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Article

Study to Explore Complexation of Crown Ether with Antidepressant Drug Prevalent in Aqueous System by Physicochemical Contrivance

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ABSTRACT

The inclusion complex of antidepressant drug molecule with crown ether (CE) 15-C-5 was prepared and characterized successfully. The inclusion complexes with CE in the aqueous medium and solid state were studied by different physicochemical methodologies. Formation of inclusion complex was confirmed by 1-H nuclear magnetic resonance and Fourier transform-infrared studies. Surface tension and conductance were studied in the aqueous system; the 1:1 stoichiometric ratio of inclusion complex was obtained. The UV-visible study supported the formation as well as stoichiometry of inclusion. Binding constant and thermodynamic parameters were calculated which supported the high stability and feasibility of the formation of the inclusion complex.

Key words: Crown ether, Inclusion complex, Antidepressant drug, Nortriptyline hydrochloride.

1. INTRODUCTION

The drug molecule nortriptyline [3-(10, 11-dihydro-5H-dibenzo[a,d] cyclohepten-5-ylidene)-*N*-methyl-1-propanamine] hydrochloride (NTPH) (Scheme 1) belongs to the class of medicines known as tricyclic antidepressant (TCAs). Depression is fetching one of the most imperilling diseases disturbing human health and quality of living [1-5]. Compared to the other TACs drug molecules, NTPH shows various advantages. The antidepressant effects of TCA are thought to be due to an overall increase in serotonergic neurotransmission and depressed individuals, NTPH exerts a positive effect on mood. TCAs can block histamine-H1 receptors, α1-adrenergic receptors which account for their sedative, and hypotensive effects, respectively. NTPH exerts less sedative side effects compared to the tertiary amine TCAs. NTHCL has also neuroprotective effects and it is used as key models of chronic neurodegeneration. It expanded as strong inhibitor of mitochondrial permeability transition (MPT) in both isolated [6] and brain. MPT results due to openings of protein pores that are formed in the inner membrane of mitochondria and allow free diffusion of molecules having molecular weight <1500 Da, resulting mitochondrial swelling and cell death [7]. NTPH can also inhibit the release of cytochrome C and capsize activation in tissue. As 15-C-5s are secure and friendly for human health and considered as safe drug carrier in human body [8], so formulating inclusion complex of NTPH with 15-C-5s could potentially introduce a new prospect and hope in drug delivery systems and also in research field [9].

Beside many other host molecules, crown ethers (CEs) are used as significant hosts in host-guest chemistry (Scheme 2). Here, the host-guest interaction imitates natural systems as well as builds various materials [10-15]. CEs are macromolecular heterocyclic compounds with essential repeating unit -CH2CH2O-[16]. A number of investigators are working on fabrication of crown ether-based stimuli-responsive materials that have exclusive characters of ion recognize ability [17-19]. A variety of current supramolecular ingredients, for instance, rotaxanes are made on these unique recognition properties of CEs [20,21]. Binding of cations with CEs having high selectivity and affinity has found marked importance in chemistry [22,23]. Formation of molecular assemblies has vast implication for the building of molecular machines having plausible use as analogous to sophisticated machines of natural systems [24,25]. Hence, fundamental investigations of the interactions between CEs and cationic species are important for their advanced applications [26,27].

In this study, the formation of the complex of the CE and NTPH has been studied in aqueous medium for the probable applications in supramolecular host-guest chemistry.

2. EXPERIMENTAL

2.1. Source and Purity of Samples

The above-mentioned drug and CE were purchased from Sigma-Aldrich, Germany. The mass fraction purity of drug and ether were ≥0.98.

2.2. Apparatus and Procedure

Mass of the solid guest and hosts were taken using Mettler Toledo AG-285 with uncertainty of ±0.0001 g and the solutions were prepared by mass dilution at 298.15 K. Precautions were taken to reduce the evaporation during mixing.

Surface tensions of the prepared solutions were measured by platinum ring detachment technique using a Tensiometer (K9, KRUSS; Germany) at 298.15 K and accuracy was ±0.1 mN m^{-1}. Temperature was maintained using circulating thermostated water through a double-walled glass vessel containing the solution.

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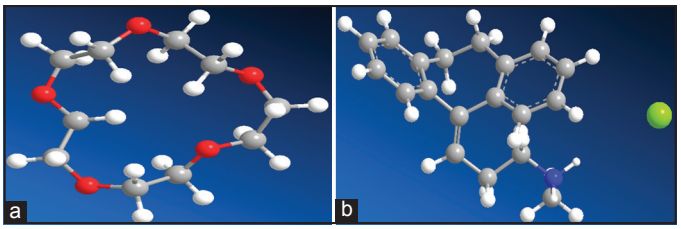
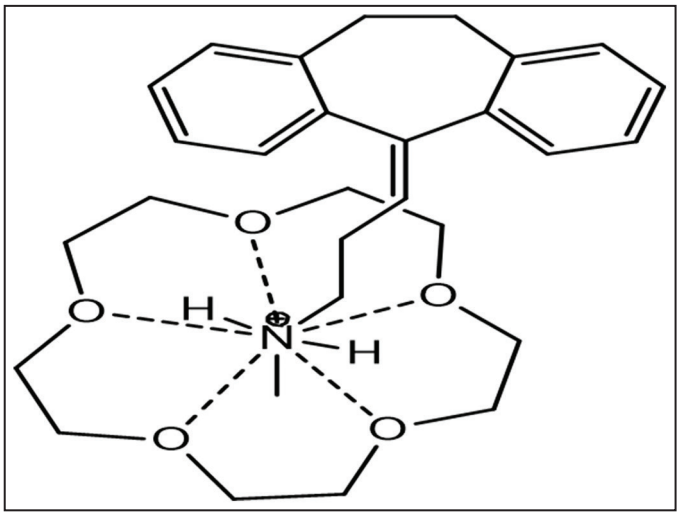


Scheme 1: Ball and stick representation of (a) 15-C-5 and (b) NTPH; gray for carbon and red for oxygen, white for hydrogen, blue for nitrogen.



Scheme 2: Schematic representation of the plausible interactions taking place in the complex.

Conductivities of the prepared solutions were studied using Mettler Toledo SevenMulti conductivity meter with uncertainty of ±1.0 μSm^{-1}. Measurement was performed in a thermostated water bath at 298.15 K with uncertainty ±0.01 K. The conductivity cell was calibrated by freshly prepared 0.01 M aqueous KCl solution.

^{1}H nuclear magnetic resonance (NMR) spectra of the solid inclusion complex prepared were recorded in D_2O using Bruker ADVANCE 400 MHz instrument. Signals are presented as values in ppm using residual protonated solvent signal at 4.79 ppm in D_2O as internal standard and all the data are reported as chemical shift.

UV-visible spectroscopic study was carried out using JASCO V-530 UV/visible spectrophotometer with wavelength accuracy of ±0.5 nm. Spectra were recorded at 297.15±1 K.

2.3. Preparation of Solid Inclusion Complex

The drug molecule and the CE were taken in 1:1 molar ratio, and they were dissolved in triply distilled water separately. The mixtures were stirred over magnetic stirrer to make homogeneous. After both the homogeneous mixtures were prepared, the NTPH solution was then added into CE solution slowly with continuous stirring, and after completion of the addition the NTPH solution, the mixture was stirred for 48 h continuously. After that, the mixture was allowed to cool at lower temperature and a solid was observed. The precipitate was filtered and washed for several times. Finally, the dry powder was obtained after drying in oven at 40°C for 24 h. The solid inclusion complex with CE was prepared following the same procedure. These solids were further analyzed and characterized by means of Fourier transform-infrared and NMR spectroscopic methods.

3. RESULTS AND DISCUSSION

3.1. JOB Plot

Using the Job's continuous variation method, the stoichiometry of the inclusion complexes was determined [28-30]. By the measurement of absorbance of a set of solutions prepared of the NTPHs and host in water in the mole fraction range of 0−1 (Table 1). Calculating ΔA × R values, we plotted it against R, where ΔA signifies the difference in absorbance of the NTPH in the pure form and complexed form and R is [NTPH]/([NTPH] + [host]). λ_{max} was found at 252 nm at 298.15 K. The ratio of guest and host, i.e., stoichiometry is obtained from the value of R at the maxima on the Job' plot such as R≈0.33, for 1:2 IC, R≈0.5 for 1:1 IC, and R≈0.66 for 2:1 IC. In this experiment of the drug and the host, the maxima in the Job's plots were obtained at R≈0.5 which is the clear indication of the formation of IC of 1:1 stoichiometry (Figure 1).

3.2. Association Constant

(Mitali Spectrochimica) The UV absorption spectra of NTPH in aqueous 15-C-5 medium were carried out in at 298.15 K. The spectral data of NTPH in various concentrations of 15-C-5 in different pH have been listed in Table S3. Both Figures 2a and b depict the absorption spectra of NTPH (2×10−4 M) in the absence and presence of 15-C-5 solutions. The strong absorption peaks of NTPH (2×10−4 M) appear at 208 nm and with addition of 15-C-5 blue shift was found. In each case, the absorbance intensities of NTPH gradually increase with increasing the concentration of β-15-C-5. This confirms the inclusion of the guest molecule into the cavity of 15-C-5 [31,32].

Various non-covalent interactions act as main driving forces throughout the complexation process by stimulating the dissolution of the guest molecule (NTPH). From Job's plot a clear indication is obtained that NTPH molecule forms 1:1 IC with 15-C-5. Hence, the IC formed between NTPH and 15-C-5 can be expressed as,

15-C-5 + NTPH ⇄ β-15-C-5 NTPH

For 1:1 complexation processes, the association constant (*K*) can been obtained from the double reciprocal plot using Benesi-Hildebrand equation [29]. The absorption values were used in the following Benesi-HNTPHdebrand equation (1) [33].

$$\frac{1}{A - A_0} = \frac{1}{K\ (A" - A_0)}\ \frac{1}{[Host]} + \frac{1}{(A" - A_0)} \quad (1)$$

Figure 3 depicts the plot of $1/(A-A_0)$ against 1/[15-C-5] for NTPH. A good linear correlation was obtained. The values of *K* are evaluated using the equation 2 (2) from the slop values of straight lines. The resultant association constant of NTPH in neutral medium has been found 5.58×10^3, which is a significant value for describing the association of the two molecules.

$$\overline{Slope(A"\ \ A\ )} \quad (2)$$

3.3. Spontaneity of Inclusion Complex Formation

Free energy change (ΔG), the thermodynamic parameter, defines the spontaneity of a process. This can be estimated from the values of association constant (*K*) using the following 3 [34,35].

$$\Delta G = -RT\ln K_a \quad (3)$$

The ΔG values for the binding partners (NTPH and 15-C-5) are negative (−ΔG), which indicates that the host-guest IC proceeded spontaneously at 298.15 K and the complexation is an exergonic process. The value of ΔG was found -21.38 kJ mol^{-1}, which is negative and indicates the spontaneity of the process.

Table 1: Values of surface tension (γ) and conductance (*k*) at the break point with corresponding concentration of 15-C-5 for NTPH at 298.15K[a].

Concentration of 15-C-5/mM	γ/mN m^{-1}	Concentration of 15-C-5/mM	κ/mS.cm^{-1}
5.16	68.52	5.17	0.45

[a]Standard uncertainties in temperature u are: u (T)=0.01 K

Table 2: Data for the surface tension study of aqueous 15-C5+NTPH (concentration of stock solution of NTPH=10mM, concentration of stock solution of CD=10mM) at 293.15 K[a].

Volume of drug	Volume of 15-C-5	Concentration of drug	Concentration of a 15-C-5	ST/mN.m^{-1}
10	0	10	0	65.2
10	1	9.091	0.909	65.9
10	1	8.333	1.667	66.2
10	1	7.692	2.307	66.6
10	1	7.143	2.857	66.9
10	1	6.667	3.333	67.3
10	1	6.25	3.75	67.5
10	1	5.882	4.117	67.7
10	1	5.556	4.444	67.9
10	1	5.263	4.736	68.2
10	1	5	5	68.4
10	1	4.762	5.238	68.5
10	1	4.545	5.454	68.5
10	1	4.348	5.652	68.6
10	1	4.167	5.833	68.6
10	1	4	6	68.6
10	1	3.846	6.153	68.6
10	1	3.704	6.296	68.6
10	1	3.571	6.428	68.6
10	1	3.448	6.551	68.6

[a]Standard uncertainties in temperature u are: u (T)=0.01 K

3.4. Surface Tension Study Reveals the Inclusion and also the Stoichiometric Ratio of the Inclusion Complexes (RNA Nucleoside SS)

Surface tension (γ) was measured at 298.15 K for aqueous 15-C-5 molecule, which was found to be almost constant with increasing molarity [36]. Surface tensions (γ) were observed with corresponding concentrations of the drug in different molarities of 15-C-5 (Table 2). The plausibility of formation of an inclusion complex can be predicted from the surface tension study, where in the formation of an inclusion complex has been confirmed from the break point in the curve of surface tension versus concentration.

The 1:1 and 1:2 stoichiometry of the host:guest inclusion complexes have been confirmed from the appearance of single and double by the break point in the γ versus conc. curve. The value of γ and the corresponding concentration of drug at the break point has been determined from the two intersecting straight lines indicating the feasibility of inclusion with increasing amount of 15-C-5 in solution [37]. However, the plots for NTPH with 15-C-5 clearly indicate single break point (Figure 3 and

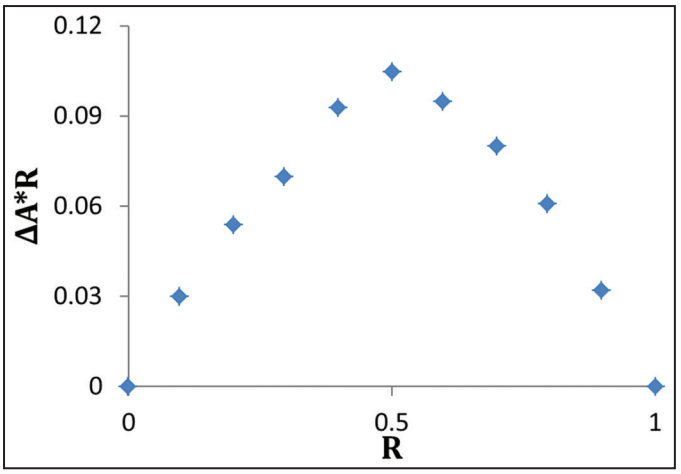


Figure 1: Job plot of NTPH-15-C-5 system at λ_{max} = 239 nm at 298.15 K. R=[NTPH]/([NTPH] + [CE]), ΔA= absorbance difference of NTPH without and with CE.

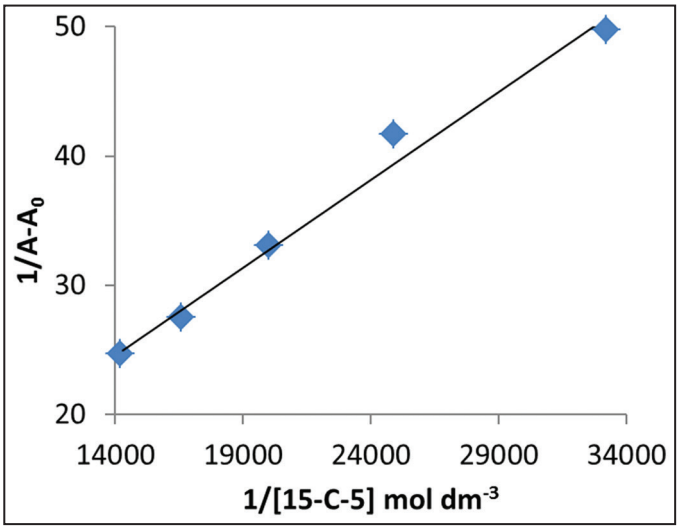


Figure 2: (a and b) Benesi-Hildebrand double reciprocal plot for the effect of 15-C-5 and NTPH at 298.15 K.

Table 1) at a specific concentration, i.e., after a certain point surface tension becomes relatively steady with increasing concentration of the nucleosides. This is the indication of the formation of an inclusion complex, which occurs by the insertion of NTPH into the cavity of 15-C-5. The NTPH enters the cavity of 15-C-5, which is geometrically allowed.

3.5. Conductivity

Conductivity study is a convincing method for exploring complexation in solution not only because it affords information for minute alteration of concentrations of the charged particles, but also it offers data for the various interactions among the particles taking place in the solution system [38]. Conductivity of a solution with NTPH and added CE provides valuable information for the complexation process between the CE and NTPH in solution [39]. In our work, complexation has been explored between NTPH and CE 15-C-5 in aqueous medium. Thus, to acquire data about complexation, conductivity of the NTPH solution with initial concentration of 10.0 mM has been measured with increasing concentration of the CEs at 293.15 K and presented in Tables 3 with increasing CE concentration. The plot of conductance has been depicted in Figure 4, in which CE concentration is shown in abscissa and conductance is shown in ordinate. A gradual decrease in conductance is observed with increasing concentration of CE with a

Table 3: Data for the conductivity study of aqueous 15-C-5+NTPH (concentration of stock solution of NTPH=10mM, concentration of stock solution of CD=10 mM) at 293.15 K[a.]

15-C-5 added (mL)	Concentration of NTPHCL (mM)	Concentration of 15-C-5 (mM)	Conductance (mS m^{-1})
0	10.000	0.000	0.81
1	9.091	0.909	0.74
2	8.333	1.667	0.69
3	7.692	2.308	0.65
4	7.143	2.857	0.62
5	6.667	3.333	0.59
6	6.250	3.750	0.55
7	5.882	4.118	0.53
8	5.556	4.444	0.50
9	5.263	4.737	0.48
10	5.000	5.000	0.46
11	4.762	5.238	0.45
12	4.545	5.455	0.44
13	4.348	5.652	0.44
14	4.167	5.833	0.44
15	4.000	6.000	0.43
16	3.846	6.154	0.43
17	3.704	6.296	0.43
18	3.571	6.429	0.43
19	3.448	6.552	0.42
20	3.333	6.667	0.42

[a]Standard uncertainties in temperature u are: u (T) = 0.01 K

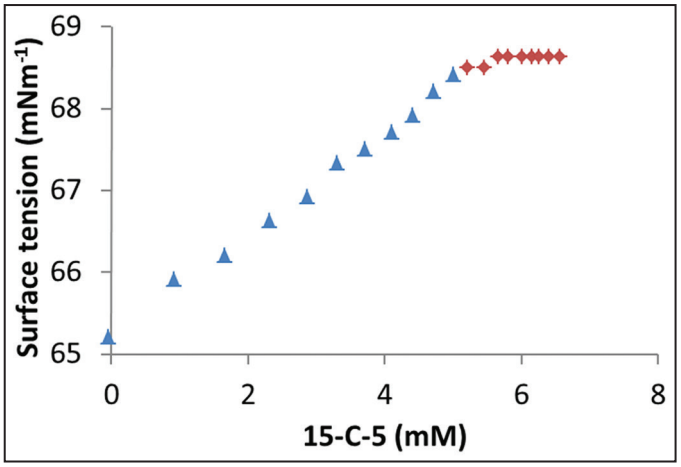


Figure 3: Plot of surface tension with increasing concentration of 15-C-5 with NTPH at 298.15 K.

break point near 5 mM concentration (Tables 1 and 3, Figure 4), which signifies the capture of the NTPH cation by the CE because NTPH being strong electrolyte cannot form ion pair in the studied solution system [40]. Hence, the complexation processes of NTPH ion with the CE have been illustrated by decrease in conductance in Figure 4, become approximately plateau as the CE/NTPH mole ratio exceed 1.0, evidently suggesting the development of adequately stable 1:1 NTPH-CE complex in aqueous solution [41].

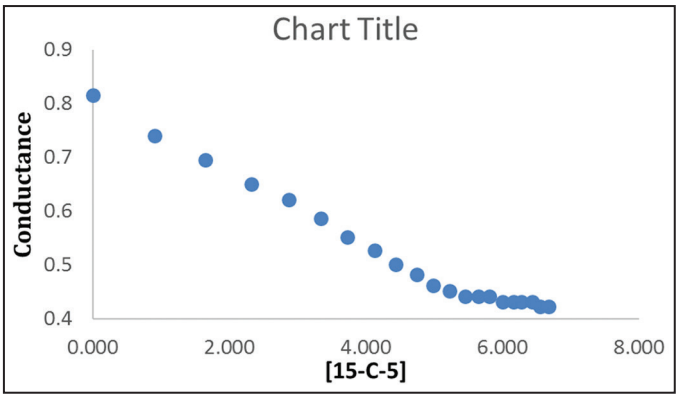


Figure 4: Variation of conductance of NTPH with 15-C-5 at 298.15 K.

3.6. 1H NMR

The complexation of NTPH with the CE, namely 15-C-5, has been explored by 1H NMR spectroscopic study in aqueous solution at 298.15 K. Figure 5 represents 1H NMR spectra of the complex of NTPH with 15-C-5, which describes slight downfield shift of the aliphatic protons of CE (C-H proton of free CE appears at δ3.35 and it is found in complex at δ3.39). The signal due to aryl protons is nearly unshifted and little broadening. On the other hand, the protons of guest molecules of the aliphatic chain show a slight change of the in their signals while present in the complex (α, β, and γ protons of free NTPH appears at δ 5.745–5.794, δ 2.765–2.866, and δ 2.38–2.444, respectively, which are found for the complex at δ5.73–5.77, δ2.68–2.74, and δ2.35–2.42, respectively). This result clearly reveals the existence of some sort of association between the electron-rich oxygen atoms of the 15-C-5 and the ammonium ion (Scheme 2) [42,43]. The aromatic part of the NTPH shows no change of their signals indicating their free state in the solvent medium.

3.7. NTPH

1H NMR (400 MHz, D2O): δ=2.528 (3H, s); 2.960–3.025 (4H, m); 5.745–5.794 (1H, t, J=7.5); 2.38–2.444 (2H, m); 2.765–2.866 (2H, m); 7.051–7.303 (8H, m).

3.8. 15-C-5

1H NMR (400 MHz, D2O): δ=3.35 (20H, s).

3.9. NTPH and 15-C-5 Complex

1H NMR (400 MHz, D2O): δ=2.504 (3H, s); 2.953–3.025 (4H, m); 3.39 (20H, s) 5.73–5.77 (1H, t, J=7.5); 2.35–2.42 (2H, m); 2.68–2.74 (2H, m); 7.040–7.303 (8H, m),

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5. CONCLUSION

The experimental findings suggest that the drug molecule binds with the CE (15-C-5) to form a complex. The oxygen atoms of the host molecule bind the positive center of the guest NTPH to form

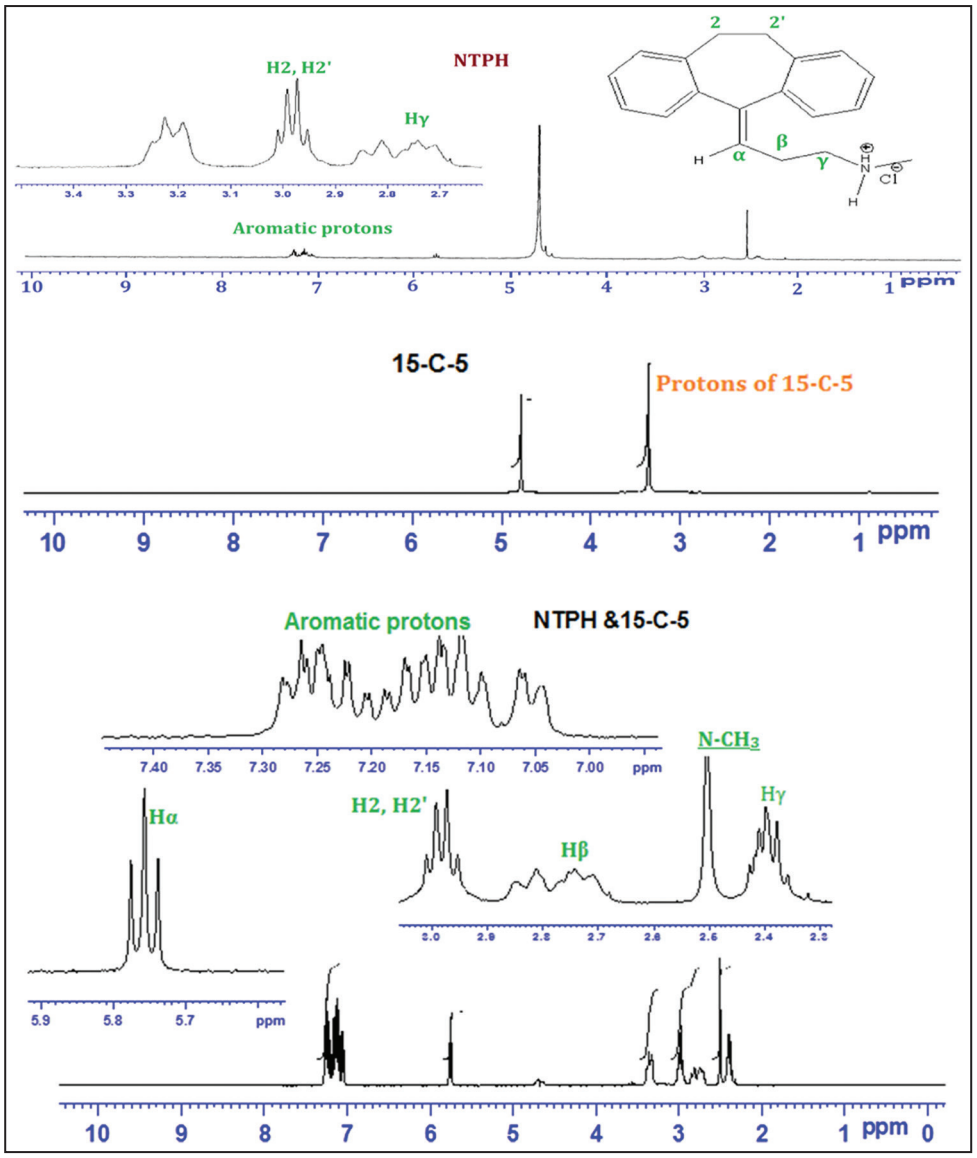

Figure 5: [1]H NMR spectra of 15-C-5, NTPH and 15-C-5, and NTPH complex of 1:1 molar ratio in D2O at 298.15 K.

a complex, which is confirmed by the 1H NMR study. One guest molecule binds with one host molecule to form complex of 1:1 stoichiometry, which was indicated by the surface tension and conductance study, and further, it was confirmed by the Job's plot from UV-vis study. The formation and the feasibility of the complex were found to be positive. The calculated ΔG^0 value was again found to be negative which revealed that the process of formation of the complex is thermodynamically feasible.

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