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Selectivity in Sodium Borohydride Reduction of Coumarin Encapsulated in β-Cyclodextrin

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Abstract: The sodium borohydride reduction of coumarin to the corresponding alkanol and alkenol has been investigated in the presence and absence of β-cyclodextrin (β-CD). Excellent selectivity is observed when β-CD-coumarin complex is reduced in solid state at 0°C and the alkenol, *cis*-*o*-hydroxycinnamyl alcohol is the major product. Complex formation and the mode of substrate insertion into the CD cavity have been analysed using various physical methods.

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides[1] formed by the α-1,4 glucosidic linkages of either 6, 7 or 8 glucose units denoted as α-, β- and γ-cyclodextrins respectively. The rigid, well defined cavity gives CDs the appearance of torus shaped molecular buckets. The interior of the CDs are fairly nonpolar due to the glucosidic oxygen and hydrogens linking the walls of the cavity. The secondary 2- and 3-hydroxyl groups are located around the wider opening of the cavity while the primary 6-hydroxyl groups are situated on the narrower opening.[2,3] The CDs are of particular interest due to their ability to form host-guest complexes with different guest molecules of appropriate size compatible with the catalytic properties, used for selective synthetic strategies.[4] The extent of complex formation quantified by association constant depends on the polarity of the host and guest molecules. However, geometric, rather than chemical factors are decisive in determining the kind of guest molecule which can penetrate into the CD cavity.[5,6] This phenomenon is responsible for the use and application of CDs as microreactors in a wide range of thermal and photochemical reactions.

It has been reported that reduction[7] of coumarin (**1**) with $LiAlH_4$ yields 3-(*o*-hydroxyphenyl)-propanol (**2**) and *cis*-*o*-hydroxycinnamyl alcohol (**3**). When treated with NaHTe it gives 3,4-dihydrocoumarin.[8] Reduction with sodium borohydride ($NaBH_4$; SBH) in ethanol gives **2**,[9] while in diglyme, a carboxylic acid namely 3-(*o*-hydroxyphenyl)propionic acid (**4**) is the major product. SBH reduction of coumarin in the presence of a Lewis acid gives 3-hydroxy-3-(2-oxyphenyl)-propane.[9] Thus it is obvious that the product distribution depends on the reagent structure or reaction conditions. Selectivity[10] in SBH reduction of CD-encapsulated cyclohexenones has been reported. Our interest[11] in selective

transformations in CD prompted us to investigate the SBH reduction of coumarin encapsulated in ß-CD and to analyse for any selectivity in the reduction. Formation of an inclusion complex with ß-CD has been evidenced by ^{1}H- and ^{13}C-NMR spectroscopy, X-ray powder diffraction patterns and IR studies and the strength of the binding by UV and fluorescence spectral studies.

EXPERIMENTAL DETAILS

Materials.

ß-CD (Sigma) and SBH (SD's) were used as received. Coumarin (Sisco) was purified by repeated crystallisation from ethanol and its purity was ascertained by gas chromatography. All organic solvents were distilled prior to use. Double distilled water was used throughout the study.

Preparation of ß-CD-coumarin complex.

ß-CD-coumarin complex was prepared by the general method reported earlier.[12] To a saturated solution of ß-CD in distilled water, equimolar amount of coumarin was added and stirred continuously for 24 hours. The precipitated inclusion complex was filtered, washed with ether to remove uncomplexed substrate and dried in an air oven at 60°C for about 2-3 hours. The white crystalline powder obtained was used as such for further studies.

Reduction of coumarin with SBH (without CD).

In Ethanol, Methanol or an aqueous solution of Na_2CO_3 (0.2 mol). Coumarin (10 mmol) was dissolved in a minimum amount (3 mL) of the respetive solvent and solid SBH (12 mmol) was slowly added while the solution was being stirred vigorously at room temperature (25-30°C). After 3 hours, the temperature was raised to 40-50°C and the stirring continued for 30 min. The reaction mixture was then hydrolysed.[9]

In Diglyme. Coumarin (10 mmol) was dissolved in a minimum amount (3 mL) of diglyme and this solution was slowly added with stirring, to 12 mmol of SBH in diglyme. The reaction mixture was set aside at room temperature for 24 hours, slightly warmed and hydrolysed.[9]

Hydrolysis was done by the cautious addition of 5-10 mL of 2N HCl. It was further diluted with ice water and then repeatedly extracted with ether. The combined ether extracts were washed several times with ice water to free it from the solvent used (diglyme), dried over anhydrous sodium sulphate and the solvent removed.[9]

Reduction in the presence of ß-CD.

In solution. Suitable quantities of a physical mixture of ß-CD and coumarin or ß-CD-coumarin complex[13] was dissolved in a minimum amount of an aqueous solution of Na_2CO_3 (0.2 mol) and reduction with SBH was carried out by employing the same procedure discussed above.

In solid state. A mixture of ß-CD-coumarin complex and an equimolar amount of SBH was mixed thoroughly using an agate mortar and kept in a dry conical flask at 0°C for 48 hours, shaken occasionally and then hydrolysed.

In all the cases, after hydrolysis and dilution with ice water, the reduction products were extracted with warm chloroform, dried over anhydrous sodium sulphate and the solvent removed. The components present in the reduction product were analysed by gas chromatography (Netel, FID detector, 2 ft. stainless steel column containing SE-30 (10%), N_2 carrier gas). Reaction products are identified by coinjection with pure components prepared by reported method[9] and the results are tabulated (*vide infra*).

Analytical methods.

Infrared spectra (neat or KBr pellet) were recorded with a Perkin-Elmer 577 IR spectrophotometer in the region 4000 cm^{-1} to 200 cm^{-1}. The X-ray diffraction patterns of the powdered samples were measured in the region of 0-57° employing CuK_α radiation (1.54 Å) from Mabe Joel Model JDX-830 powder diffractometer. To confirm the formation of ß-CD complex, ^1H- and ^{13}C-NMR spectra of ß-CD complex were recorded in D_2O and DMSO respectively with a JOEL GCX-400 NMR spectrometer with TMS (tetramethylsilane) as the internal standard.

Determination of formation constants.

Solutions containing different amounts of ß-CD stock solution (10 mmol) and a constant amount of coumarin (0.1 mL; 10 mmol) were prepared in 10 mL flasks and stirred well. The concentration of ß-CD was varied from 1-50 times as that of coumarin. UV-absorption spectra were recorded with a UV/VIS JASCO 7800 spectrophotometer and optical densities were monitored at various wavelengths ranging from 200-300 nm (using spectroscopic grade methanol as the solvent at 25°C). Using the Benesi-Hildebrand method,[14] the dissociation constant, K_D, was obtained from the plot of $a_o b_o/\Delta OD$ vs a_o+b_o, where a_o and b_o being concentration of ß-CD and coumarin respectively (Formation constant $K_f = 1/K_D$).

In the same way, emission spectra were recorded with a JASCO FP 770 spectrofluorometer and intensities were monitored in the wavelength region 300-600 nm. Employing the modified Benesi-Hildebrand method[15] the linear plot of $b_o/\Delta I$ vs $1/a_o$ yielded the slope ($1/aK_f$) and intercept ($1/a$), where 'a' is the proportionality constant. The emission spectra show a slight hyperchromic shift, providing additional evidence for the complex formation.

Host-guest ratio was calculated by adopting the following procedure. A known amount of the solid complex was dissolved in a minimum amount of distilled water and the guest coumarin was extracted with warm chloroform. The amount of the recovered coumarin was estimated gravimetrically after the removal of chloroform.

IR and ^1H-NMR spectral data of reduction products.

^1H-NMR spectra were recorded at 90 MHz on a Perkin-Elmer (R32) spectrometer in solution using tetramethylsilane as internal standard.

3-(o-Hydroxyphenyl)propanol (**2**)

IR (neat) (cm^{-1}) : 3500-3000 (broad), 2900, 1430, 1230-1210

NMR ($CDCl_3$) (δ) : 1.8-1.9 (m,2H), 2.7-2.8 (t,2H), 3.6 (t,2H), 6.7-7.3 (m,5H, including phenolic hydroxyl),

(aliphatic hydroxyl signal is not observed between 0-10 δ).

cis-*o*-Hydroxycinnamyl alcohol (3)

IR (KBr) (cm^{-1}) : 3300-3400 (broad), 3020, 1430, 1240

NMR (Acetone-d_6) (δ) : 4.4 (d,2H), 6.05 (m,1H), 6.6-7.4 (m,5H, includes an olefinic H), (hydroxyl signals are not observed).

RESULTS AND DISCUSSION

Characterisation of CD complex.

Evidences for the existence of an inclusion complex of coumarin with ß-CD are obtained from physical methods such as IR, X-ray powder diffraction, ^{1}H- and ^{13}C-NMR and also from formation constants of ß-CD inclusion complexes obtained from absorbance and fluorescence measurements.

Infrared spectra. Though IR measurements are not employed for detecting inclusion compounds (due to the superposition of host and guest bands), in some cases where the substrate has characteristic absorbance in regions where ß-CD does not absorb, IR spectum is found useful.[16] In the present study the ν C=O stretching observed at 1670 cm^{-1} in the free coumarin was found shifted with reduced intensity to 1680-1690 cm^{-1} in the ß-CD complex. Similarly, aromatic C-H stretching and bending frequencies (for disubstituted alkene) observed at 3000 and 1370 cm^{-1} respectively in coumarin moved to 2870 and 1390 cm^{-1} respectively in the complex. In addition, decrease in intensities of many bands are observed in ß-CD complex of coumarin. It is interesting to note that the spectrum of a physical mixture of ß-CD and coumarin resembles more of the substrates than that of their complex spectrum.

X-ray powder diffraction. The X-ray powder diffraction patterns for ß-CD, coumarin, ß-CD-coumarin complex and the physical mixture of host and guest are given in Figure 1. A comparison of X-ray diffraction patterns of ß-CD and coumarin with that of the complex reveals marked differences. The peaks at 2θ corresponding to 8.9°, 10.3°, 12.3°, 26.8° for ß-CD and 22.9° for coumarin are absent in the complex whereas these peaks are observed in the physical mixture. This can be interpreted as an approximate superposition of the components namely ß-CD and coumarin, in the physical mixture but not in the complex. Moreover, other peaks found at 2θ of 10.3°, 20.7°, 25.2° for ß-CD and 11.4° and 16.0° for coumarin are shifted to 10.7°, 21.1°, 25.9°, 11.8° and 15.4° respectively in the ß-CD complex. This may be due to the insertion of coumarin into the ß-CD cavity. It is also observed that due to the complexation of coumarin with ß-CD, the shifting and enhancement intensities of certain peaks of ß-CD or coumarin are found in the complex. The medium intense peak at (2θ) 19.6° for ß-CD and at 19.9° for coumarin merge to give a strong peak at 20.5° for the complex confirming the inclusion of coumarin into the CD cavity. These observations reinforce the evidence from IR spectral analysis that the precipitated solid obtained from ß-CD and coumarin is a microcrystalline inclusion complex formed between them.

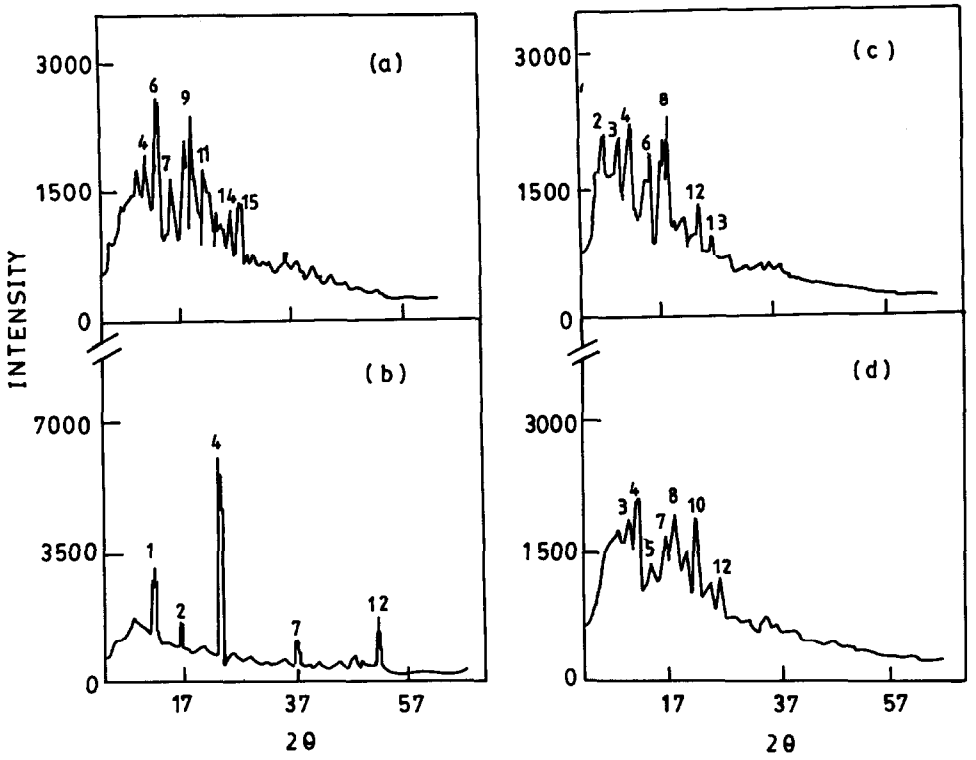


Figure 1. X-ray powder diffraction patterns of (a) β-CD, (b) coumarin, (c) β-CD-coumarin complex and (d) β-CD-coumarin physical mixture.

^{1}H-NMR spectra. Complex formation is also evidenced from 400 MHz ^{1}H-NMR spectral studies of β-CD complex of coumarin in D_2O as solvent. The CD protons are identified on the basis of their specific coupling pattern. In Table 1, the chemical shifts of β-CD protons of uncomplexed and complexed coumarin are presented and the data provide an interesting insight into the complexation pattern. While H_1 proton undergoes strong deshielding the other protons namely H_2, H_3, H_4, H_5 and H_6 undergo strong shielding. The effect is more pronounced on the H_2, H_3 and H_5 protons. It is interesting to note that the shifts are quite strong compared to other substrates.[11,17] The unusually stronger shifts arise due to the anisotropic effects of induced magnetic field of three functional groups namely aryl ring, carbon-carbon and carbon-oxygen double bonds (Figure 2). (While in earlier reported cases of other β-CD complexes[11,17] the anisotropic effect is attributed to the presence of only aryl ring). Also in the study of photodimerization of coumarins in solid inclusion complexes[18] a distinct ^{1}H-NMR chemical shift near δ 5.0 for H_1 proton has been reported. The rigid structure of the substrate forces the three groups to align in a parallel orientation. The very strong deshielding observed in H_1 proton may be attributed to the anisotropic effect of C=O, in whose deshielding cone the H_1 proton falls.

Table 1. 400 MHz ^{1}H-NMR chemical shifts of cyclodextrin protons[a]

Compound	H_1	H_2	H_3	H_4	H_5	H_6
ß-CD	2065.7	1502.9	1628.6	1471.4	1582.9	1591.4
ß-CD-coumarin complex	2298.9	1331.6	1429.5	1345.3	1429.5	1461.1

[a] Chemical shifts are expressed in Hz; solvent D_2O.

^{13}C-NMR spectra. The ^{13}C-NMR chemical shifts of different carbon atoms of ß-CD, coumarin and ß-CD-coumarin complex are given in Table 2. All the carbon atoms in ß-CD are deshielded as a result of complexation. As far as the ß-CD carbon atoms are concerned, the largest shifts are observed on C_3 and C_5 as these two carbon atoms are more inside the cavity and the smallest shifts are observed on C_1 and C_4 which are more exposed outside the cavity. The ^{13}C-NMR chemical shifts of the coumarin in its complexed state also provide useful information. The largest shift is observed in C_4 indicating that this is the most hindered site in the ß-CD complex for the attack by SBH. The shifts are insignificant in the case of carbonyl carbon, C_3 and C_7, which prefer to reside outside the cavity (see Figure 2). Among the several possible orientations,[18] the one presented in Figure 2 seems to be appropriate and in accordance with spectral data.

Table 2. 400 MHz ^{13}C-NMR chemical shifts (Hz) of ß-CD, coumarin and the ß-CD-coumarin complex [a,b]

ß-CD		ß-CD-coumarin complex	coumarin		ß-CD-coumarin complex
carbon atoms	(δ)	($\Delta\delta$)[c]	carbon atoms	(δ)	($\Delta\delta$)[c]
1[d]	102.018	-0.050	carbonyl	160.099	-0.032
2	72.419	-0.080	C_3	166.382	-0.015
3	72.905	-0.171	C_4	144.251	+0.106
4	81.648	-0.035	C_5	116.321	-0.045
5	71.933	-0.156	C_6	124.548	+0.046
6	59.912	-0.095	C_7	128.525	+0.015
			C_8	132.001	+0.061
			C_9	118.856	-0.030
			C_{10}	153.646	-0.060

[a] Chemical shift values are assigned with DMSO signals as the base in both the complexes and the free substrates; [b] At room temperature; [c] + and - signs indicate deshielding and shielding respectively; [d] Numbering of carbon atoms of ß-CD and coumarin is given in Figure 2.

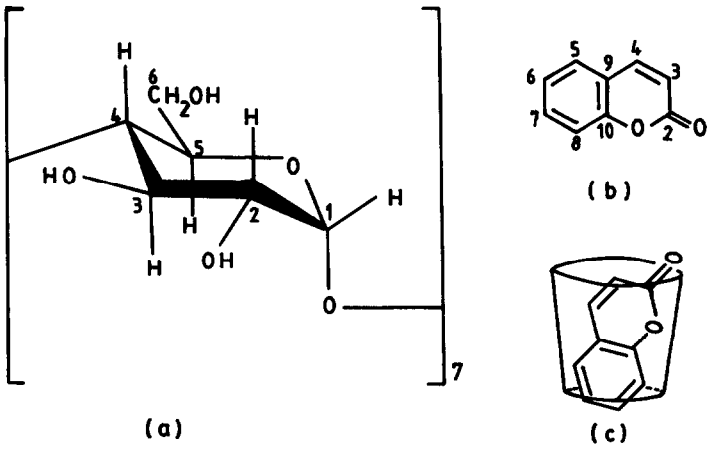


Figure 2. Structures of (a) β-CD, (b) coumarin and (c) postulated conformation of β-CD-coumarin complex.

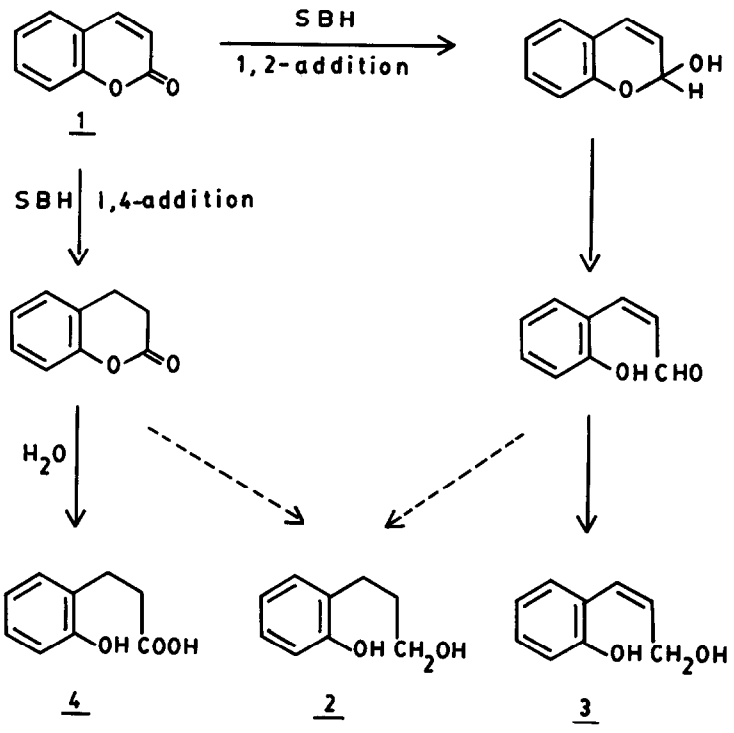
Formation Constant. Based on UV-absorption and emission spectral studies (using the method of Benesi and Hildebrand[14,15]) the formation constants (K_f) are evaluated as 1100 M^{-1} (from UV at 276 nm) and 1400 M^{-1} (from emission studies with λ_{ex} at 276 nm and λ_{em} at 392 nm). The high K_f values suggest that the β-CD forms a strong complex with coumarin.

Complex formation is also evidenced from the determination of molar host-guest ratio by gravimetric method. The ratio is 1:1.23 for β-CD-coumarin complex. The higher ratio of coumarin may be due to the presence of both 1:1 (major) and 1:2 (minor) complexes.

Regiospecific sodium borohydride reduction.

Enones are known to undergo SBH reduction to yield the corresponding alkanols or alkenols (related to 1,4- and 1,2-hydride addition) with the product ratio depending on the reagent or reaction conditions.[10] With an enone ,such as coumarin, a 1,4-attack by SBH followed by hydrolysis yields the saturated carboxylic acid **4** and 1,2-addition leads to alkanediol **2** and alkenediol **3** (Scheme 1).[9]

The percentage yield and the relative amounts of the various products in the SBH reduction of coumarin in different solvents obtained in the present study are summarised in Table 3. Reduction in alcohol or in 0.2mol Na_2CO_3 leads to the saturated **2** or unsaturated **3** diols. However, with diglyme the saturated carboxylic acid **4** is found to be the major product of the reduction. This is expected since SBH in diglyme (a non-hydroxylic solvent) is a very mild reagent and it can reduce only aldehydes but not ketones.[19] When it is employed for the reduction of coumarin, 1,4-addition is the major mode of attack and this may be attributed to the relative rates, thermodynamic stability and steric hindrance to nucleophilic attack at the two possible sites.[20,21] In all the cases, increasing the amount of SBH resulted in an increase in the yield of alkanol (**2**) at the expense of **3**.[22]



Scheme 1.

Table 3. Percentage yields of products in the reduction of coumarin with SBH in the absence of β-CD[a]

Medium	Percentage Conversion	Product distribution (%)			
		2	3	4	c
Na_2CO_3	81 (94)[b]	56 (89)	12 (-)	- -	13 (5)
Methanol	93 (99)	37 (88)	47 (8)	- -	9 (2)
Ethanol	96 (98)	18 (56)	52 (19)	18 (12)	8 (11)
Diglyme	87 (100)	19 (29)	13 (-)	46 (65)	9 (6)

[a] Coumarin and SBH are taken in 1:1.2 molar ratio; stirred for 3 hours at room temperature. Analysed by GC (error limit ± 5%).
[b] Numbers in parentheses are the results for 1:2.2 ratio of coumarin and SBH respectively. [c] Unidentified products.

When the reduction of a physical mixture of β-CD-coumarin-SBH (in the ratio 0.5:1:1.2) is carried out in Na_2CO_3 solution, there is no appreciable change in the percentage conversion as well as product distribution (Table 4). Increase in the molar ratio of CD resulted in a

significant decrease in 2 and 4 with the subsequent increase in the yield of 3. Reduction of the 1:1 complex of the β-CD with coumarin in Na_2CO_3 at room temperature yielded products in ratios analogous to that of the reduction of physical mixture. Obviously stirring of β-CD complex of coumarin in Na_2CO_3 solution resulted in the appreciable dissociation of coumarin from the cavity. Here also, as observed with uncomplexed coumarin, increase in the amount of SBH leads to increase in the yield of 2.

Table 4. Percentage yields of products in the reduction of coumarin with SBH in the presence of β-CD

Components	Molar ratio			Percentage Conversion	Product distribution (%)		
	β-CD	Cou	SBH		2	3	4
β-CD-cou-SBH	0.5	1	1.2	81 (97)[b]	43 (95)	10 (2)	28 (-)
physical	1	1	1.2	72 (74)	39 (59)	15 (11)	18 (4)
mixture[a]	3	1	1.2	97 (90)	9 (80)	80 (9)	8 (1)
β-CD-cou (1:1) complex[a]			1.2	81 (99)	58 (99)	13 (-)	10 (-)
β-CD-cou (1:1) complex[c]			1.2	79	--	69	10

[a] Coumarin or β-CD-coumarin complex and SBH are taken in 1:1.2 molar ratio; stirred for 3 hours at room temperature in aqueous Na_2CO_3. Analysed by GC (error limit ± 5%). [b] Numbers in parentheses are the results for 1:2.2 ratio of coumarin and SBH respectively. [c] Reaction carried out in solid state at 0°C for two days with occasional shaking.

A remarkable feature was observed when β-CD-coumarin 1:1 complex was reduced in solid state in a dry conical flask at 0°C with SBH with occasional shaking for two days. About 80% of coumarin was reduced. The predominant product is the alkenol 3, with the total exclusion of alkanol. This may be explained on the basis of the structure of inclusion complex of coumarin with β-CD (Figure 2), in which the 1,2 position of the enone is more exposed and any approach to C_4 will be sterically hindered. Thus, reduction of β-CD-coumarin complex in solution leads to 1,2- and 1,4-addition products and the reduction of the β-CD solid complex results in regioselective 1,2-reduction as the major reaction course due to the rigidity of the structure of this complex.

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