2.2 Di-Functionalization of β-Cyclodextrin

2.2.1 Experimental

2.2.1.1 Materials

β-Cyclodextrin was obtained from Signet Chemical Corporation, Mumbai as a gift sample and dried overnight under a vacuum oven at 60^{o}C, then used without further purification. Biphenyl-4,4'-disulfonyl chloride (recrystallized from chloroform), potassium iodide, potassium thiocyante, sodium azide and triphenylphosphine were purchased from Sigma-Aldrich. *N,N'*-dimethylformamide (DMF), pyridine, and tetrachloroethylene were purchased from Merck (Germany) and dried over molecular sieves for 1 day then distilled under reduced pressure before use. All other chemicals were procured locally and used without further purifications. Double distilled water was used during the all experiment.

2.2.1.2 Measurements

The FT-IR spectra of the compounds were recorded on a Shimadzu 8400S Fourier Transform Infrared Spectrometer by KBr pellet method at 10^{-4} resolution and 30 scan at room temperature. AR grade KBr was used for the preparation of pellet. The UV-Visible absorbance spectra were recorded on a Shimadzu UV-Vis-2450, UV-Vis spectrophotometer. ^{1}H-NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 400 MHz at room temperature where tetra-methylsilane (TMS) was used as internal standard. The chemical shifts are given in δ ppm from TMS signal. TLC was carried out on silica gel plates (Merck 60-F254). For the structural drawing and molecular modeling studies, the software Chem Office 2004 (Chem 3D Ultra 8.0version) was used.

2.2.1.3 Synthesis of 6^{A},6^{D}-biphenyl bridged β-Cyclodextrin (1)

A 500 mL three neck round bottom flask equipped with a magnetic stir bar, a Schlenk adapter and a rubber septum was charged with 11.35 gm (0.01 mol)) of dry β-cyclodextrin and 150 mL of anhydrous pyridine. The resulting solution was stirred at 50°C under nitrogen atmosphere, while 3.51 gm (0.01 mol) of biphenyl-4,4′-disulfonyl chloride dissolved in 100 mL pyridine was cautiously added drop wise in 1 h. After

that the reaction mixture was allowed to stir at 50°C for an additional 3 h in the same conditions. The solvent was removed under vacuum on a rotary evaporator at 40°C and the residue obtained was subjected to reversed-phase column chromatography using a gradient elution of 0-40% acetonitrile in water. After, removing the bulk of the acetonitrile on a rotary evaporator, the resulting aqueous suspension was lyophilized to dryness. This afforded 6.15 gm (40%) of $6^A,6^D$-biphenyl bridged β-cyclodextrin as a colorless solid.

2.2.1.4 Synthesis of $6^A,6^D$-diiodo $6^A,6^D$-dideoxy β-Cyclodextrin (2)

A 100 mL three neck round bottom flask equipped with a magnetic stirbar, a Schlenk adapter and a rubber septum was charged with 5.42 gm (3.52 mmol) of $6^A,6^D$-biphenyl bridged β-cyclodextrin, 17.53 gm (0.106 mol) of dry, powdered potassium iodide and 15 mL of anhydrous *N,N'*-dimethylformamide (DMF). The resulting suspension was stirred at 80°C under nitrogen atmosphere for 2 h. After cooling to room temperature, the solids were separated by centrifugation and the supernatant was decanted. The solid precipitate was washed with a second portion of anhydrous DMF and the supernatants were combined and concentrated in vacuum. The residue was then dissolved in 14 mL of water and cooled in an ice bath before 0.75 mL (7.3 mmol) of tetrachloroethylene was added with rapid stirring. The precipitated inclusion complex was filtered on a medium glass frit and washed with a small portion of acetone before it was dried under vacuum. This afforded 4.69 gm (90% yield) of $6^A,6^D$-diiodo $6^A,6^D$-dideoxy β-cyclodextrin as a slightly yellow solid.

2.2.1.5 Synthesis of $6^A,6^D$-diazido $6^A,6^D$-dideoxy β-Cyclodextrin (3)

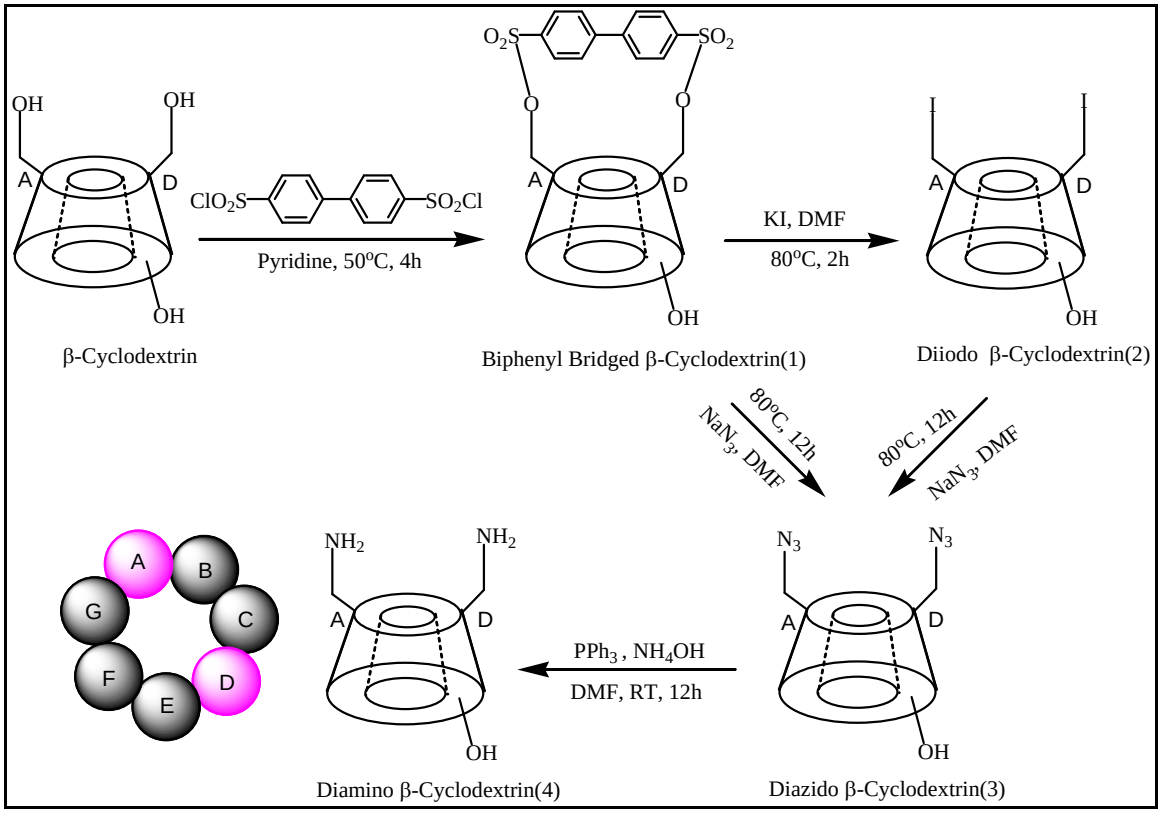
A 100 mL three neck round bottom flask equipped with a magnetic stir bar cotted with Teflon, a Schlenk adapter and a septum was charged with 3.90 gm (2.88 mmol) of β-cyclodextrin diiodide, 1.12 gm (0.019 mol) of sodium azide and 10 mL of anhydrous *N,N'*-dimethylformamide (DMF). The resulting suspension was stirred at 80°C under nitrogen atmosphere for 12 h. The solvent was removed on a rotary evaporator under reduced pressure and obtained residue was dissolved in 150 mL of water. This diluted solution was subjected to ultrafiltration by using polymer membrane filtration (MWCO 650 Da) to remove the excess salt. After removing salt the resulting aqueous suspension was freeze-dried to get 3.54 gm (90%) white solid which was used for the next stage.

2.2.1.6 Synthesis of 6^A,6^D-diamino 6^A,6^D-dideoxy β-Cyclodextrin (4)

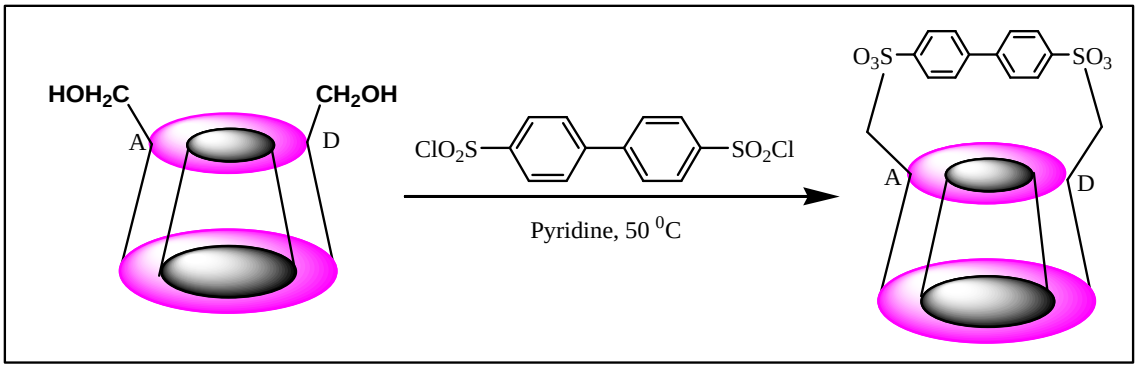
A 100 mL three neck round bottom flask equipped with a magnetic stirbar and a septum was charged with 1.232 gm (1.04 mmol) of β-cyclodextrin bisazide and 50 mL of anhydrous *N,N'*-dimethylformamide (DMF). To this stirring suspension was added 0.898 gm (3.42 mmol) of triphenylphosphine. The resulting suspension was stirred for 1 h at ambient temperature before 10 mL of concentrated aqueous ammonia was added. The addition of ammonia was accompanied by a rapid gas evolution and the solution became homogeneous. After 12 h, solvent was removed under vacuum rottavapor and obtained residue was mixed with water and washed twice with benzene to remove the phosphonium oxides. The solution was adjusted to pH-4 by addition of 0.1N HCl solution and diluted with 100 mL of water. This diluted solution was subjected to ultrafiltration by using polymer membrane (MWCO 650 Da). The resulted aqueous solution was freeze dried to get dry 1.10 gm (90%) white product of diamino β-cyclodextrin.

2.2.1.7 Synthesis of 6^A, 6^D-diisothiocyanto 6^A, 6^D-dideoxy β-cyclodextrin (5)

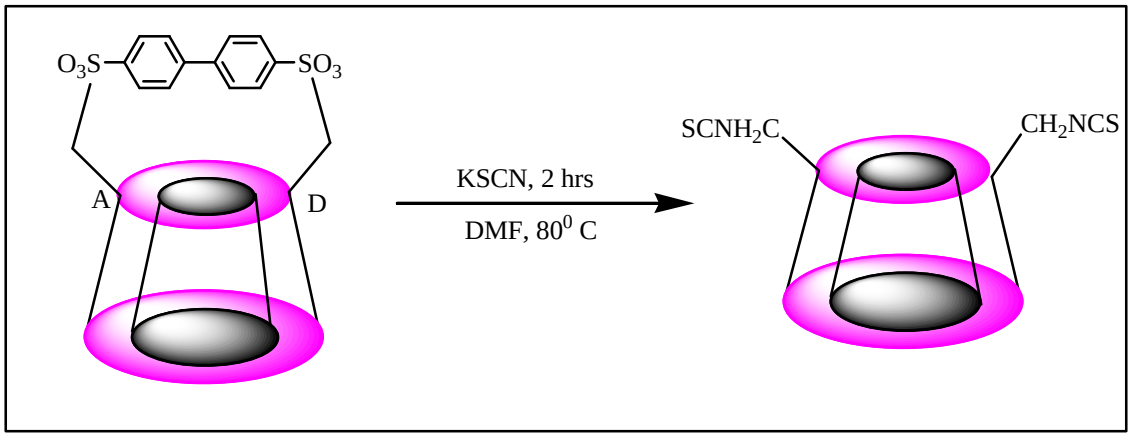
A solution of (1) 2 g (0.00138 moles) in 15ml DMF and 0.4 g (0.00412 moles) of dry KSCN was stirred at 80^0C under nitrogen atmosphere for 2h. After cooling to room temperature the solids were separated by centrifugation and supernatant was decanted. The solid precipitates were washed twice with DMF. The residue was dissolved in small amount of water and cooled, before acetone was added with rapid stirring. The precipitate was filtered and dried under vacuum, and dissolved in 50ml of water. Then the byproduct potassium biphenyl-4, 4'-disulphonate formed during the reaction was removed by ultra-filtration using MWCO 1K. This affords 75.8% (1.5 g) of 6^A, 6^D-diisothiocyanto 6^A, 6^D-dideoxy β-Cyclodextrin as colorless solid.



Scheme 2.2.1 Synthetic scheme for the synthesis of selectively difunctionalized β-cyclodextrins



Scheme 2.2.2 Synthesis of 6^A, 6^D-biphenyl bridged β-Cyclodextrin monomer



Scheme 2.2.3 Synthesis of 6^A, 6^D-diisothiocyanto 6^A, 6^D-dideoxy β-cyclodextrin monomer

2.2.2 Results and Discussion

The regioselectively modified $6^A,6^D$-diamino $6^A,6^D$-dideoxy β-cyclodextrin was synthesized by the route shown in scheme 2.2.1 following the primary reports of I. Tabushi *et al*[20]. The capping reaction was successfully carried out by treating the β-cyclodextrin with biphenyl 4,4'-disulfonyl chloride, which has enough long geometry that it can direct the reaction on A to D position hydroxyl groups of β-cyclodextrin on the primary rim. The reaction of biphenyl bridged-β-cyclodextrin with dry powder potassium iodide in dry DMF gave the diiodo β-CD derivative, which further react with sodium azide to afford diazido β-CD derivative. The reaction of diazido β-CD with triphenylphosphine in DMF followed by hydrolysis of iminophosphorane intermediate with NH_4OH gave the $6^A,6^D$-diamino $6^A,6^D$-dideoxy β-cyclodextrin. The reaction of biphenyl bridged-β-cyclodextrin with dry powder potassium isothiocyanate in dry DMF gave the diisothiocyanated β-CD monomer.

2.2.2.1 Biphenyl 4,4'-disulfonyl -A,D-Capped β-cyclodextrin (1)

The major bands in FTIR (KBr) spectrum (Figure 2.2.1) are at ν 3400cm^{-1} (OH, b) , 2885 cm^{-1} (C-O, s), 1160 cm^{-1} (strong band due to SO_2), 834 cm^{-1} (Para substituted benzene). The band at 3400 cm^{-1} is due to OH groups of the cyclodextrin molecule and it indicates the absence of extended hydrogen bonding between hydroxyls. This is in contrast to the FTIR spectra of crystalline β-CD. The ^{13}C-NMR (DMSO-d_6, 400 MHz) of the Biphenyl 4,4'-disulfonyl-A,D-Capped β-cyclodextrin (Figure 2.2.2) shows biphenyl aromatic carbons chemical shift at δ_C: 126.17, 126.80, 127.23, 128.23, 139.78, 142.23, 146.10 and 147.31. It also observed due to the primary hydroxyl group substitution the signals of the C-6 carbon of the aliphatic cyclodextrin shift up field from 59.93 ppm to 41.67 ppm. Thus ^{13}C NMR confirmed that the biphenyl-4, 4'-disulphonyl chloride has reacted with primary hydroxyl thus making a bridge on the primary side of β-cyclodextrin molecule.

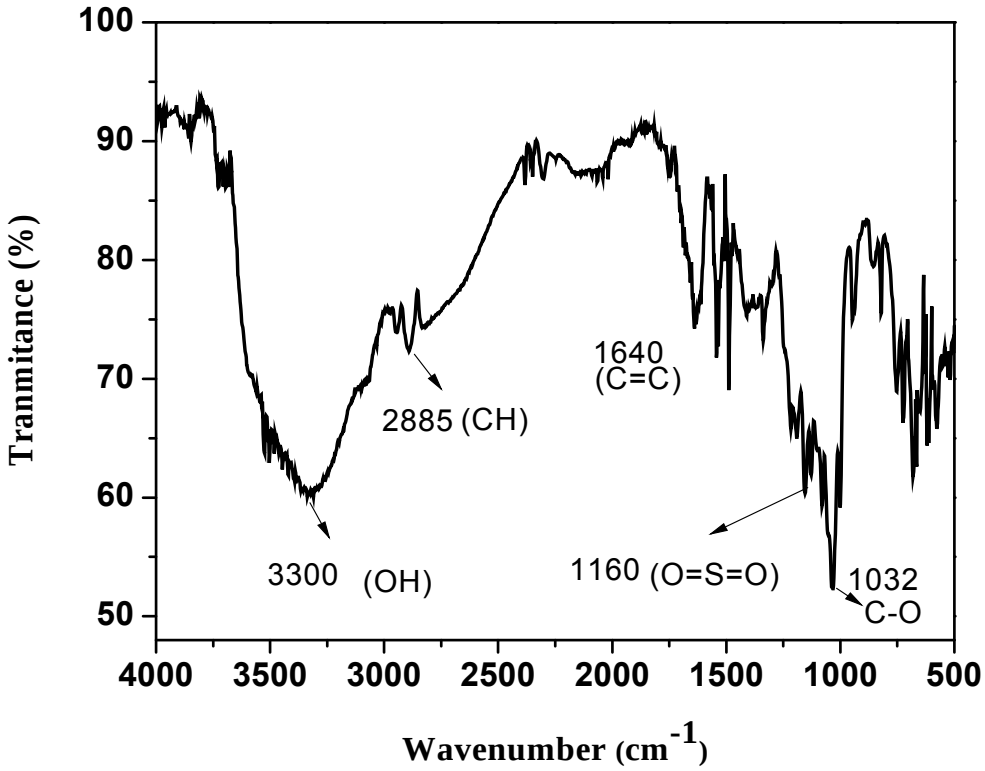


Figure 2.2.1 FTIR spectrum of $6^A,6^D$-biphenyl bridged β-cyclodextrin.

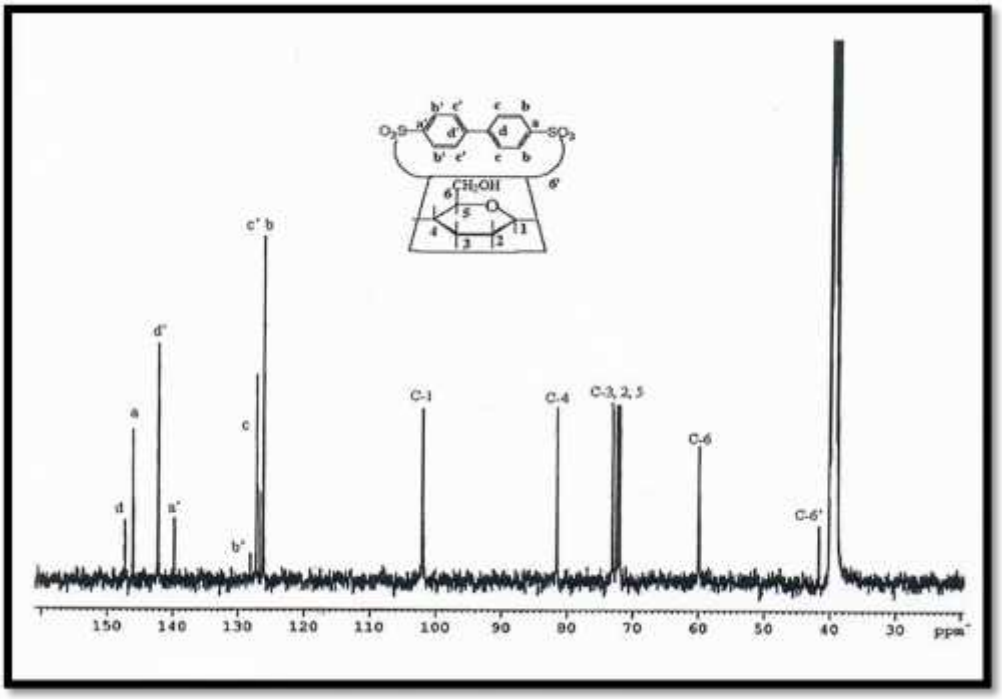


Figure 2.2.2 ^{13}C NMR spectrum of biphenyl bridged β-cyclodextrin in DMSO-d_6

2.2.2.2 $6^A,6^D$-diiodo $6^A,6^D$-dideoxy β-Cyclodextrin (2)

The FTIR spectrum of $6^A,6^D$-diiodo $6^A,6^D$-dideoxy β-cyclodextrin is shown in Figure 2.2.3. The spectrum depicted the absorbance band at 3400 cm^{-1} and 1156 cm^{-1} peak was observed due to –OH stretching and $–CH_2$-I stretching (rocking and wagging band), which confirms that biphenyl ring easily removed from the biphenyl bridged β-cyclodextrin by the nucleophilic addition of the potassium iodide.

The ^{1}H NMR spectrum of the $6^A,6^D$-diiodo $6^A,6^D$-dideoxy β-cyclodextrin is shown in Figure 2.2.4. The spectrum shows only the typical glucose unit's proton signals of β-cyclodextrin along with removal of aromatic biphenyl protons in aromatic region. These results confirmed that the biphenyl ring was removed from the biphenyl bridged β-cyclodextrin due to the nucleophilic substitution.

The ^{13}C NMR spectrum of $6^A,6^D$-diiodo $6^A,6^D$-dideoxy β-cyclodextrin is shown in Figure 2.2.5 also support the same observation showed all the typical carbon chemical shifts of cyclodextrin glucose units along with one new carbon chemical shift C-6' at 10 ppm (adjacent to –I) due to the substitution of two primary hydroxyl groups of the β-CD.

2.2.2.3 6^A, 6^D-diazido $6^A,6^D$-dideoxy β-Cyclodextrin (4)

The FTIR spectrum of the $6^A,6^D$-diazido $6^A,6^D$-dideoxy β-cyclodextrin is shown in Figure 2.2.6. The spectrum exhibited the absorbance band at 3400 cm^{-1} and 2037 cm^{-1} were observed due to presence –OH stretching and $-N_3$ asymmetrical stretching, which confirms that replacement of two iodo groups from the $6^A,6^D$-diiodo $6^A,6^D$-dideoxy β-cyclodextrin by the nucleophilic addition of the sodium azide.

The ^{1}H-NMR (Figure 2.2.7) and ^{13}C-NMR (Figure 2.2.8) also confirmed the removal of iodo groups from $6^A,6^D$-diiodo $6^A,6^D$-dideoxy β-cyclodextrin showed only protons and carbon chemical shifts of β-cyclodextrin's glucose units along with substituted protons and carbon shifts at two C-6' position of β-cyclodextrin.

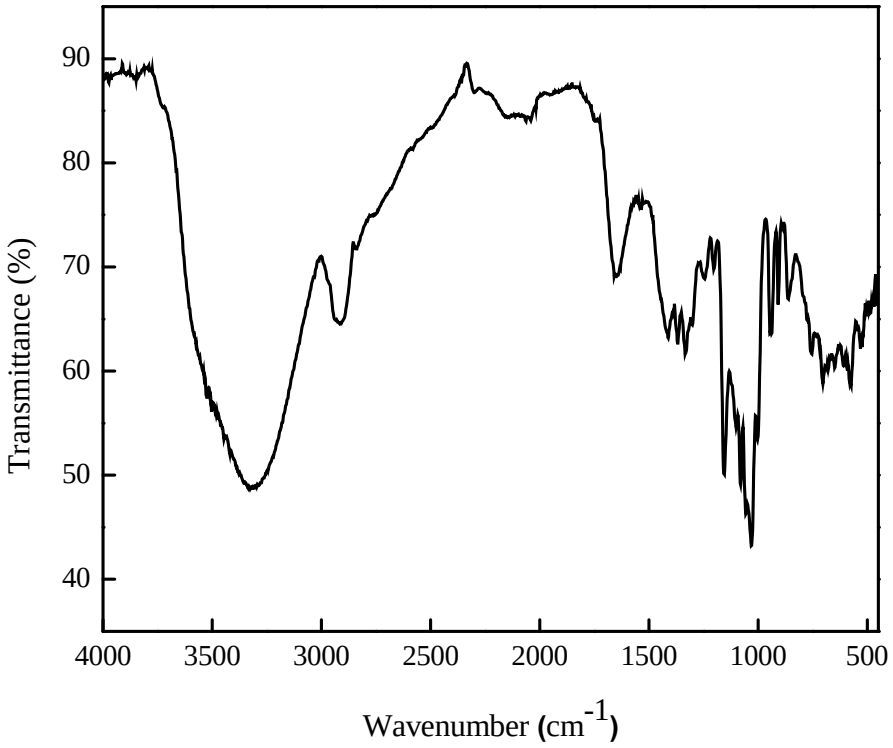


Figure 2.2.3 FTIR spectrum of $6^A,6^D$-diiodo $6^A,6^D$-dideoxy β-cyclodextrin.

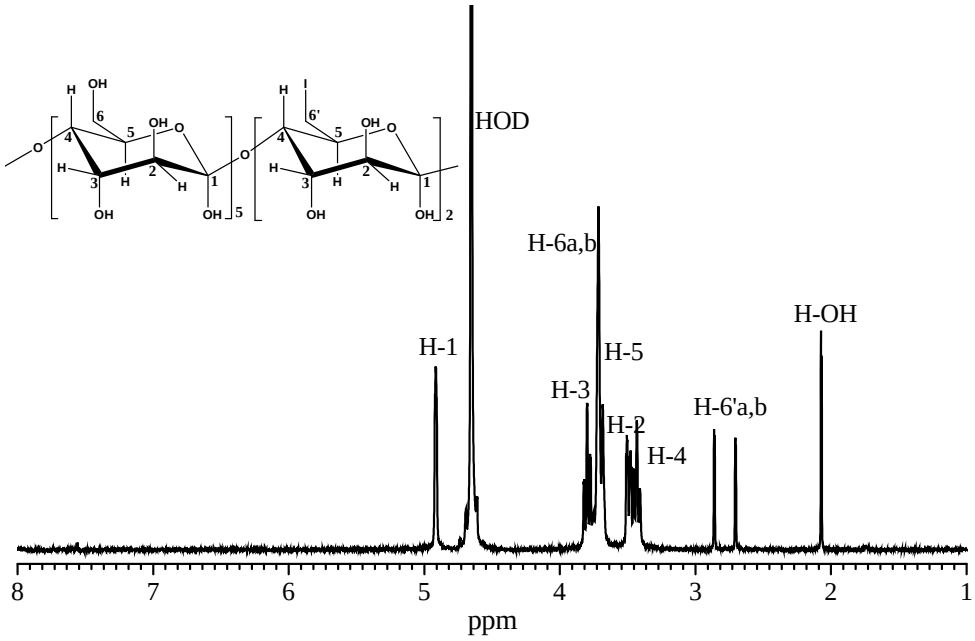


Figure 2.2.4 ^{1}H NMR spectrum of 6^{A},6^{D}-diiodo 6^{A},6^{D}-dideoxy β-cyclodextrin in D_2O.

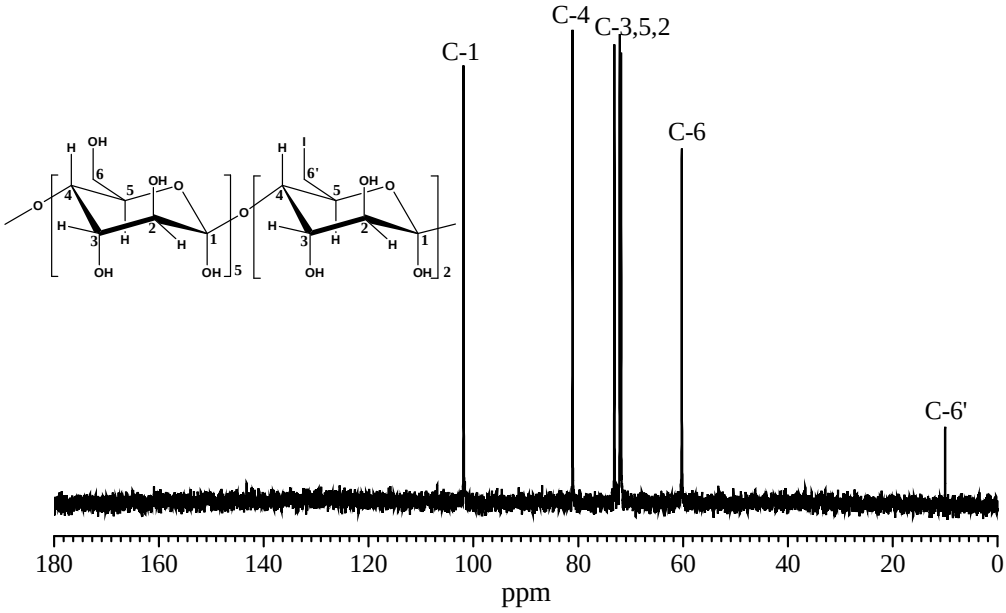


Figure 2.2.5 ^{13}C NMR spectrum of $6^{A},6^{D}$-diiodo $6^{A},6^{D}$-dideoxy β-cyclodextrin in D_2O.

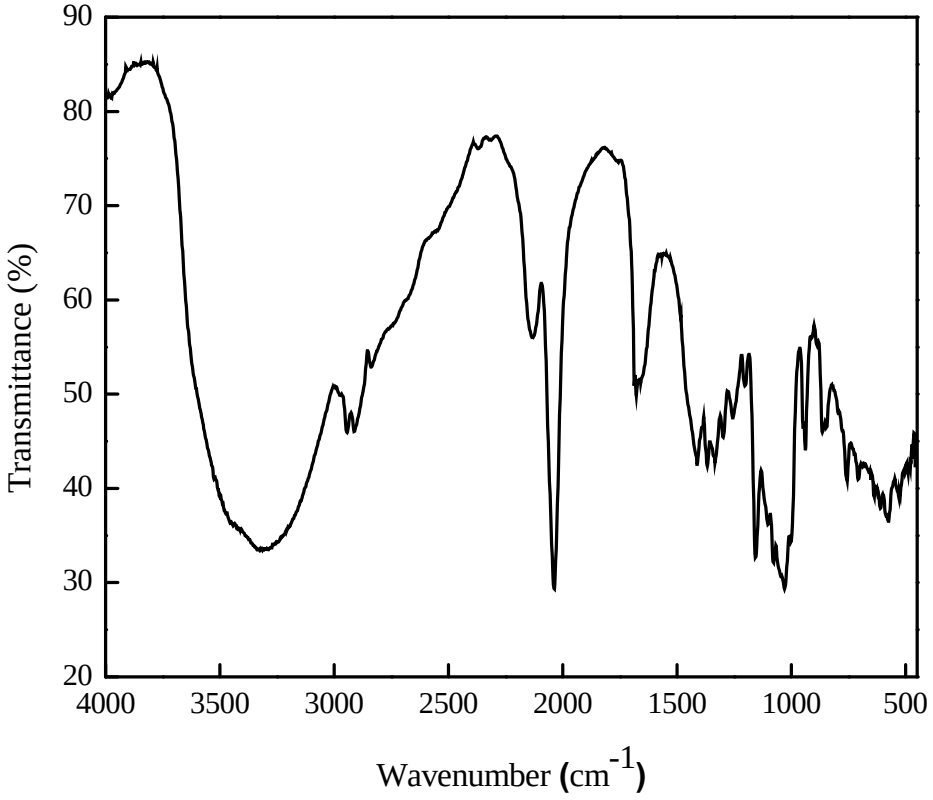


Figure 2.2.6 FTIR spectrum of 6^{A},6^{D}-diazido 6^{A},6^{D}-dideoxy β-cyclodextrin.

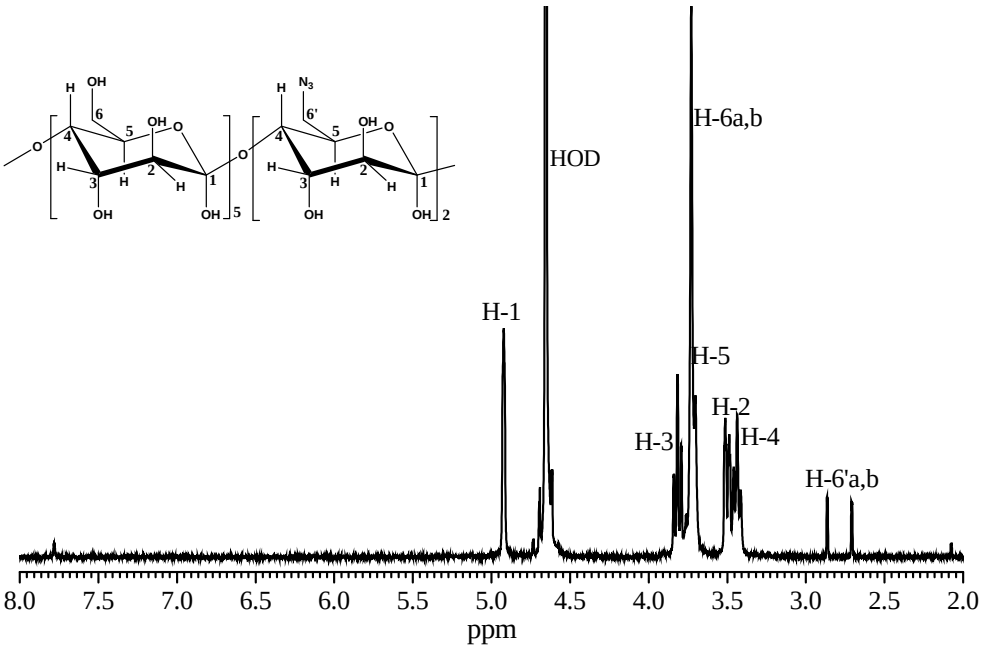


Figure 2.2.7 ^{1}H NMR spectrum of 6^{A},6^{D}-diazido 6^{A},6^{D}-dideoxy β-cyclodextrin D_2O.

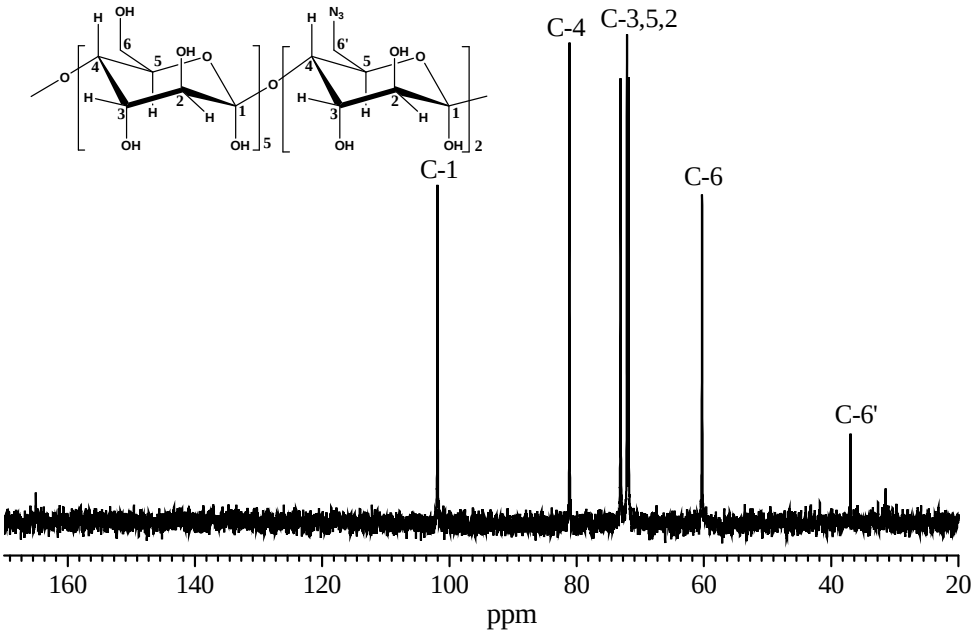


Figure 2.2.8 ^{13}C NMR spectrum of $6^{A},6^{D}$-diazido $6^{A},6^{D}$-dideoxy β-cyclodextrin in D_2O.

2.2.2.4 $6^A,6^D$-diamino $6^A,6^D$-dideoxy β-Cyclodextrin (5)

The FTIR spectrum of the $6^A,6^D$-diamino $6^A,6^D$-dideoxy β-cyclodextrin is shown in Figure 2.2.9. The spectrum depicted the absorbance at 3400 cm^{-1} and 3200 cm^{-1} were observed due to -OH stretching hydrogen bonded and stretching of $-NH_2$, 2900 cm^{-1}(-CH stretching), 1620 cm^{-1}, 1490 cm^{-1} (ammonium combination bands). The disappearances of azide stretching band at 2037 cm^{-1} suggest that complete reduction of azide functional groups into amine functional groups.

Figure 2.3.0 and Figure 2.3.1 shows the ^1H NMR spectrum and ^{13}C NMR spectrum of of $6^A,6^D$-diamino $6^A,6^D$-dideoxy β-cyclodextrin. The ^1H NMR spectrum showed the δ ppm 4.82 (m, 5H-C (5)) and 4.83 (d, 2H-C (5)) that is shift downfield due to substitution of two –OH groups with $–NH_2$ groups. The anisotropic effects of the σ electrons of a C-C bond are small compared to the circulating π electrons and the axis of the C-C bond is the axis of the deshielding cone. Due to anisotropic cone in a rigid cyclodextrin an equatorial proton (α-D-glucose unit) at C1 gives a signal around δ 5.6 (downfield). The chemical shifts of protons, i.e., O-H protons in alcohols and N-H protons in amines depend on the concentration. In concentrated solutions these protons are deshielded by hydrogen bonding when these absorb at lower field (δ 3.5 amine, N-H, δ 4.5 for an alcohol O-H). For ^1H NMR $6^A,6^D$-diamino $6^A,6^D$-dideoxy β-cyclodextrin is diluted with a non-hydrogen bonding solvent (DMSO), hydrogen bonding becomes less important and consequently these resonances are observed at higher field at δ 2.0. In the $-CH_2-NH_2$ coupling is not observed and both the protons of $-CH_2-$ and $–NH_2$ appear as sharp signal at 5 to 6 ppm chemical shift region.

The ^{13}C NMR spectrum of $6^A,6^D$-diamino $6^A,6^D$-dideoxy β-cyclodextrin is shown in Figure 2.3.2. The spectrum showed aliphatic carbon chemical shifts of β-cyclodextrin at δ ppm : 101.85 (C-1), 72.42 (C-2), 73.04 (C-3), 82.29 (C-4), 72.26 (C-5), 6.27 (C-6), 30.27 (C-6’). It is observed that due to the primary hydroxyl group substitution the signal of the substituted C-6’ carbon of the cyclodextrin shift upfield from 60.27 ppm to 30.27 ppm. These NMR that confirmed that the $–NH_2$ groups has been attached at the primary hydroxyl side of β-cyclodextrin molecule.

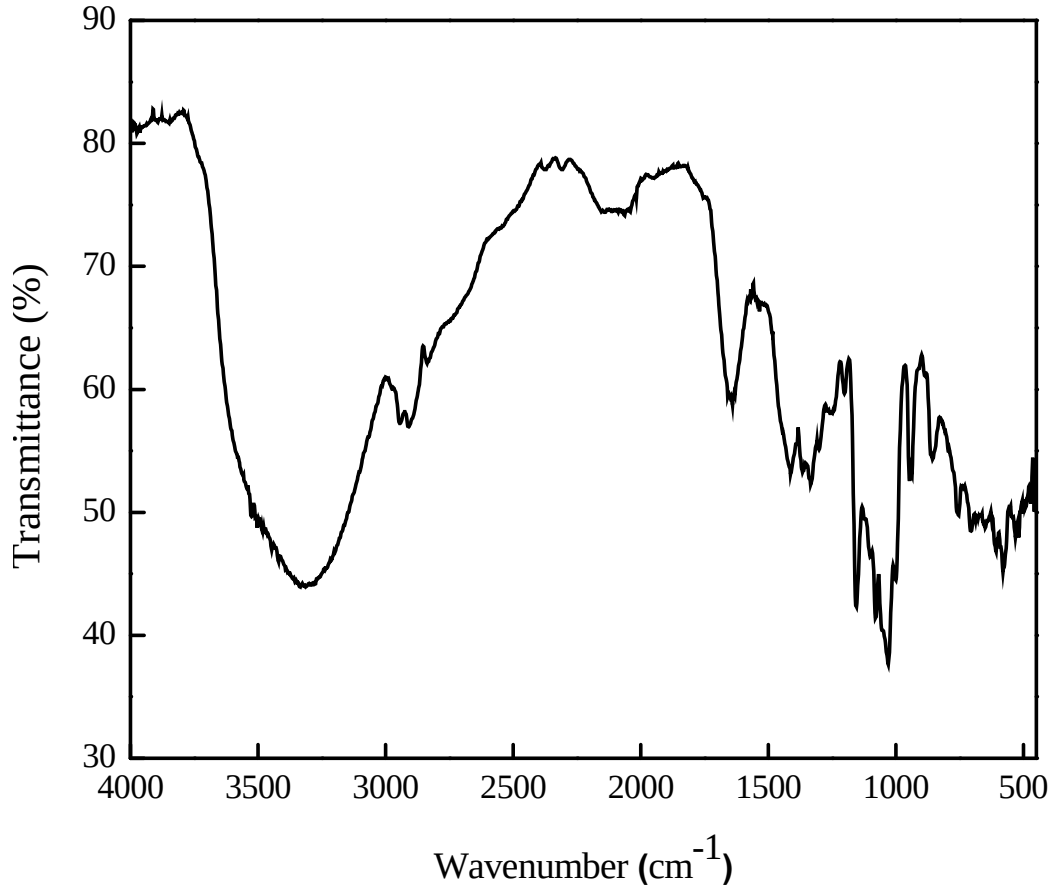


Figure 2.2.9 FTIR spectrum of $6^A,6^D$-diamino $6^A,6^D$-dideoxy β-cyclodextrin.

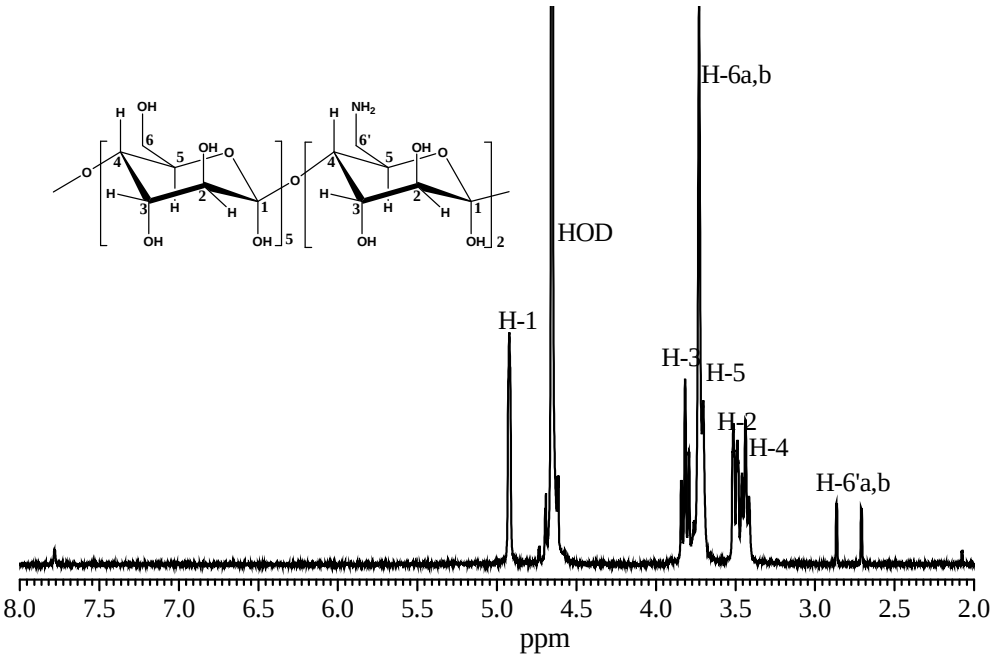


Figure 2.3.0 ^{1}H NMR spectrum of $6^{A},6^{D}$-diamino $6^{A},6^{D}$-dideoxy β-cyclodextrin in D_2O.

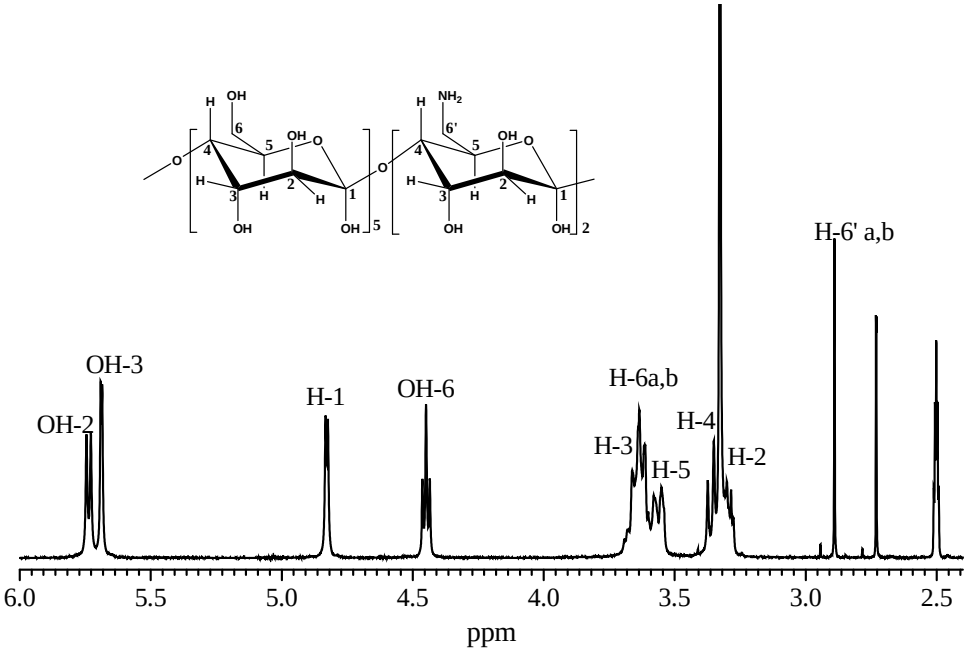


Figure 2.3.1 ^{1}H NMR spectrum of 6^{A},6^{D}-diamino 6^{A},6^{D}-dideoxy β-cyclodextrin in DMSO-d_6.

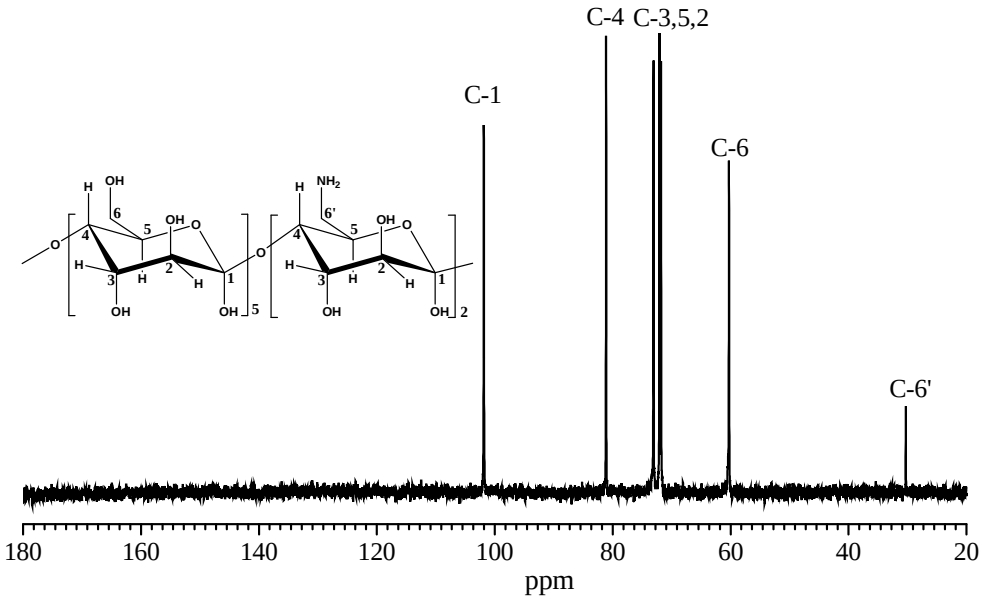


Figure 2.3.2 ^{13}C NMR spectrum of $6^A,6^D$-diamino $6^A,6^D$-dideoxy β-cyclodextrin in D_2O.

2.2.2.5 6^A, 6^D-diisothiocyanto 6^A, 6^D-dideoxy β-cyclodextrin (5)

The major bands in IR (KBr) spectrum (Figure 2.3.3) are at ν 3400cm^{-1} (OH, b), 2927cm^{-1} (C-O, s), 2069cm^{-1} (-NCS, vs). The band at 2069cm^{-1} is due to the presence of isothiocyante (-NCS) group and it indicates the presence of the isothiocyanate group on to the β-cyclodextrin molecule and absence of band above 2100cm^{-1} clearly shows there is no formation of thiocyanto (-SCN) group on β-cyclodextrin molecule. The ^{1}H NMR of the 6^A, 6^D-diisothiocyanto 6^A, 6^D-dideoxy β-Cyclodextrin is shown in (Figure 2.3.4). The signals assigned to the protons of 6^A, 6^D-diisothiocyanto 6^A, 6^D-dideoxy β-cyclodextrin are ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.27 (m, 14H-C_6), δ 3.38 (t, 7H-C_4), δ 3.54 (m, 7H-C_4), δ 3.66 (m, 7H-C_3), δ 4.49 (m, 5H-C_5), δ 4.82 (d, 2H-C_5), δ 5.6 (d, 7H-C_1). Here the signals of two protons of C (5) show downfield shift at δ 4.82 (d, 2H-C (5)) and at 4.49 (m, 5H-C (5)) due to disubstitution of two –OH groups with –NCS groups. The ^{13}C NMR (DMSO-d_6, 400 MHz) of 6^A, 6^D-dideoxy 6^A, 6^D di-isothiocyante β-cyclodextrin (Figure.2.3.5) shows chemical shift of aliphatic carbons of cyclodextrin at δ 36.96 (C-6'), δ 60.02 (C-6), δ 72.89 (C-5), δ 73.28 (C-2), 73.90 (C-3), 82.38 (C-4), 102.77 (C-1), 164.97 (N=C=S). It is observed that due to the primary hydroxyl group substitution the signal of the substituted C-6' carbon of the aliphatic cyclodextrin shifts up field from 60.02ppm to 36.96ppm. So from this (FT-IR, ^{1}H NMR,^{13}C NMR) data conclude that the attachment of NCS group takes place on capped cyclodextrin at A, D position to form 6^A, 6^D-diisothiocyanto 6^A, 6^D-dideoxy β-cyclodextrin and also confirmed the formation of 6^A, 6^D-diisothiocyanto 6^A, 6^D-dideoxy β-cyclodextrin by the elemental analysis shows that [C 43.53, H 5.77, N 1.87] which is equal to calculated value [C 42.17, H 5.79, and N 2.24]. These CHN analysis data confirm that the two –NCS groups are substituted at the primary hydroxyl side of β-cyclodextrin molecule.

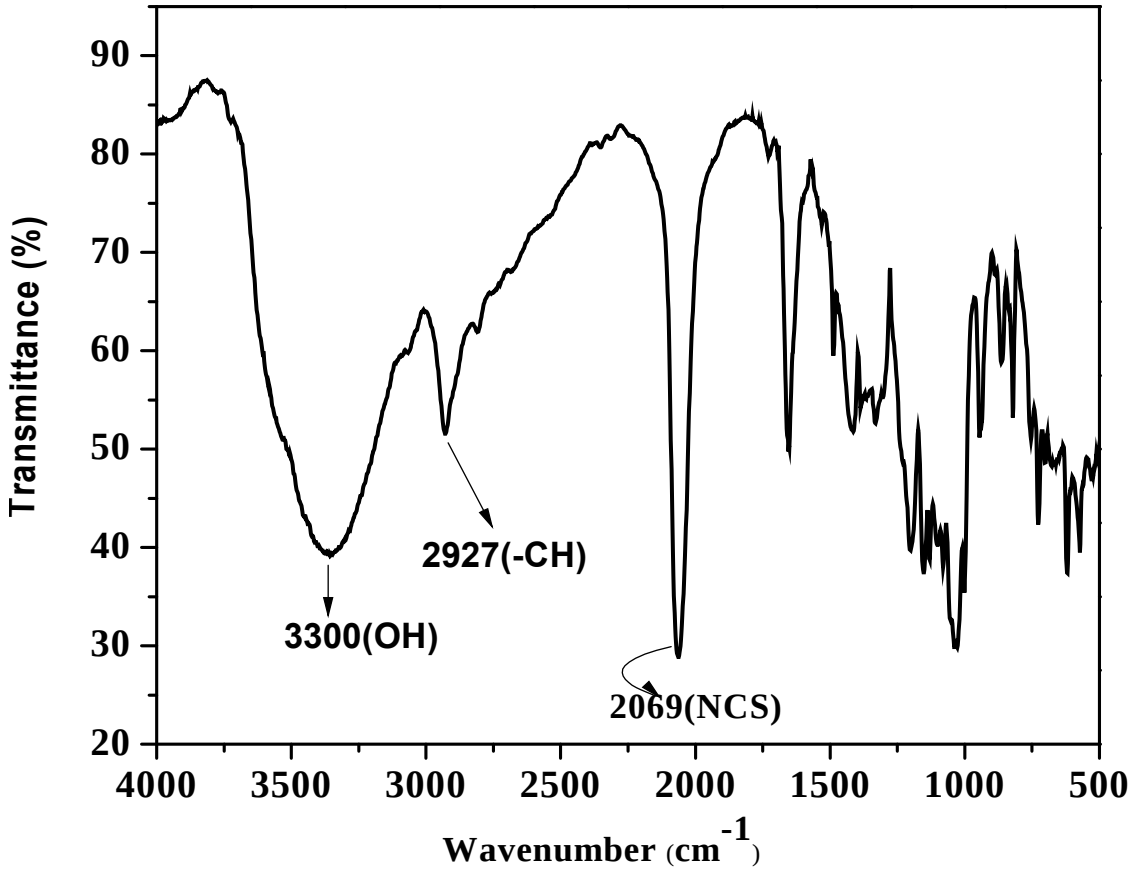


Figure 2.3.3 FTIR of 6^A, 6^D-dideoxy 6^A, 6^D di-isothiocyante β-Cyclodextrin

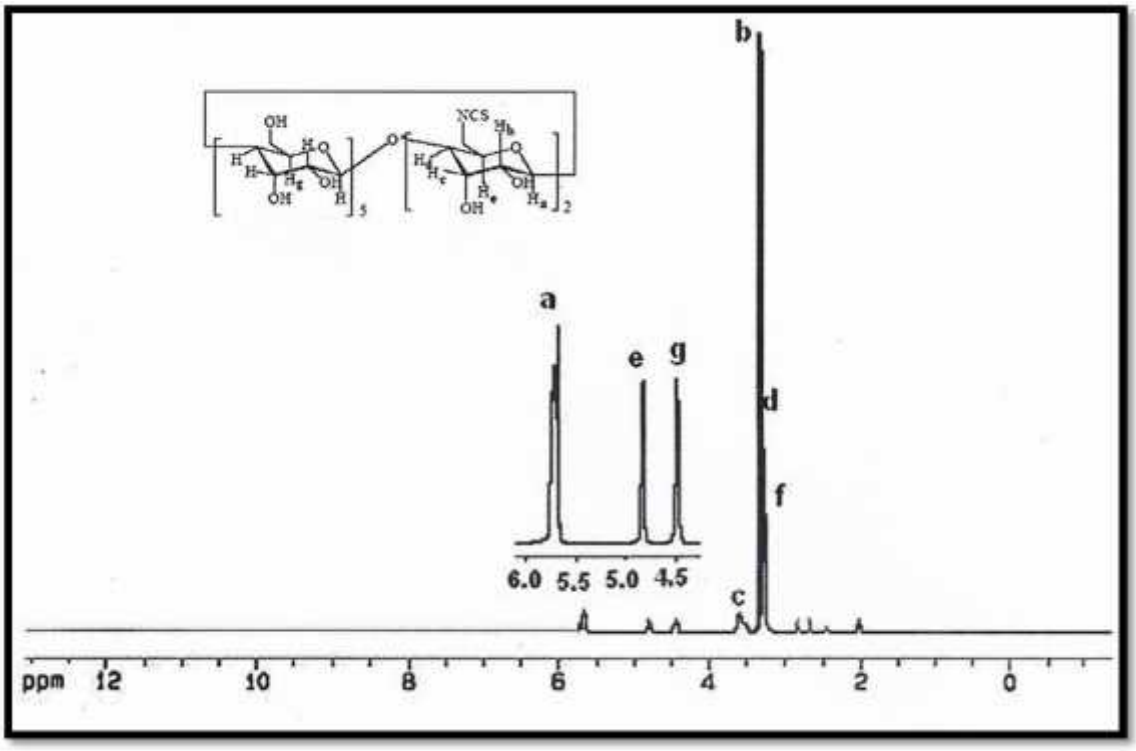


Figure 2.3.4 ^{1}H NMR of 6^{A}, 6^{D}-dideoxy 6^{A}, 6^{D} di-isothiocyante β-Cyclodextrin

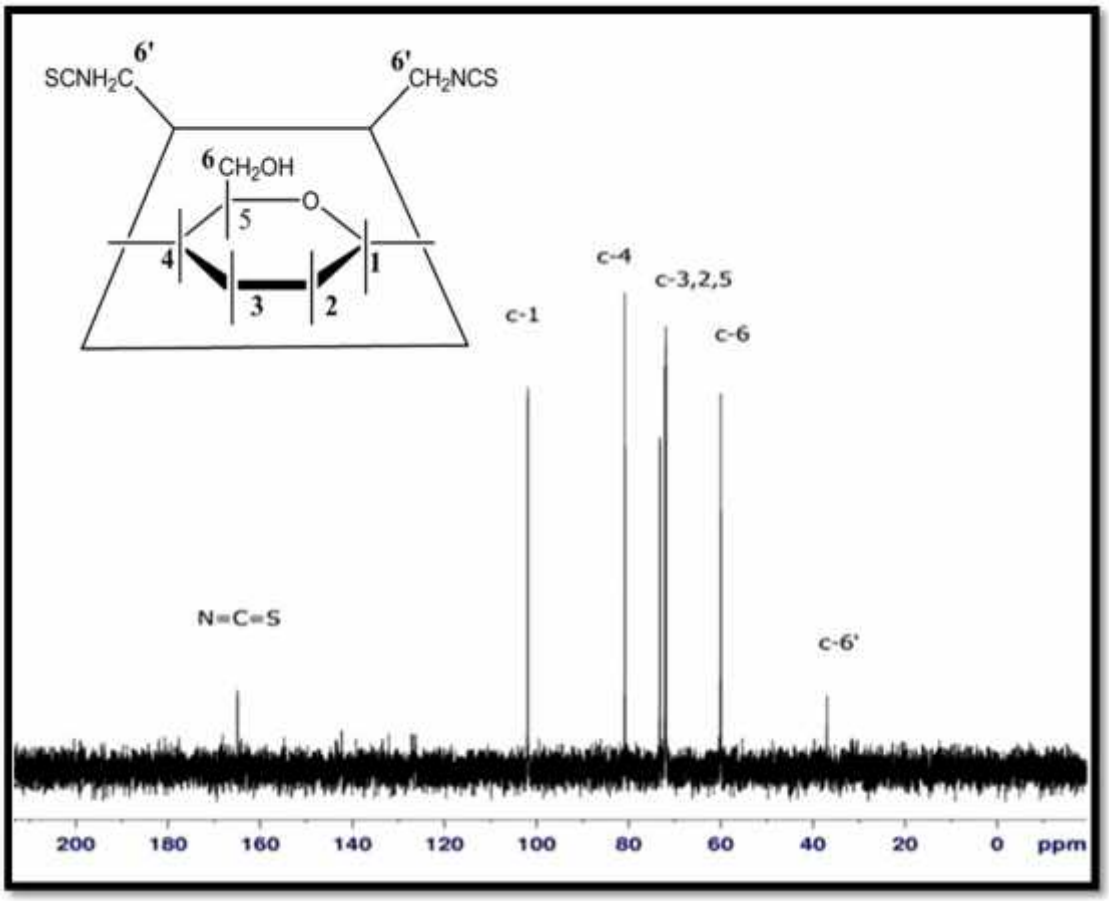


Figure 2.3.5 ^{13}C NMR of 6^{A}, 6^{D}-dideoxy 6^{A}, 6^{D} di-isothiocyante β-Cyclodextrin

2.2.3 Conclusions

In summary, the short and effective syntheses of mono-6-isothiocyanato-6-deoxy-β-Cyclodextrin monomer and selectively difuntionalized derivatives of β-cyclodextrin such as biphenyl bridge A,D capped β-CD, diiodo β-CD, diazido β-CD and diamino β-CD were synthesized by oxidoreductive substitution reactions without protection of hydroxyl groups were described. In this synthesis procedure more reactive arene sulfonyl ester functional groups on the primary hydroxyl side of β-cyclodextrin was introduced. These modified di-substituted β-cyclodextrin derivatives shows higher water solubility and moderate reactivity over the parent β-cyclodextrin. This selectively functionalized β-cyclodextrins are useful monomers for the synthesis of cyclodextrin polymers in which β-cyclodextrins are incorporated into the main-chain of the polymers and also we find a new and efficient synthesis of 6^A, 6^D-diisothiocyanto 6^A, 6^D-dideoxy β-cyclodextrin which brings efficient high yielding, soft and safe (without hazardous phosgene, carbon disulphide and analogous) synthetic methodologies for CDs isothiocyanate scale-up preparation. This is very practical method needs no fastidious protection/deprotection sequence or sophisticated separation procedures and will also be promising for further reactions with sensitive and/or sophisticated structures, with regards to the generally mild reaction conditions. The proposed method could be considered as a valuable and interesting alternative to the sole usual phosgene / thiophosgene isocynation / iosthiocyanation. Moreover, the reaction offers the opportunity and versatility to obtain a large panel of mono substituted, disubstitued and trisubstituted thioureido-CDs derivatives in one step and high yields and now this study is underway. Also the same method can be applied to the remaining CD derivatives (α, γ).

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