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Controlling photoreactions with confinement: Photochemistry of benzoin alkyl ethers within water soluble *p*-sulfonato calix[n]arenes

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Dedicated to dear friend and colleague Professor Harou Inoue on the occasion of his 60th birthday.

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ABSTRACT

This publication pertains to the exploration of supramolecular assemblies to control excited state chemistry. One of our long-range scientific goals is to develop, on the basis of well-established rules of molecular organic photochemistry and supramolecular chemistry, a model to predict the photobehavior of organic molecules in restricted spaces, in general. We present the results of our studies on the photochemistry of benzoin alkyl ethers included within calixarenes in water. While in isotropic solution benzoin alkyl ethers yield products of Norrish Type I reaction, as guest–host complex with calixarenes they preferentially yield products of Norrish Type II reaction. The current observation suggests that rules of physical organic chemistry and photochemistry developed based on solution chemistry cannot be simply extended to supramolecular assemblies.

1. Introduction

The photochemistry of benzoin ethers (**1a**–**3a**, Scheme 1) is of considerable interest in view of their extensive commercial usage as photosensitizers in coatings and printing technologies [1]. This has prompted extensive investigation of their photochemistry [2]. They undergo α-cleavage (Type I) to form a benzoyl–benzyl radical pair, which undergoes subsequent free radical reaction to give the pinacol ether and benzil as the major products and benzaldehyde as minor product. γ-Hydrogen abstraction reaction (Type II) does not compete with α-cleavage that is the predominant reaction in solution. This could be due to the low occupancy of the benzoin ethers in the necessary *s-cis* conformation or the high rate and efficiency of Type I reaction ($k_\alpha = 10^{10}\ s^{-1}$ and $k_H = 10^9\ s^{-1}$ in case of α-alkoxy acetophenones) [2]. The objective of the current investigation is to probe whether encapsulation of benzoin alkyl ethers within calixarenes (Na-CA[6] and Na-CA[8]; Scheme 2) would impose any restriction in the mobility and conformational control of the encapsulated guest molecule and thereby induce product selectivity. We anticipated that the encapsulation of the benzoin alkyl ethers would not influence the rate of the Type I reaction. However, it is expected to increase the probability of the recombination of the radical pair from the α-cleavage thereby decreasing the efficiency of formation of the Type I products.

2. Results

2.1. Complexation studies

The complexation behavior of the benzoin alkyl ethers with the sodium salt of the calixarenes Na-CA[6] and Na-CA[8] was investigated by ^{1}H NMR titration experiments. The complexation behavior of benzoin methyl ether representative of all the three substrates in this study was carried out in detail. The ^{1}H NMR spectrum of benzoin methyl ether in D_2O and in presence of the monomer sodium salt of 4-hydroxybenzene sulfonic acid (HBS), hosts Na-CA[6] and Na-CA[8] are presented in Fig. 1. The guest proton signals were shifted upfield in the CA complexes. The aromatic proton signals of the guest were shifted upfield to a greater extent (0.3–0.7 ppm) than the –CH and the methoxy proton signals (0.1–0.15 ppm). However there was no appreciable upfield shift in the guest proton signals (<0.1 ppm) in presence of the monomer HBS, suggesting that the upfield shift observed in the case of the CA complexes is indicative of inclusion of the guest within the host cavity. To better understand the complexation behavior of the benzoin alkyl ethers, ^{1}H NMR titrations of BME (benzoin methyl ether) against both Na-CA[6] and Na-CA[8] were carried out. The ^{1}H NMR spectrum of BME and BME@Na-CA[8] obtained by subsequent addition of Na-

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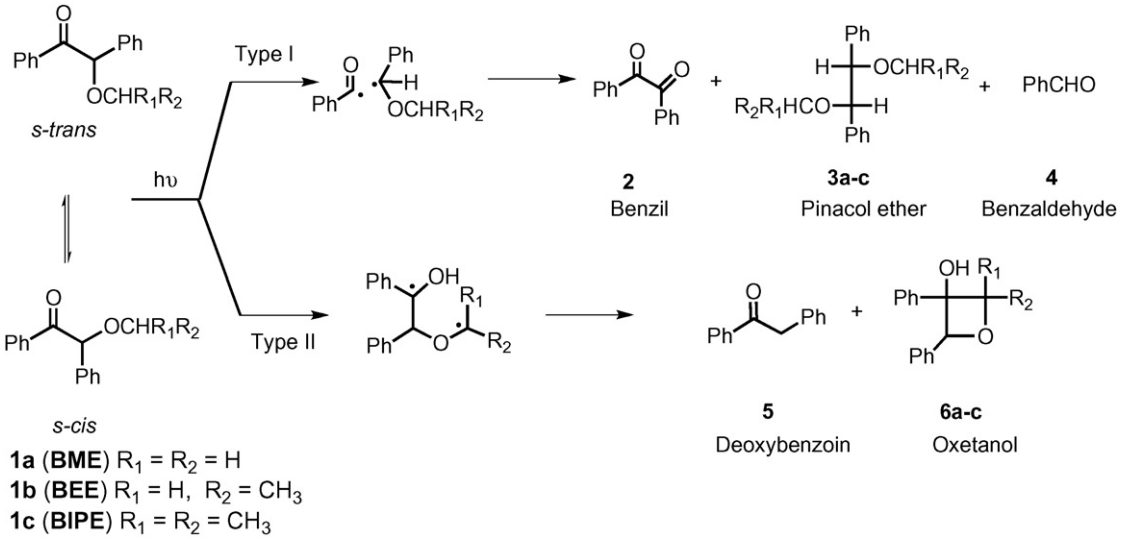
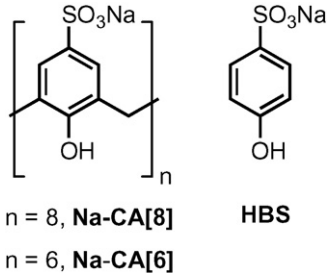


Scheme 1.



Scheme 2.

CA[8] is presented in Fig. 2. Continuous upfield shift in the guest proton NMR signals and absence of two independent signals, one due to the complexed and the other due to the uncomplexed guest molecule suggested a fast exchange between the complexed and uncomplexed guest in the NMR time scale (400 MHz). Larger shift of the aromatic proton signals (0.3–0.7 ppm) compared to alkoxy and the –CH proton signals (0.1–0.15 ppm) suggested the inclusion of the aromatic groups of the guest within the calixarene cavity and exposure of the relatively hydrophilic alkoxy group to aqueous exterior. A proton NMR titration carried out for the host Na-CA[6] under identical conditions is presented in Fig. 3. Similar to that of Na-CA[8], the aromatic proton signals shifted upfield by 0.3–0.5 ppm while the shift in the alkoxy proton signal and the –CH proton signal was less than 0.15 ppm, suggesting the inclusion of the aromatic groups and the exposure of the alkoxy groups to aqueous outside. From the titration studies data, a linear plot was obtained for the change in chemical shift vs. concentration of both host Na-CA[6] and Na-CA[8] suggesting a G:H = 1:1 complex in each case (Section 5). The association constants for the complexation of BME with Na-CA[6] and Na-CA[8] were estimated to be $1.37 \times 10^2\ M^{-1}$ and $3.86 \times 10^2\ M^{-1}$ respectively (the procedure for determination of the association constants is explained in Section 5). The difference in binding constants suggests that the binding affinity towards a given guest is cavity size dependent and furthermore it is stronger with Na-CA[8].

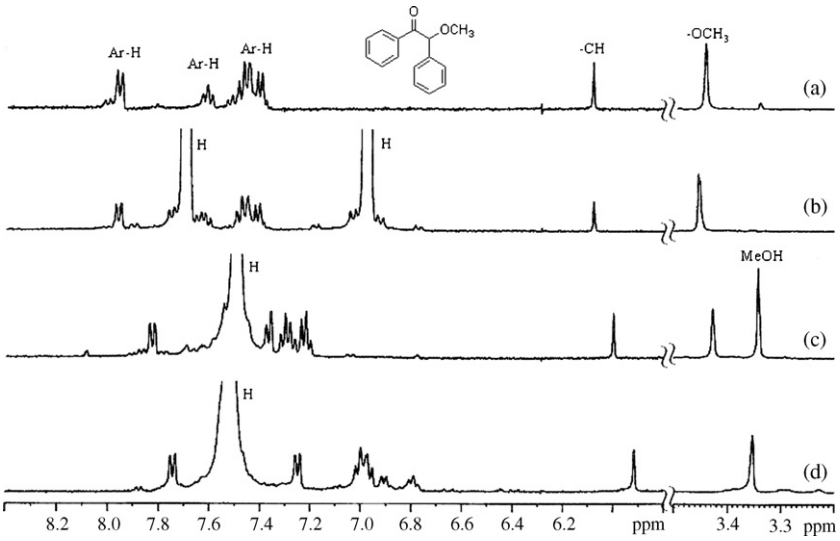


Fig. 1. ^{1}H NMR spectrum of the complexes of BME. (a) BME in D_2O, (b) BME in presence of 16 equivalents of HBS, (c) BME in presence of ~2 equivalents of Na-CA[6] and (d) BME in presence of ~2 equivalents of Na-CA[8] in D_2O. H represents the aromatic signals of the host.

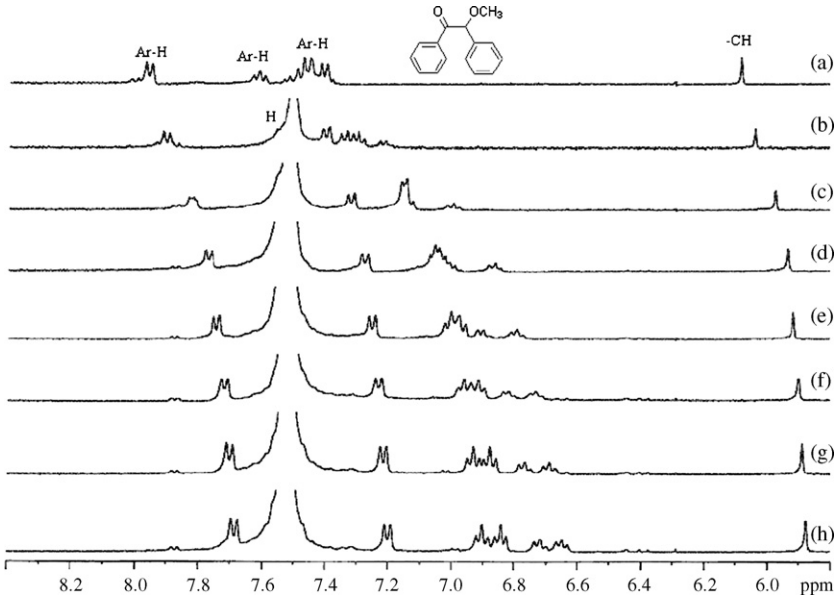


Fig. 2. ^{1}H NMR titration of BME vs. Na-CA[8] in D_2O. (a) BME only, (b) BME:Na-CA[8] = 1:0.4, (c) BME:Na-CA[8] = 1:0.9, (d) BME:Na-CA[8] = 1:1.4, (e) BME:Na-CA[8] = 1:1.8, (f) BME:Na-CA[8] = 1:2.2, (g) BME:Na-CA[8] = 1:2.7 and (h) BME:Na-CA[8] = 1:3.3. Signal marked with H is the aromatic proton signal of the host.

2.2. Photochemical studies

In the excited state, benzoin alkyl ethers are capable of undergoing α-cleavage (Type I) and hydrogen abstraction (Type II) reactions. Upon irradiation in solution, benzoyl–benzyl radical pair, the product of α-cleavage, yields pinacol ether and benzil as major products with minor amount of benzaldehyde [2]. Generally Type II products deoxybenzoin and the corresponding oxetanol are formed in minor amounts. The product distributions obtained upon photolysis of the benzoin alkyl ethers as aqueous solutions and as complexes of HBS, Na-CA[6] and Na-CA[8] are summarized in Table 1. As expected, irradiation of the BME in aqueous solution resulted in the formation of pinacol ether as the major product (92%) and deoxybenzoin as the minor product (8%). Although an equal amount of the benzoyl radical coupling product benzil is expected, it was formed in lower amounts compared to pinacol ether. The formation of lower amounts of benzil is attributed to the conversion of benzoyl radical to benzaldehyde and benzoic acid in water. Since these secondary products are soluble in water, quantitative estimation of these products was not possible and hence the Type I and Type II reaction product yields were monitored by the relative GC yields of pinacol ether to deoxybenzoin and oxetanol respectively. Similar to BME, aqueous solution irradiation of the other substrates BEE and BIPE resulted in the formation of the corresponding pinacol ether as the major product (88% and 93% respectively for BEE and BIPE).

Interestingly, photolysis of the complex of BME@Na-CA[8] (G:H = 1:8 mixing ratio) resulted in the formation of the Type II product deoxybenzoin as the major product (96%) and small amounts of pinacol ether (4%). Similar irradiation of the Na-CA[6] complex of BME (G:H = 1:8 mixing ratio) resulted in formation of

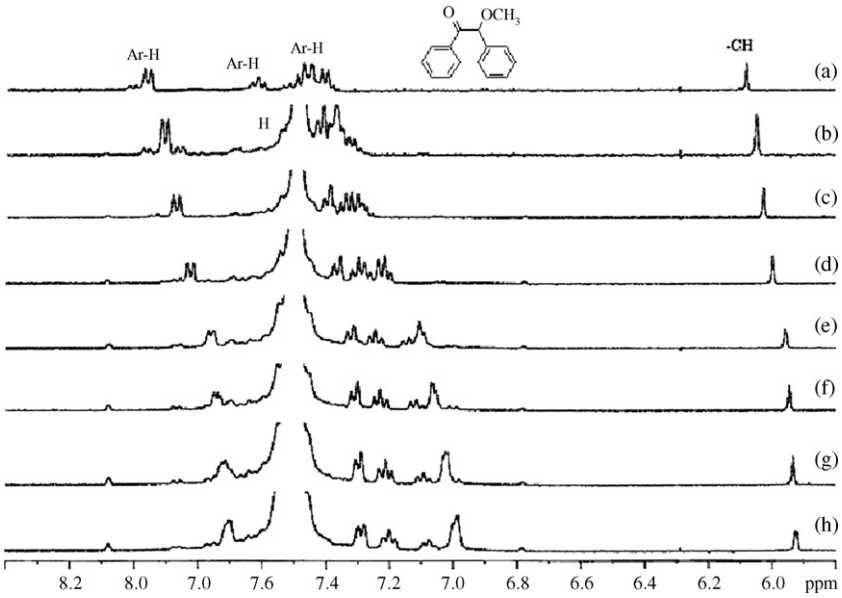


Fig. 3. ^{1}H NMR titration of BME vs. Na-CA[6] in D_2O. (a) BME only, (b) BME:Na-CA[6] = 1:0.4, (c) BME:Na-CA[6] = 1:1, (d) BME:Na-CA[6] = 1:1.7, (e) BME:Na-CA[6] = 1:2.3, (f) BME:Na-CA[6] = 1:2.9, (g) BME:Na-CA[6] = 1:3.4 and (h) BME:Na-CA[6] = 1:4. Signal marked with H is the aromatic proton signal of the host.

Table 1
Product distribution (%relative yield) obtained during the photolysis of 1a–1c[a] within Na-CA[6], Na-CA[8] and as aqueous solution.

Guest	Medium	Guest:Host[b]	Pinacol ether (Type I)	Deoxybenzoin (Type II)
BME	Water	–	92	8
BME	Na-CA[8]	1:4	9	91
BME	Na-CA[8]	1:8	4	96
BME	Na-CA[6]	1:4	43	57
BME	Na-CA[6]	1:8	30	70
BME	HBS[c]	1:64	96	4
BEE	Water	–	88	12
BEE	Na-CA[8]	1:4	18	82
BEE	Na-CA[8]	1:8	4	96
BEE	Na-CA[6]	1:4	48	52
BEE	Na-CA[6]	1:8	32	68
BIPE	Water	–	93	7
BIPE	Na-CA[8]	1:4	23	77
BIPE	Na-CA[8]	1:8	15	85
BIPE	Na-CA[6]	1:4	43	57
BIPE	Na-CA[6]	1:8	35	65

[a] The ratio of products obtained for ~35% conversion of the reactant based on GC analysis. Oxetanol was formed in less than 3% upon irradiation of **1a**–**c** in water.
[b] The numbers represent the mixing ratios of the host and the guest, stoichiometry of the complex is believed to be G:H = 1:1.
[c] The monomer sodium salt of hydroxy benzene sulfonic acid was used.

deoxybenzoin (70%, as the major product and 30% of pinacol ether as the minor product. As a control, irradiation of BME was carried out under identical conditions in presence of 64 equivalents of the monomer HBS, which resulted in the formation of 96% pinacol ether similar to that of aqueous solution irradiation. In summary, in presence of calixarenes the formation of Type II product deoxybenzoin in high yields (70–96%) was observed. Similar irradiation of BEE and BIPE as calixarene complexes yielded deoxybenzoin as the major product (77–96% with Na-CA[8] and 52–57% with Na-CA[6]). The relatively lower yields of deoxybenzoin with Na-CA[6] complexes are due to the lower association constant ($137\ M^{-1}$) of BME with Na-CA[6].

3. Discussion

The upfield shift in the guest proton signals in NMR spectra suggests the inclusion of the benzoin ethers within calixarene hosts. The guest proton signals did not shift upfield in the presence of the monomer HBS, suggesting that a circular and continuous array of the monomeric HBS units is required to effectively include the guest molecule. Further the upfield shift in the aromatic proton signals of the guest (0.3–0.7 ppm) was higher than the upfield shift in the –CH and alkoxy proton signals (0.1–0.15 ppm) suggesting the inclusion of the hydrophobic aromatic groups and the exposure of the –CH and alkoxy group to aqueous outside. Based on the NMR studies, we propose a structure for the complex as shown in Fig. 4. The association constants for the complexation of BME with Na-CA[6] and Na-CA[8] were estimated to be $1.37 \times 10^2\ M^{-1}$ and $3.86 \times 10^2\ M^{-1}$ respectively based on NMR titration studies. The difference in binding constants suggests that the binding affinity towards a given guest is cavity size dependent. The estimated binding constants are comparable to the binding of neutral molecules with *p*-sulfonato calix[n]arenes reported in the literature [3]. The relatively lower association constants (compared to the binding of cationic guests with CAs) indicate that an excess of host (G:H = 1:8) would be required to drive the equilibrium of complexation to the complexed state. Hence an excess of host was used for photolysis purposes. The product distributions obtained upon photolysis of the benzoin alkyl ethers are summarized in Table 1. It is clear that aqueous solution irradiation of the benzoin alkyl ethers resulted in the formation of the corresponding Type I product pinacol ether as the major product while irradiation as Na-CA[8] complexes resulted in the formation of Type II product deoxybenzoin as the major product. Preferential formation of deoxybenzoin in presence of Na-CA[8] could be attributed to the inclusion of the benzoin alkyl ethers in a conformation that favors γ-hydrogen abstraction within Na-CA[8] (Fig. 4). Though the guest molecule is in a conformation that favors γ-hydrogen abstraction within Na-CA[8], it can still undergo α-cleavage. However due to the inclusion of the guest molecule within Na-CA[8], the benzoyl–benzyl radical pair resulting from α-cleavage, gets entrapped within the host resulting in the regeneration of the reactant and thereby retarding the formation of Type I products. The minor amount of Type I products is thus attributed to reaction from uncomplexed guest in water and cage escape products. Thus the product selectivity observed within Na-CA[8] is mainly due to two factors, conformational control and cage effect. If our proposed model and the above asumptions are true, the smaller cavity of Na-CA[6] (compared to Na-CA[8]) should result in the cage escape of the excited reactant leading to the decrease in the yields of the Type II products. The product distribution obtained upon photolysis of the benzoin ethers as Na-CA[6] complexes is in agreement with this proposition. The relative yields of deoxybenzoin obtained from the Na-CA[6] falls in the range of 52–70%. The control experiment using the monomer HBS suggests that a circular array of the HBS units linked by methylene groups is required for the inclusion of the benzoin ethers in the favorable conformation for γ-hydrogen abstraction. The photolysis of BME in presence of HBS resulted in the formation of Type I product pinacol ether.

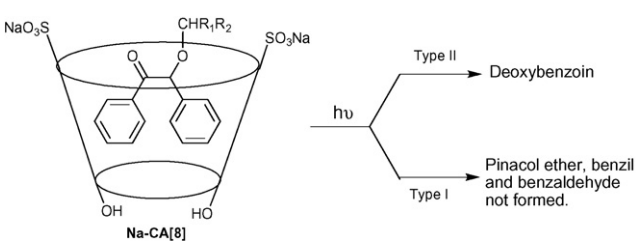


Fig. 4. Schematic model for the complex of benzoin alkyl ethers within **Na-CA[8]**. The host is assumed to be in the "all cone" conformation, the exact conformation is not known as this time.

Since we believe that conformation control is one of the main factors dictating the formation of the Type II product, we attempted to gain some idea regarding the conformational energies of the conformers of BEE using *ab initio* calculations at RB3LYP/6-31G(*) level [4]. The computations of BEE at RB3LYP level, 6-31G(*) basis set using Gaussian 98 program resulted in three conformers of close energies (Fig. 5). The computed molecular dimensions suggest that the three conformers could fit within the cavity of both Na-CA[6] and Na-CA[8]. Further, the computed energies for the three conformers indicate that conformer III (—C=O and –OEt are *gauche* to each other) is less stable compared to conformers I and II. In conformer I, the carbonyl and the –OEt groups are *anti* to each other and the distance between carbonyl oxygen and γH is 3.24 Å, while in conformer II, the carbonyl and the –OEt groups are *syn* to each other and the distance between carbonyl oxygen and γH is 2.54 Å. Based on computational data, upon irradiation while both conformer I and II will undergo α-cleavage, conformer II is more likely to undergo γ-hydrogen abstraction. Conformer II is slightly higher in energy (0.5 kcal/mol) than conformer I. In spite of slightly higher energy ^{1}H NMR and photochemical results suggest that the guest molecule prefers conformer II within the calixarene cavity.

In the past, the photolysis of benzoin alkyl ethers have been carried out in various organized media such as micelles [5], cyclodextrins [6], cavitands [7], nafion [8], polymers [9] and dendrimers [10]. The product selectivity obtained within the cal-

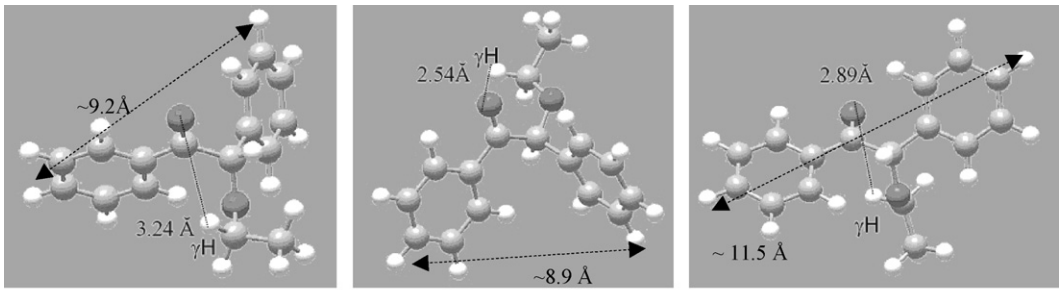


Fig. 5. Geometry optimized conformers of **BEE** using RB3LYP/6-31G(*). Relative energy difference between given conformer and most stable conformer is shown in parenthesis.

Table 2
Product distribution obtained upon photolysis of benzoin ethyl ether within various organized media.

Medium[a]	Pinacol ethers	Benzaldehyde	Benzil	Oxetanol	Deoxybenzoin	Rearrangement products	Type I:Type II
β-CD	39	45	6	4	6	–	90:10
Nafion[b]	2	–	1	42	31	24	26:74
OA	3	–	–	11	72	14	17:83
NaCh	66	–	–	20	12	2	68:32
SDS	38	–	18	–	44	–	56:44
Polymer	14	–	–	14	59	13	27:73
Na-CA[6]	32	–	–	–	68	–	32:68
Na-CA[8]	4	–	–	–	96	–	4:96

[a] OA: Octa acid (water soluble cavitand), NaCh: sodium cholate micelles, SDS: sodium dodecyl sulfate, Polymer: styrene based water soluble polymer.
[b] Irradiated in the solid state.

ixarenes Na-CA[6] and Na-CA[8] is unique in the fact that it results in the formation of deoxybenzoin in major amounts among the various Type II products. The product distributions obtained upon photolysis of BEE within various organized media as aqueous solutions are summarized in Table 2.

It is clearly evident that only in presence of hosts such as octa acid, SDS, water soluble polymer and nafion, Type II product is favored while with other hosts such as β-CD Type I products are favored. As stated earlier, the calixarene hosts are unique in the way that photolysis of the benzoin ethers as calixarene complexes results in the formation of deoxybenzoin as the major Type II product with formation of less than 3% of the corresponding oxetanol. Further it is reported in the literature that the benzoin ethers are inert in the crystalline state [11]. Therefore deoxybenzoin is formed within the cavity of the host and not from uncomplexed microcrystalline guest molecules in water.

4. Conclusion

In summary we have demonstrated the inclusion of neutral guests such as benzoin alkyl ethers within water soluble sulfonato calixarenes. These calixarenes engulf the reactant benzoin alkyl ethers in a preferred *s-cis* conformation favorable for hydrogen abstraction reaction. This preferable mode of encapsulation leads to the selective formation of the Type II product deoxybenzoin within calixarenes.

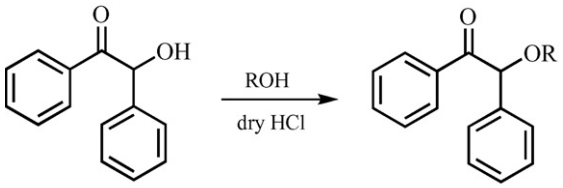
5. Experimental

5.1. Synthesis of calixarenes

The synthesis of calixarenes Na-CA[6] and Na-CA[8] was carried out following reported literature procedures [12].

5.2. Synthesis of benzoin alkyl ethers

Benzoin alkyl ethers were synthesized as per the scheme below using the respective alcohol (methanol or ethanol or isopropanol).



Where R = methyl or ethyl or isopropyl

In a typical procedure for BME, 3 g of benzoin was dissolved in 30 mL of methanol and the solution was stirred at 40 °C. Dry HCl generated in an independent assembly was passed through this mixture for 24 h and the progress of the reaction was monitored by TLC. The reaction mass was cooled to room temperature and diluted with ice + water. The products were extracted using diethyl ether and the organic layer was washed with water. The dried organic layer was concentrated to obtain the crude product. The crude product was purified by column chromatography using 10% hexane/ethyl acetate solvent as the eluent. The product formation was confirmed by GCMS and ^{1}H NMR analysis.

5.3. Complexation and irradiation procedure

The benzoin alkyl ethers (**1a–c**) are sparingly soluble in water. For complex preparation, the required equivalents of the guest was added to an aqueous solution of the host and stirred for 6 h. The complex formation was confirmed by ^{1}H NMR. The pH of the solution was ~8. The complexes were irradiated for ~10 min using a

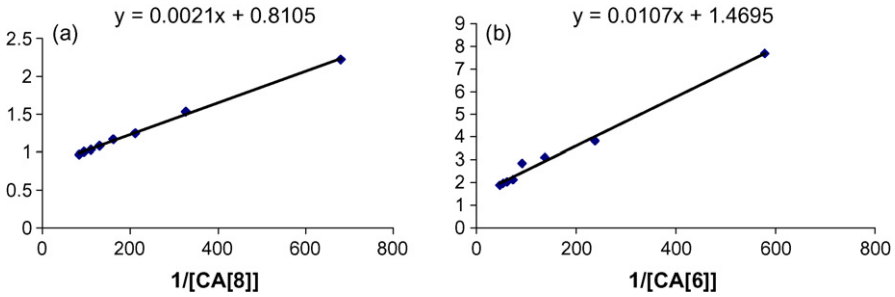


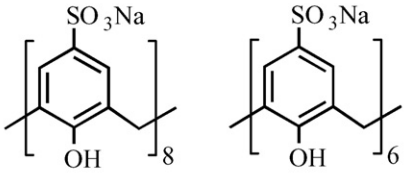
Fig. 6. (a) Plot of $1/\Delta$ vs. 1/[CA[8]]. (b) Plot of $1/\Delta$ vs. 1/[CA[6]].

450 W medium pressure mercury vapor lamp. The photoproducts were extracted using ethyl acetate. A known amount of benzophenone was added as an internal standard before GC analysis. The mass balance was 65–70% excluding benzaldehyde. Photoproducts were analysed by HP 5890 series-II GC using an SE-30 capillary column, error limit ± 3%.

5.4. Determination of host–guest association constants [13]

The association constants were calculated for the following equilibrium shown in Eq. (1)

$$G + H \rightleftharpoons H.G \quad (1)$$

Host  Guest

Na-CA[8] **Na-CA[6]**

Binding of benzoin methyl ether with hosts Na-CA[6] and Na-CA[8] was fast on the NMR time scale (400 MHz) and the determination of K required titration studies. The shift of the aromatic proton (H_a) signals of benzoin methyl ether was recorded after each addition (~1.5–2 mg) of the host. The plot of $1/\Delta$ vs. 1/[Host] is shown in Fig. 6.

K according to Eq. (1) is given by

$$K = \frac{[H.G]}{[H][G]}$$

$$\frac{1}{\Delta} = \frac{1}{(\Delta_{11}K[H])} + \frac{1}{\Delta_{11}}$$

where K is the association constant, $\Delta = \delta - \delta_{guest}$ and $\Delta_{11} = \delta_{complex} - \delta_{guest}$ the observed chemical shift δ is the average of the chemical shifts of the guest and the complex, $\delta_{complex}$ is the chemical shift of the complex, δ_{guest} is the chemical shift of the guest and [H] is the concentration of host.

For host Na-CA[8] (with guest BME), $K = 3.86 \times 10^2\ M^{-1}$ and for host Na-CA[6] (with guest BME), $K = 1.37 \times 10^2\ M^{-1}$.

Acknowledgment

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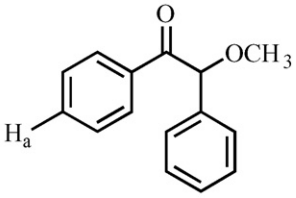

BME

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