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Modification of Photochemical Reactivity by Cyclodextrin Complexation: Product Selectivity in Photo-Fries Rearrangement

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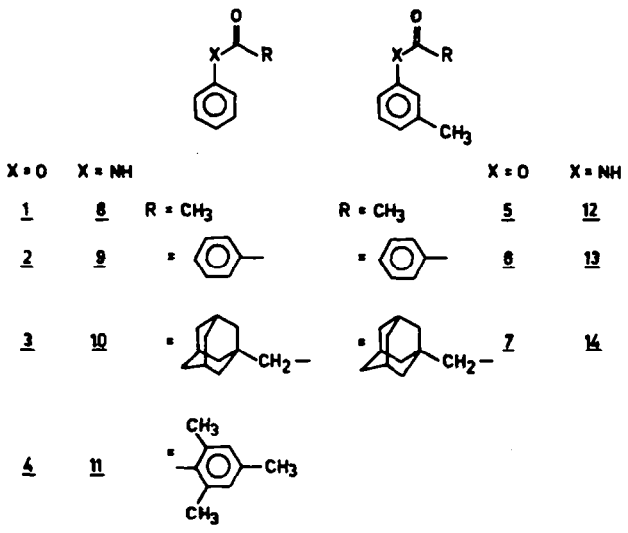
Abstract : Cyclodextrin encapsulation, both in the solid state and in aqueous solution brings about a remarkable regulation of the photo-Fries rearrangement of phenyl esters and anilides. In comparison to the non-selective mixture of ortho and para-rearranged isomers along with the deacylated product obtained in organic solvents, the solid β–cyclodextrin complexes of unsubstituted esters and anilides show a remarkable 'ortho-selectivity'. An impressive 'regio-selectivity' among the two ortho-rearranged isomers is observed for meta-substituted esters and anilides upon irradiation as β-cyclodextrin complexes. Specific orientations of the unsubstituted and meta-substituted esters and anilides in the β-cyclodextrin cavity are suggested to be responsible for the observed selectivity.

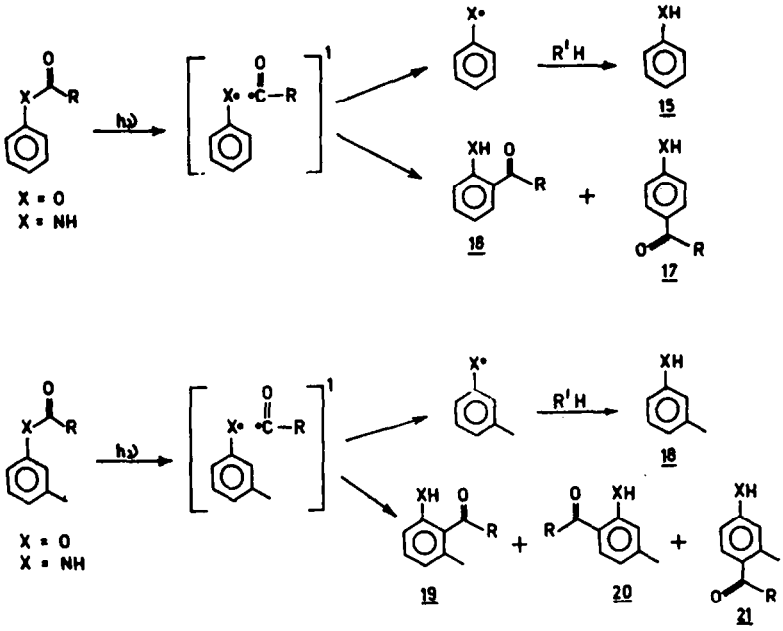
INTRODUCTION

Recent years have seen a great surge of interest among chemists to effect selective chemical transformations[1]. Of the various host-guest systems studied in this context, perhaps the most popular have been the cyclodextrins[2], the cavities of which are sufficiently hydrophobic to provide residence for nonpolar guests in aqueous solution. One of the many different ways in which cyclodextrins could influence a chemical reaction, would be by sterically blocking certain potential sites of the substrate by their very mode of complexation, from intermolecular attack. The results presented below illustrate the importance of such an effect in a well known reaction, namely, photo-Fries rearrangement of phenyl esters and anilides (Scheme 1).

The photo-Fries rearrangement of phenyl esters is established[3] to involve an initial cleavage of the phenyl ester to produce a phenoxy and an acyl radical entrapped in a solvent cage which may recombine in three different ways (Scheme 2). Any escape of the phenoxy radical from the solvent cage with subsequent hydrogen abstraction from the solvent would result in the formation of phenol. When the phenyl ester has a meta-substituent, the photo-Fries rearrangement can then produce two ortho-rearranged products along with the para and the deacylated products (Scheme 2). The corresponding photo-rearrangement of either the unsubstituted or meta-substituted anilides is expected to follow a similar pathway to that of the latter[4].



Scheme 1



Scheme 2

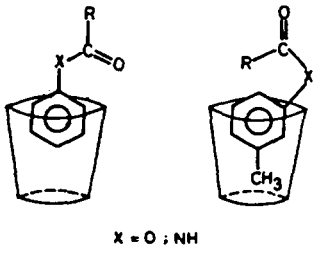


Figure 1

Earlier attempts to study the photo-Fries rearrangement of phenyl acetate[5] and phenyl benzoate[6] in aqueous β-cyclodextrin medium, where less than one equivalent of β-cyclodextrin was present in the aqueous medium per each equivalent of the substrate, have been known. A similar study of the photobehaviour of acetanilide and benzanilide in aqueous β-cyclodextrin solutions has also been reported[7]. Both these studies report the formation of increased amounts of the para-rearranged isomer in comparison to water as the medium. Based on our experience in using β-cyclodextrin as the reaction medium[8], it was perceived that to observe the maximum influence of the host on a reaction, it must be studied in the presence of an excess of β-cyclodextrin. Further, when the photolysis of solid complexes is conducted, the rigid packing of the surrounding molecules would restrict the freedom of motion of the substrate in the solid state to a much greater extent than in aqueous solution, thus leading to a greater influence by the host. With these in mind, a systematic investigation of the photo-Fries rearrangement of unsubstituted and meta-substituted phenyl esters and anilides in β-cyclodextrin medium was undertaken.

RESULTS AND DISCUSSION

β-Cyclodextrin inclusion complexes of 1-14 (Scheme 1) were precipitated from a saturated aqueous solution of cyclodextrin upon addition of one equivalent of the guest. The precipitate was filtered, washed with ether and dried to get solid complexes suitable for photolysis. Aqueous solutions of the complexes were obtained by dissolving the above complex in an excess of water containing an additional nine equivalents of β-cyclodextrin. Excess cyclodextrin was required to tilt the equilibrium towards the complexed form. The presence of an inclusion complex in the solid state was inferred by comparing the X-ray powder diffractograms of the solid complexes with those of the pure cyclodextrin, of the pure solid guest, and of a mechanical mixture of the solid guest and cyclodextrin. The diffraction patterns of the last three differed from those of the solid cyclodextrin complexes indicating the presence of microcrystalline inclusion complexes. Additional support for the presence of an inclusion complex in the solid state comes from the observation that a known weight of the complex, when extracted with chloroform yielded one equivalent of the guest in all the cases, showing that a stoichiometric 1:1 complex was formed between the host and the guest.

In order to ascertain complexation in the aqueous phase, dissociation constant measurements were made for the esters 1 and 5. The dissociation constants determined by absorption spectrophotometry[9] show that moderately stable complexes exist for substrates 1 (K_d = 9.33 x 10^{-3} ML^{-1}) and 5 (K_d = 3.46 x 10^{-3} ML^{-1}) in aqueous cyclodextrin solutions. Dissociation constant measurements for the rest of the complexes could not be carried out owing to the limited solubility of these esters and anilides in water. Further evidence for complexation in the aqueous phase comes from the H^1-NMR analyses of D_2O solutions of the complexes. Esters 1 and 5 and anilides 8 and 12 were chosen for H^1-NMR analyses in the aqueous phase. H^1-NMR data of the cyclodextrin complexes of substrates 1, 5, 8 and 12 and those of pure cyclodextrin are summarized in Table 1. While the chemical shifts of the outer protons H_1, H_2 and H_4 remain virtually unaffected, the protons H_3 and H_5 undergo notable shifts in their resonance positions upon complexation, with H_6 undergoing only a marginal shift. On the basis of literature reports on a number of cyclodextrin complexes[10], the above results can be considered as an indication of complex formation between β-cyclodextrin and the aromatic substrates, the chemical shift changes arising due to the diamagnetic anisotropy effect of the phenyl ring. In all the four cases studied, it was noted that the H_5 proton underwent a much larger shift than the H_3 protons. For the above substrates the orientation given in Figure 1 is consistent with the H^1-NMR results.

Table 1: H^1- NMR Chemical Shifts for Cycledextrin Complexes of 1,5,8 and 12.

Cyclodextrin proton	Uncomplexed cyclodextrin	Chemical shifts (Hz) for complexes of 1	5	8	12
H_1	1359.6	1360.5	1360.5	1359.1	1359.3
H_2	975.7	976.0	973.1	978.0	978.0
H_3	1059.6	1045.5	1039.2	1045.5	1044.2
H_4	958.4	959.8	958.8	954.3	954.3
H_5	1030.0	1000.7	1000.3	994.0	996.1
H_6	1039.1	1036.5	1036.0	1030.3	1029.6

Table 2: Product Distribution upon Photolysis of Phenyl esters and Anilides under Various Coditions

Medium/condition for photolysis	Yields of products (Refer Scheme 2)[a]				
	Esters (1-4)			Anilides (8-11)	
	ortho (16)	para (17)	phenol (18)	ortho (16)	para (17)
	Phenyl acetate (1)			*Anilide (8)*	
Benzene	59	38	2	70	29
Methanol	28	39	34	97	3
β-Cyclodextrin (water)[b]	89	11	-	99	1
β-Cyclodextrin (solid)[c]	84	14	-	>99	-
	Phenyl benzoate (2)			*Benzanilide (9)*	
Benzene	55	30	15	65	35
Methanol	48	30	14	80	20
β-Cyclodextrin (water)	99	1		>99	-
β-Cyclodextrin (solid)	99	1		>99	-
	Phenyl adamantyl acetate (3)			*α-Adamantyl acetanilide (10)*	
Benzene	63	26	3	72	28
Methanol	58	21	3	88	11
β-Cyclodextrin (water)	99	1		94	6
β-Cyclodextrin	99	1		>99	-
	Phenyl 2,4,6-trimethyl benzoate (4)			*Mesitoic acid anilide (11)*	
Methanol	39	46	9	65	35
β-Cyclodextrin (water)	99	1		99	-
β-Cyclodextrin (solid)	>99	-		>99	-

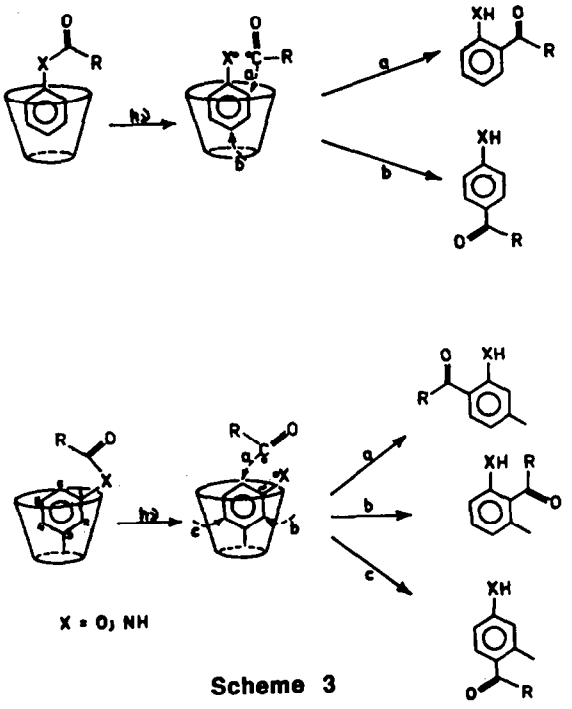
(a) analysed by gc; error limit ± 5%. (b) cyclodextrin was used in ten molar excess.
(c) 1:1 complex was used.

The product distribution upon photolysis of the substrates 1-14 in homogeneous solutions and as their cyclodextrin complexes are summarized in Tables 2 and 3. Conversions were limited to less than 20%. The rearranged products 16, 17 and 19-21 in each case, were characterised on the basis of their H_1-NMR, IR spectral and elemental analyses data. Interesting differences in product distribution between homogeneous solution and aqueous cyclodextrin solutions are clearly seen (Tables 2 and 3). It can be seen that for the substrates 1-4 and 8-11 in ethanol and in water, a mixture of products 15-17 were formed. As the amount of β-cyclodextrin present in the aqueous phase increased, the formation of the deacylated product and the para-rearranged product decreased with an increased formation of the ortho-rearranged product. The most striking observation was made in the solid cyclodextrin complexes of these substrates, which upon photolysis, yielded only the ortho-rearranged product in quantitative yields. In the case of substrates 5-7 and 12-14 also, while a mixture of products 18-21 were formed (Scheme 2) in organic solvents and in water, aqueous β-cyclodextrin solutions revealed an increased preference for the formation of the two ortho-rearranged isomers 19 and 20, with a suppression of the formation of deacylated phenol 18, and the para rearranged isomer, 21. Most remarkably, out of the two ortho-rearranged products, an increased preference for the isomer 20, namely, 2-hydroxy 4-methylphenylketone in the case of esters and 2-amino 4-methylphenylketone in the case of the anilides was noticed as the amount of β-cyclodextrin present in the aqueous phase was increased. The solid β-cyclodextrin complexes of these substrates revealed a near-quantitative formation of the isomer 20, as the sole product.

The remarkable observation of 'ortho-selectivity' in the solid β–cyclodextrin complexes of substrates 1-4 and 8-11 is in accordance with the formation of inclusion complexes with structures shown in Scheme 3. It can be seen that in such an orientation, the β-cyclodextrin sleeve protects the para position of the aromatic ring from attack by the acyl radical exposing the two ortho positions for the reaction. Further, the tight packing of the surrounding molecules, in a solid complex, provides a 'cage-like' environment which forces the acyl radical either to recombine with the phenoxy radical to regenerate the starting material, or to attack the exposed ortho positions (Scheme 3). For substrates 5-7 and 12-14, Figure 1 shows the most probable orientation in the β-cyclodextrin complex. It may be seen that in such an orientation, the cyclodextrin sleeve encircles the molecule in such a way that only one ortho position is exposed for attack. Thus the acyl radical, once formed, is forced to move towards the only accessible 6-ortho-position in the solid β-cyclodextrin complexes, thus generating the isomer 20 as the sole product.

The results of aqueous β-cyclodextrin complexes, as seen in the cases of all the substrates 1-14 are intermediary between those in water and those in the solid β-cyclodextrin complexes. This may be expected due to the existence of a 'non-cage' situation in aqueous β-cyclodextrin complexes where both the complexed substrate and the initially formed redicals are free to escape into the aqueous exterior with the result of reactions occurring from both the bound and the free substrates. The addition of more cyclodextrin shifts the equilibrium towards the complexed state, thus improving the selectivity observed. Based on these arguments, if the dynamic equilibrium can be totally shifted in favour of the complexed substrate, then the maximum selectivity must be observed for the reaction under those circumstances.

One particularly intriguing aspect of the present investigation was that, in all the substrates studied, 1-14, good selectivity was observed in the solid β-cyclodextrin complexes, irrespective of the nature of the carboxylic substituent of the esters and anilides. When the guest species has more that one binding site, the formation of more than one type of complex is probable. Thus, there would be an equilibrium between different forms of the complexes, with



Scheme 3

Table 3: Product Distribution upon Photolysis of *meta*-Methyl phenyl esters and *meta*-Methyl anilides.

Medium/Condition	Yields of Photoproducts (Refer Scheme 2)[a]					
	Esters			Anilides		
	ortho-1 19	*ortho-2* 20	*para* 21	*ortho-1* 19	*ortho-2* 20	*para* 21
	3-Methyl phenyl acetate (5)			3-Methyl acetanilide (12)		
Ethanol	36	37	13	26	43	30
β-Cyclodextrin (water)[b]	42	54	-	18	75	6
β-Cyclodextrin (solid)[c]	5	95	-	9	91	-
	3-Methyl phenyl benzoate (6)			3-Methyl benzalide (13)		
Ethanol	25	29	30	28	42	30
β-Cyclodextrin (water)	34	66	-	36	64	-
β-Cyclodextrin (solid)	4	96	-	-	>99	-
	3-Methyl phenyl adamantyl-acetate (7)			α-Adamantyl 3-methyl acetanilide (14)		
Ethanol	32	26	9	33	33	33
β-Cyclodextrin (water)	15	85	-	16	83	-
β-Cyclodextrin (solid)	7	93	-	-	>99	-

(a) analysed by gc; error limit ± 5%; (b) cyclodextrin was used in ten molar excess; (c) 1:1 solid complex was used.

the more stable form existing predominantly. Surprisingly, phenyl esters 2, 3 and 7 and anilides 9, 10 and 14 with multiple binding sites rearranged in a selective manner in β-cyclodextrin medium. It may be seen from Tables 2 and 3 that even the presence of a strongly binding adamantyl group in the substrate did not lead to a drop in selectivity. In the absence of unequivocal evidence for the mode of complexation for all the substrates, on the basis of the observed results, it may only be speculated that the orientation of the substrate in the β-cyclodextrin cavity is the same for all the substrates investigated irrespective of the nature of the carboxylic substituent.

EXPERIMENTAL

β-Cyclodextrin (Sigma) was used as received. The substrates 1-14 were prepared by reported procedures[11] and were purified by vacuum distillation (in the case of liquids) or by repeated crystallisation (in the case of solids). The purity of the substrates (>98%) was ascertained by gas chromatographic analyses before using them for irradiations. Distilled water and distilled solvents were used for irradiations and extractions.

Preparation and Identification of Complexes: β-Cyclodextrin complexes of substrates 1-14 were prepared by the methods reported elsewhere[12]. Precipitated inclusion complexes were filtered, washed with ether to remove uncomplexed substrates and dried (50°) to obtain solid samples for irradiation. A typical solid sample used for irradiation contained 50 mg of the substrate. On the other hand, aqueous solutions of the complexes containing 20 mg of the substrate were prepared by dissolving the solid complexes in about 100 mL of water to which a nine molar excess of cyclodextrin was added and the solutions were stirred to obtain transparent solutions for irradiation.

X-ray powder diffractograms were recorded for the solid complexes, pure cyclodextrins, pure guests (in the case of solid guests) and for a thoroughly mixed sample of the guest and the cyclodextrin in a Philips powder diffractometer by employing monochromatic CuK_α radiation. Complexation in the aqueous phase was detected by recording 270 MHz H_1-NMR spectra (Bruker WH-270 spectrometer) for D_2O solutions containing 5 mg of β-cyclodextrin in 0.5 mL of D_2O to which 0.5 equivalents of the guest were added and stirred magnetically for 12 h. The H_1-NMR studies were carried out for esters 1 and 5 and anilides 8 and 12 containing increasing ratios of the guest to cyclodextrin. Solubility constraints of the guests prevented the H_1-NMR analyses of rest of the substrates.

Photolysis: Photolysis of the solid complexes of substrates 1-14 were done in petri dishes covered with quartz plates in a Rayonet reactor fitted with 254 nm mercury lamps. Aqueous solutions of cyclodextrin complexes and homogeneous solutions of substrates 1-14 in ethanol containing 20 mg/100 mL of solvent were irradiated in quartz tubes in a similar reactor. Irradiations were done for 12-24 h and the percentage conversion was maintained below 20% in all the cases. The cyclodextrin complexes, following irradiation, were extracted with warm chloroform after dissolving them in an excess of water. The product mixture obtained after evaporation of the solvent was analysed by gas chromatography (Chemito Model 3800). The analyses were carried out by using a 10% SE-30 column (20% SE-30 column was used for substrates 12 and 14) of dimensions 8' x 1/8" in the temperature range of 120-250°C programmed at the rate of 10°C/minute.

The ortho and para-rearranged isomers of each substrate investigated was characterised in the following manner. About 500 mg of the substrate in 50 mL of ethanol was irradiated (254 nm) for 48 h for nearly complete conversion and the resultant products after stripping off the solvent were chromatographed (silica gel-hexane/chloroform) to obtain pure rearranged isomers, which were characterised based on their H_1-NMR and IR data (data for for the photoproducts of the anilides are listed below). All the photoproducts gave satisfactory elemental analysis data. H_1-NMR of the esters were found to be similar to those of the corresponding anilides[13].

The rearranged products isolated from the photolysis mixture were also characterised by comparison of their spectral properties with those of the products of thermal rearrangement of the esters with anhydrous $AlCl_3$. A mixture of 5 g of $AlCl_3$ and 500 mg of the ester was heated with stirring for 2 hours in carbon disulphide until the mixture thickened to a brown mass. This was worked up and column chromatography (silica gel- hexane/ethyl acetate) of the resulting mixture gave the para-rearranged product. The spectral properties and GC retention times of this isomer were compared with those obtained upon photolysis.

Spectral data of the photo-products:

2-Aminophenylmesitylketone (16 X=NH; R=2,4,6-trimethylphenyl)	IR(Neat) cm^{-1}	3450, 3320, 2900,1600, 1560, 1430, 1230, 900,740.
	H^1-NMR(CCl_4)	7.1,m(2H),6.75,s(2H), 6.5,(2H),2.3,s(3H),2.1,s(3H).
4-Aminophenylmesitylketone (17 X=NH; R=2,4,6-trimethylphenyl)	IR(Neat)cm^{-1}	3440, 3340, 3200, 2900, 1580, 1300, 1270, 1150, 900.
	H^1-NMR(CCl_4)	7.43, d, J=8Hz (2H), 6.72,s (2H), 6.35, d, J=8Hz(2H), 2.3,s(3H), 2.0,s(3H).
1-Adamantyl(2'-amino) acetophenone. (16 X=NH; R= -CH_2Ad)	IR(Neat) cm^{-1}	3470, 3330, 2970, 1700,1640, 1560, 1440, 1190, 730.
	H^1-NMR(CCl_4)	7.76-6.36,m(4H), 2.6,s(2H),2.0,m(3H), 1.7,bs(12H).
1-Adamantyl(4'-amino) acetophenone (17 X=NH; R= -CH_2Ad)	IR(Neat) cm^{-1}	3460, 3340, 3200, 2900, 1700, 1580, 1430, 1250, 1160, 740.
	H^1-NMR(CCl_4)	7.7,d,J=8Hz(2H), 6.53,d,J=8Hz(2H), 2.55,s(2H),1.98,m (3H), 1.66, bs(12H).
2-Amino 4-methyl acetophenone (20 X=NH; R=CH_3)	IR(Neat) cm^{-1}	3450, 3320, 2900, 1630, 1560, 1420, 1340, 1230, 1150, 960, 770.
	H^1-NMR(CCl_4)	7.25,d,J=12Hz(1H), 6.3,m(2H),2.45,s(3H), 2.2,s(3H).
1-Adamantyl(2'-amino 4-methyl)acetophenone (20 X=NH; R=-CH_2 Ad)	H^1-NMR($CDCl_3$)	7.3,d, J=12Hz(1H), 6.25,m(2H),2.5s, 2.5 s(2H), 2.2, s (3H), 1.9, m (3H), 1.65,bs(12H).
2-Amino 6-methyl benzophenone (19 X=NH; R=Ph)	IR(Neat) cm^{-1}	3440, 3320, 2900, 1610,1570, 1450, 1230, 885, 740, 680.
	H^1-NMR($CDCl_3$)	7.8,d,J=7Hz(2H), 7.6-7.4,m(3H),7.08, t J=7.8Hz(1H),6.56,m (2H), 2.0,s (3H).
2-Amino 4-methyl benzophenone (20 X=NH; R=Ph)	IR(Neat) cm^{-1}	3440, 3360, 2900, 1635, 1600, 1360, 1260, 900, 770, 690.
	H^1-NMR($CDCl_3$)	7.63-7.4,m(5H), 7.32,d,J=8Hz(1H), 6.5,s(1H), 6.36,d, J=8Hz(1H), 2.16,s (3H).
4-Amino 2-methyl benzophenone (21 X=NH; R=Ph)	IR(Nujol)cm^{-1}	3380, 3300, 3200, 2900, 1620, 1590, 1550, 1310, 1240, 890, 810, 730, 690.
	H^1-NMR($CDCl_3$)	7.74,d,J=7.2Hz(2H), 7.54-7.4,m(3H), 7.24,d, J=8.2Hz(1H),6.57,d, J=1.8Hz(1H),6.46,dd, J_1=8.2Hz, J_2=1.8Hz(1H), 2.41,s(3H).

Measurement of Dissociation Constants: The increase in absorbance of substrate in their electronic spectra upon addition of cyclodextrin was used to calculate the dissociation constants by the method of Benesi and Hilderbrand[9]. Owing to the poor solubility of the rest of the substrates in water, these studies could be carried out only for substrates 1 and 5 with β-cyclodextrin. A stock solution containing (10^{-3} M) of the substrate in methanol was made and 100 μL alliquots from this were added to 10 mL standard flasks. Varying volumes (0-2 mL) of β–cyclodextrin solution were added to these from a stock solution of 10^{-2} M of cyclodextrin. The solutions were magnetically stirred and their absorption spectra were recorded (Shimadzu UV-180 spectrophotometer) in the range of 225-350 nm. The increase in absorbance at 270 nm were noted with increasing cyclodextrin concentration and this was used to calculate the dissociation constant values.

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