complexes of stilbene with CDs and their hydroxypropyl derivatives. With an increase in cavity diameter (from α to γ-CD), the ratio decreases. This significant reduction in stereoselectivity is attributed to a) presence of a polar environment provided by the secondary hydroxyl/methoxyl groups at the wider rim of the CD cavity in stabilizing the carbocationic intermediate and b) steric hindrance to the attack of the tribromide.[16]

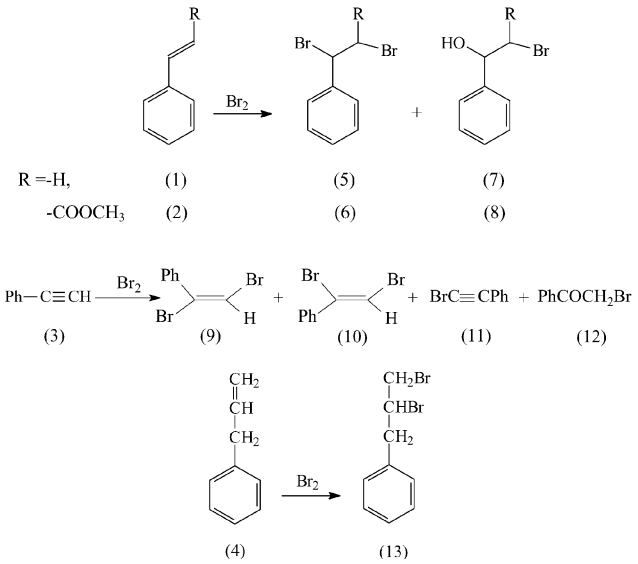


Scheme 1 Mechanism of bromine addition to olefins.

Thus, it will be interesting to study bromination of unsymmetrical olefins and acetylenes in the presence of CDs to gain a better understanding of the role of the CD in influencing the mechanism and stereochemistry of bromination. It is relevant to note that bromine addition to styrene[17] in an acetic acid medium gives a substantial amount of acetoxybromides in addition to the major product, namely dibromides, and the reaction is nonstereospecific. Bromination of methyl esters of cinnamic acid[18] in aqueous acetic acid gives a mixture of *erythro*-2,3-dibromo-3-phenylpropionate ester and *erythro*-2-bromo-3-hydroxy-3-phenylpropionate ester, which are formed in a completely stereo- and regiospecific *anti*-addition mode. In the bromination of phenylacetylene[19] in an acetic acid medium, 25% of bromoacetylene, 42% of *trans*-, 19% of *cis*-dibromide and 14% of phenacyl bromide are obtained. In the present study, bromination of styrene (**1**), methyl cinnamate (**2**) phenylacetylene (**3**) and allylbenzene (**4**) is carried out in the presence of cyclodextrins and the observed results are discussed (Scheme 2).

† Electronic supplementary information (ESI) available: preparation and characterization of cyclodextrin complexes and preparation of **5**–**13**. See http://www.rsc.org/suppdata/ob/b4/b418685k/

DOI: 10.1039/b418685k



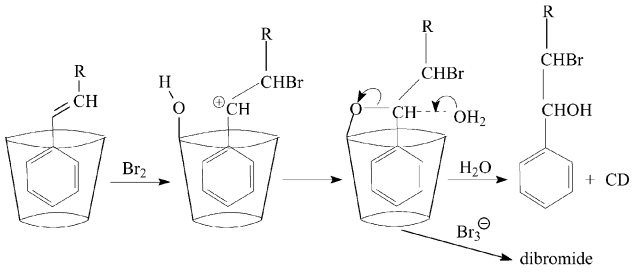
Scheme 2 Structures of reactants and products in the bromination of styrene, methyl cinnamate, phenylacetylene and allylbenzene by molecular bromine.

Results and discussion

Bromination of **1** in CCl_4 (without CD) yields the dibromide **5** as the exclusive product. However, a remarkable change in product selectivity is observed when the α-CD complex of styrene is brominated and bromohydrin **7** is obtained as the exclusive product. In bromination with the β-CD complex, the percentage of **7** decreases and the two products **5** and **7** are formed in equal amounts. This trend continues in the bromination of the γ-CD complex also. As the distance between the carbonium ion to the secondary hydroxyl group increases, as one goes from α- to γ-CD (Table 1), the proportion of bromohydrin decreases and that of dibromide increases.

A similar trend is also observed in the bromination of another aryl olefin, methyl cinnamate **2**. When bromination of **2** is carried out in aqueous methanol or CCl_4 (Table 1), **6** is obtained as the only product and the mechanism as depicted in Scheme 1 may be visualized. However, in bromination of CD complexes of **2**, in addition to the dibromide **6** a significant amount of **8** is formed (as in the case of bromination of styrene). With an increase in size of the CD, the percentage of **8** decreases and that of **6** increases (Table 1). It is relevant to note here that in a 75% CH_3OH–25% water mixture as the reaction medium no methanol incorporated product is obtained, indicating that participation by CD-hydroxyl groups alone play a major role in stabilizing the carbonium ion intermediate than the solvent molecules.

To account for the observed product selectivity upon CD encapsulation, the following mechanism (Scheme 3) is visualized. Inclusion into the CD cavity, followed by addition of the bromonium ion results in the predominant formation of an acyclic, open benzylcarbonium ion (in preference to fully-bridged or weakly bridged cyclic intermediate), which can be stabilized by the aryl ring and also by the secondary hydroxyl groups present in the rim of the CD cavity. The resultant intermediate (attempts to isolate this intermediate were unsuccessful) may be attacked by either the $Br_3^{\ominus}$ (leading to dibromide) or by water molecules leading to bromohydrin (which may be either the cyclodextrin-bound high energy water included into the CD cavity at the time of complex formation, or the solvent water used for extracting the substrate from the complex). As the size of the CD cavity becomes smaller, as in α-CD, not only is the attack by the second bromine more hindered, but formation of the intermediate between the hydroxyl group of CD and the open carbonium ion can also take place more readily. Consequently, in these cases, the formation of bromohydrin takes place more readily.



Scheme 3 Mechanism of bromination of CD-included styrene and methyl cinnamate.

To gain further evidence for participation of CD hydroxyl groups in stabilizing the intermediate acyclic carbonium ion, bromination of **1** and **2** is also extended to studies of CD

Table 1 Product distribution in bromination of styrene **1**/methyl cinnamate **2** in solution and in CD complex[a]

Medium	Substrate	Conversion (%)	Percentage of: Dibromide (**5**/**6**)	Bromohydrin (**7**/**8**)	Dibromide/bromohydrin ratio
CCl_4	**1**	95.5	95.5	—	High
α-CD	**1**	100.0	—	100.0	~ 0.01
β-CD	**1**	89.0	48.0	41.0	1.17
γ-CD	**1**	100.0	62.0	38.0	1.61
HP-α-CD[b]	**1**	100.0	—	100.0	~ 0.01
HP-β-CD[b]	**1**	100.0	—	100.0	~ 0.01
DM-β-CD[c]	**1**	90.7	24.8	65.9	0.37
TRIME-β-CD[d]	**1**	100.0	100.0	—	High
CCl_4	**2**	90.0	90.0	—	High
75% CH_3OH–H_2O	**2**	100.0	52.5	47.5	1.10
α-CD	**2**	84.0	37.8	46.2	0.82
β-CD	**2**	90.8	52.6	38.2	1.37
γ-CD	**2**	94.1	66.7	27.4	2.43
HP-α-CD[b]	**2**	69.2	46.8	22.4	2.09
HP-β-CD[b]	**2**	85.9	64.4	21.5	3.00
DM-β-CD[c]	**2**	92.9	64.5	28.4	2.27
TRIME-β-CD[d]	**2**	88.3	88.3	—	High

[a] Analysed by GC, error limit ±2%. [b] Randomly hydroxypropyl-α/β-cyclodextrin. [c] Heptakis (2,6-di-*O*-methyl)-β-cyclodextrin. [d] Heptakis (2,3,6-tri-*O*-methyl)-β-cyclodextrin.

derivatives (Table 1). With hydroxylpropyl-α-CD (HP-α-CD) and HP-β-CD (both containing only one hydroxyl group in the secondary rim), bromination of **1** produces only bromohydrin (**7**). With DM-β-CD (which also contains only one hydroxyl group in the secondary rim), a high yield of bromohydrin is obtained. However, bromination with permethylated-β-CD (TRIME-β-CD) only dibromide is obtained as the exclusive product, clearly indicating that the secondary hydroxyl group of β-CD plays a decisive role in stabilizing the carbocationic intermediate. A similar trend is also obtained in bromination of **2** in presence of cyclodextrin derivatives (Table 1).

It is also interesting to note that in an earlier report,[20] asymmetric bromination, when carried out in microcrystalline CD complexes of **1** in the gas–solid state, produces predominantly (−)-1,2-dibromo-1-phenylethane. Chiral induction for the reaction of the α-CD complex leads to a nine-fold increase compared to that of the the β-CD complex, reflecting the more compact and tight CD complex in the former. Bromination in a homogeneous solution containing α- or β-CD complexes gives no **5** but racemic **7**. This chiral induction in the gas–solid halogenation using the solid CD complexes is attributed to the ability to hold rigidly a chiral conformation in the crystalline state. In the present study, it is not attempted to measure precisely the extent of chiral induction taking place inside the CD cavity.

To substantiate our generalization that the hydroxyl group of CD is actively involved and stabilizes the carbonium ion intermediate bromination is extended to phenylacetylene **3**, in which the hindrance to attack of the second bromide ion is expected to be less as the carbon–carbon triple bond is axially oriented with respect to the CD cavity. The product distribution and their relative percentages are given in Table 2 and the structures of different products obtained in bromination of **3** are given in Scheme 1.

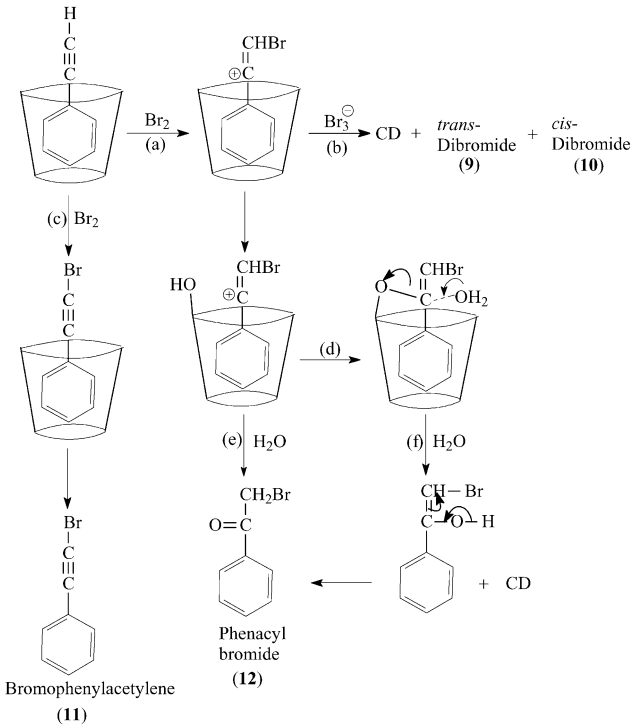
The data presented in Table 2 show that while bromination of **3** in CCl_4 yields the *trans*-dibromide **9** as the major product, the reaction when carried out in acetic acid yields a mixture of **9** and **10**, together with a small amount of **11**. This is in accordance with a previous report[19] on bromination of phenylacetylene in an acetic acid medium. However, when CD complexes of **3** are brominated, several interesting features are observed in contrast to solution bromination: a) *cis*-dibromide **10** is obtained in larger amounts than the *trans*-dibromide **9**, b) significant amounts of bromophenylacetylene **11** are obtained and c) phenacyl bromide **12** (formed from the ketonisation of bromohydrin of **3**) is also obtained in good yield.

The observed product distribution in the bromination of **3** can be explained (Scheme 4) as follows: in route (a), inclusion into the CD cavity followed by addition of bromine leads to preferential formation of open carbonium ion, which on further reaction (route (b)) yields dibromides **9** and **10**. As attack by the second bromine from the rear is sterically hindered by the CD hydroxyls (which stabilize the open carbonium ion), more of *cis*-dibromide **10** is formed when compared to the *trans*-dibromide **9**. Substitution of acetylenic hydrogen by bromine (route (c)) leads to bromophenylacetylene **11**. As this is the least hindered attack, yields of **11** are substantial in CD complexes compared

Table 2 Products distribution in bromination of phenylacetylene[a,b]

	Percentage of:					
Medium	**3**	**9**	**10**	**11**	**12**	*trans*/*cis* (**9**/**10**) ratio
CCl_4	54.4	41.7	2.9	1.0	—	14.40
Acetic acid	—	55.0	30.0	12.0	3.0	1.83
α-CD	—	21.5	44.3	21.2	13.0	0.49
β-CD	—	15.3	40.1	26.0	18.6	0.38
γ-CD	—	7.2	19.3	27.0	46.5	0.30

[a] Analysed by GC, error limit ±2%. [b] For structures of **3** and **9–12** refer to Scheme 2.



Scheme 4 Mechanism of bromination of phenylacetylene included inside the CD cavity.

to solution bromination. In addition, phenacyl bromide **12** is also formed and these results can be rationalized as shown in Scheme 4. The α-bromocarbonium ion may be stabilized (route (d)) by interaction with the secondary hydroxyl groups of CD and the resultant intermediate may undergo subsequent hydrolysis (route (f)). Direct attack by water on the open carbonium ion is also likely (route (e)) which takes place more readily with γ-CD.

To gain additional support for our generalization that the active participation of secondary hydroxyl groups of CD stabilizes the initially formed α-bromocarbonium ion intermediates, bromination of allylbenzene **4** as its CD complex is carried out. Only the dibromide **13** is observed, analogous to the corresponding solution bromination. This result is not unexpected. Though the aryl ring of **4** penetrates the CD cavity, the site of bromination is farther removed from the influence of CD and its hydroxyl groups. Thus, complexation by CD affects neither the rate nor the product distribution in bromination of **4**. This result also provides evidence for the absence of any inclusion of bromine into the CD cavity under the present experimental conditions. It is relevant to note here that in ring bromination of phenols catalyzed by CDs, bromine complexed in CD is proposed[21] to account for the observed catalytic activity.

To understand the interaction between CD hydroxyls and the carbonium ion intermediate, molecular modeling studies[22] are carried out with CD complexes (Fig. 1). The results presented in Table 3 show that the distance between the α-carbon atom of the substrate and the oxygen of the secondary hydroxyl in CD is within 4 Å in all the olefins and also the distance increases as the size of the CD cavity increases. This explains the decrease in the formation of bromohydrin with an increase in the size of the CD cavity. Complexation energies of CD–olefin complexes are also calculated. These values, presented in Table 3, show that α-CD forms stronger complexes indicating a more stable and deep binding. As the size of the CD increases, the complexation tends to be less pronounced.

Conclusions

The results observed in the present study into bromination of CD complexed olefins **1–4** amply demonstrate the efficiency of

Table 3 Calculated complexation energies (kcal mol^{-1}) and distance between the α- and β-carbon atom of the olefins with the oxygen atom of the secondary hydroxyl group of CD

Complex	Complexation energies[a]	Distance between α-C and 2° OH/Å	Distance between β-C and 2° OH/Å
α-CD + Styrene	−27.33	3.45	3.40
β-CD + Styrene	−24.16	3.61	3.68
γ-CD + Styrene	−17.86	4.64	3.69
α-CD + Methyl cinnamate	−26.70	4.01	3.85
β-CD + Methyl cinnamate	−31.49	4.10	3.76
γ-CD + Methyl cinnamate	−28.96	4.38	4.25
α-CD + Phenylacetylene	−44.20	3.38	3.36
β-CD + Phenylacetylene	−22.21	4.32	3.84
γ-CD + Phenylacetylene	−16.52	4.37	3.47

[a] Complexation energy ($E_{complex} - E_{host} - E_{guest}$) obtained by CVFF force field, a RMS derivative for each substrate of 0.001 is achieved.

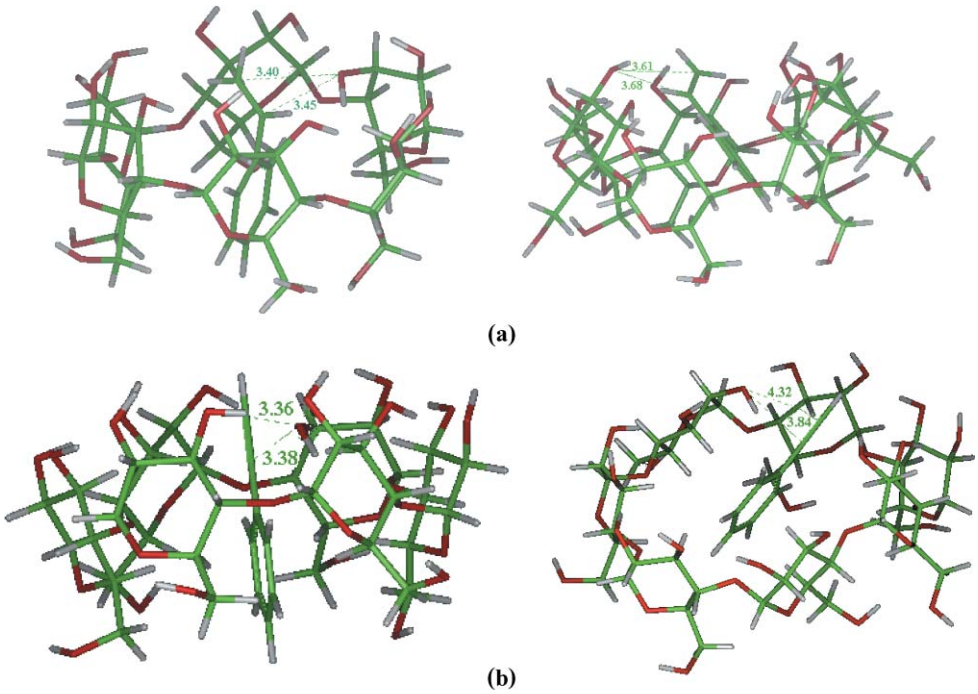


Fig. 1 CVFF-optimized cyclodextrin inclusion complexes; a) α- and β- CD complexes of styrene, b) α- and β- CD complexes of phenylacetylene.

CDs in stabilizing acyclic, open carbocationic intermediates at the expense of bridged bromonium ion and, hence, modify the reactivity of the included guest olefins. Results with various CDs and CD derivatives provide chemical evidence for the participation of the secondary hydroxyl groups of cyclodextrin in the present study. Also, the possibility of direct attack of inner cavity water molecules on the carbocation intermediate to yield bromohydrins directly (without participation by CD hydroxyl groups) may be ruled out as the yield of bromohydrin is found to depend on the size of the CD cavity.

Experimental

Materials

Cyclodextrins α- and γ- (American Maize Products, Indiana), β- (Aldrich), hydroxypropyl-β- (DS 6, randomly hydroxypropylated, a gift-sample from Cerestar, USA), hydroxylpropyl-α- (Nihon Shokuhin Kako Co. Ltd., Japan) and dimethyl-β- (DS 1.8, non-recrystallizable, randomly methylated, a gift-sample from Wacker-Chemie, Germany) were used as received. TRIME-β-CD (heptakis (2,3,6-tri-*O*-methyl)-β-cyclodextrin) was prepared from β-cyclodextrin in dry DMF at 0 °C with excess methyl iodide in the presence of NaH.[23] Bromine (Merck), styrene (Aldrich), methyl cinnamate (Merck), phenylacetylene (Aldrich) and allylbenzene (Aldrich) were used as received without further purifications and a stock solution of bromine was prepared by dissolving 74 mL of bromine in 100 mL of CCl_4 and making up to 250 mL in a standard measuring flask. 1 : 1 CD complexes were prepared† as reported earlier.[24]

Complex formation of the substrates **1–4** with cyclodextrins was inferred by calculating the formation constants (K_f) using Benasi–Hildebrand method.[25] With α-, β- and γ- CDs the formation constants (K_f per mol^{-1} dm^3) for **1** are 290, 345 and 375 respectively; for **2** 215, 227 and 285 respectively; for **3** 185, 265 and 305 respectively and for **4** 225, 315 and 320 respectively. The values are fairly high indicative of the formation of strong complexes between the CDs and the guest. The small, yet significant increase in K_f values with increase in CD size may be rationalised due to formation of small amount of higher order complexes also, in addition to 1 : 1 complexes. α-, β- and γ- CD complexes of substrates **1–4** were also characterized by their ^{1}H-NMR spectra.[26]

General procedure for bromination of substrates 1–4 in solution and in CD complexes

Substrates **1–4** were dissolved in 20 mL of CCl_4 taken in a conical flask. To this solution, 12 mL of a stock solution of bromine was added dropwise with constant stirring at 0 °C. After the reaction was over in about 30 min, the excess bromine was removed with sodium thiosulfate solution and the products were analyzed. In

a typical CD meditated bromination reaction, 0.1 g of the 1 : 1 complex was thoroughly mixed with an equimolar amount of bromine in CCl_4 and kept at 0 °C for 3 h. After completion of the reaction the excess bromine was removed and the complex was dissolved in water, the products extracted with hot $CHCl_3$ and analyzed by capillary GC (Shimadzu 17A, SE-30 (5%) column with high purity N_2 as carrier gas). The products were identified by coinjection with authentic samples prepared by reported procedures[17–19,27] and also by their ^{1}H-NMR spectra.†

Molecular modeling studies

Molecular mechanics calculations[22] were carried out for all the olefins inside α, β and γ CDs using Insight II Discover program in IRIX system. Calculations are done in a vacuum and structures are minimized using a CVFF force field and the RMS derivative 0.001 is achieved in each case.

Acknowledgements

Financial assistance from Council of Scientific and Industrial Research (CSIR), New Delhi is gratefully acknowledged. K. P. thanks UGC-DRS support to MKU for GC-MS facility.

References

1 (*a*) I. Tabushi, K. Yamamura, K. Fujita and H. Kawakubo, *J. Am. Chem. Soc.*, 1979, **101**, 1019; (*b*) Y. Ihara, E. Nakanishi, M. Nango and J. Koga, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 1901.
2 (*a*) K. Pitchumani, M. C. Durai Manickam and C. Srinivasan, *Tetrahedron Lett.*, 1991, **32**, 2975; (*b*) K. Pitchumani, M. C. Durai Manickam and C. Srinivasan, *J. Photochem. Photobiol., A*, 2002, **149**, 131.
3 (*a*) K. Pitchumani, P. Velusamy and C. Srinivasan, *Tetrahedron*, 1994, **50**, 12979; (*b*) A. Ueno, *Supramol. Sci.*, 1996, **3**, 31.
4 (*a*) M. S. Syamala and V. Ramamurthy, *Tetrahedron*, 1988, **44**, 7234; (*b*) G. Dasaratha Reddy, G. Usha, K. V. Ramanathan and V. Ramamurthy, *J. Org. Chem.*, 1986, **51**, 3085.
5 N. Baba, Y. Matsumura and T. Sugimoto, *Tetrahedron Lett.*, 1978, **19**, 4281.
6 S. Banfi, S. Colonna and S. Julia, *Synth. Commun.*, 1983, **13**, 1049.
7 A. W. Czarnik, *J. Org. Chem.*, 1984, **49**, 924.
8 J. Drabowicz and M. Mikolajczyk, *Phosphorus Sulfur Relat. Elem.*, 1984, **21**, 245.
9 Y. Tanaka, H. Sakuraba and H. Nakanishi, *J. Chem. Soc., Chem. Commun.*, 1983, 947.
10 M. F. Ruasse, *Acc. Chem. Res.*, 1990, **23**, 87.
11 G. Bellucci, R. Bianchini, C. Chiappe, R. S. Brown and H. S. Tilk, *J. Am. Chem. Soc.*, 1991, **113**, 8012.
12 G. Bellucci, C. Chiappe, R. Bianchini, D. Lenoir and R. Herges, *J. Am. Chem. Soc.*, 1995, **117**, 12001.
13 G. Bellucci, R. Bianchini and C. Chiappe, *J. Org. Chem.*, 1991, **56**, 3067.
14 M. F. Ruasse, G. L. Moro, B. Galland, R. Bianchini, C. Chiappe and G. Bellucci, *J. Am. Chem. Soc.*, 1997, **119**, 12492.
15 M. C. Durai Manickam, K. Pitchumani and C. Srinivasan, *J. Inclusion Phenom. Macrocyclic Chem.*, 2002, **43**, 207.
16 R. E. Buckles, J. M. Bader and R. J. Thurmaier, *J. Org. Chem.*, 1962, **27**, 4523.
17 J. H. Rolston and K. Yates, *J. Am. Chem. Soc.*, 1969, **91**, 1469.
18 S. D. Young and E. Berliner, *J. Org. Chem.*, 1979, **44**, 1088.
19 J. A. Pincock and K. Yates, *Can. J. Chem.*, 1970, **48**, 3332.
20 H. Sakuraba, H. Ishizaki, Y. Tanaka and T. Shimizu, *J. Inclusion Phenom.*, 1987, **5**, 449.
21 O. S. Tee and J. M. Bennett, *J. Am. Chem. Soc.*, 1988, **110**, 3226.
22 (*a*) J. I. Choe and S. K. Chang, *Bull. Korean Chem. Soc.*, 2002, 23; (*b*) *Discover User Guide*, Accelrys Inc., 2001.
23 (*a*) V. Schurig, M. Jung, D. Schmalzing, M. Schleimer, J. Duvekot, J. C. Buyten, J. A. Peene and P. Mussche, *J. High Resolut. Chromatogr.*, 1990, **13**, 470; (*b*) Z. Chen, J. S. Bradshaw and M. L. Lee, *Tetrahedron Lett.*, 1996, **37**, 6831; (*c*) J. L. Mieusset, D. Krois, M. Pacar, L. Brecker, G. Giester and U. H. Brinker, *Org. Lett.*, 2004, **6**, 1967.
24 (*a*) K. Pitchumani, S. Devanathan and V. Ramamurthy, *J. Photochem. Photobiol., A: Chem.*, 1992, **69**, 201; (*b*) G. Dasaratha Reddy and V. Ramamurthy, *J. Org. Chem.*, 1987, **52**, 3952.
25 H. A. Benesi and J. H. Hildebrand, *J. Am. Chem. Soc.*, 1949, **71**, 2703.
26 P. V. Demarco and A. V. Thakkar, *J. Chem. Soc., Chem. Commun.*, 1970, 2.
27 S. Kato, *Bull. Inst. Phys. Chem. Res.*, 1932, **11**, 756, (*CA*, 1932, **26**, 5260).