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Research paper

Exploration of inclusion complexes of neurotransmitters with β-cyclodextrin by physicochemical techniques

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ABSTRACT

Molecular assemblies of β-cyclodextrin with few of the most important neurotransmitters, *viz.*, dopamine hydrochloride, tyramine hydrochloride and (±)-epinephrine hydrochloride in aqueous medium have been explored by reliable spectroscopic and physicochemical techniques as potential drug delivery systems. Job plots confirm the 1:1 host–guest inclusion complexes, while surface tension and conductivity studies illustrate the inclusion process. The inclusion complexes were characterized by ^{1}H NMR spectroscopy and association constants have been calculated by using Benesi–Hildebrand method. Thermodynamic parameters for the formation of inclusion complexes have been derived by van't Hoff equation, which demonstrate that the overall inclusion processes are thermodynamically favorable.

1. Introduction

Molecular recognition is of profound importance in biology and therapeutics, the physical chemistry of this phenomenon acknowledges that binding is often associated with loss in configurational entropy, but the overall thermodynamics is yet to be well understood [1,2]. The cyclodextrins (CDs) are of particular interest in this regard. Among various approaches CDs have contributed a lot to this aspect of drug delivery, because of having fairly rigid and well-defined hydrophobic cavities and hydrophilic outer surfaces, they can act as molecular receptors (hosts) for a wide variety of organic and inorganic, as well as biological and pharmaceutical guest molecules, forming host–guest complexes or supramolecular assemblies [3,4]. The cavity size of β-cyclodextrin (β-CD) is more appropriate than other CDs to encapsulate a great variety of molecules [5,6]. The drugs, to be pharmacologically active, must possess some degree of aqueous solubility, as well as they should be lipophilic to permeate the biological membranes via passive diffusion [7,8]. If a drug is hydrophilic, the dissolved drug molecule will not penetrate from the aqueous exterior into a lipophilic biomembrane. The use of β-CD on drug solubility, bioavailability, safety, stability and as a carrier in drug formulation may be achieved by formation of inclusion complexes with drug molecules; in fact, the use of β-CD already has a long history in pharmacy [9–11].

Dopamine is an important neurotransmitter (NT) in the mammalian central nervous system and is a member of catecholamines [12,13]. It is involved in neuropsychiatric disorders such as Perkinson's disease, which is the second most common central nervous system disorder [14,15]. Tyramine is also a NT and acts as a catecholamine releasing agent, having nonpsychoactive peripheral sympathomimetic effects [16]. Epinephrine is a hormone and a NT, serves as chemical mediators for conveying the nerve impulses to effectors organs [17]. Epinephrine remains a useful medicine for several emergency indications and is used as a drug to treat cardiac arrest and other cardiac dysrhythmias [18,19].

Few previous workers demonstrated interactions between similar guest molecules and CD [20,21]. Pardave et al. demonstrated electrochemical and spectrophotometric studies of interaction

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between dopamine and β-CD, whereas, Rajendiran et al. showed interaction between epinephrine and CD [22–24]. In the present article formation of inclusion complexes of three NTs, *e.g.*, dopamine hydrochloride (DH), tyramine hydrochloride (TH) and (±)-epinephrine hydrochloride (EH) with *β*-CD (Scheme 1) have been explored by UV–Vis spectroscopy, surface tension, conductivity and ^{1}H NMR study. Associated thermodynamic parameters have also been evaluated to communicate a quantitative idea about encapsulation of the above NTs while complexed with *β*-CD.

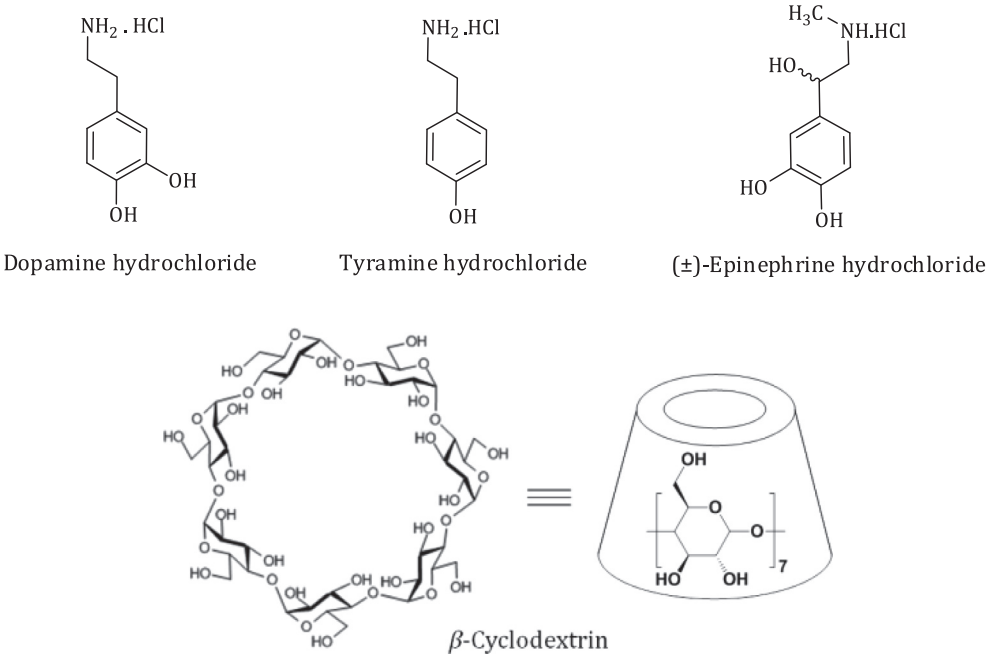
2. Result and discussion

2.1. Job plot demonstrates the stoichiometry of the host–guest assembly

Job's method of continuous variation was applied to recognize the stoichiometry of the host–guest assembly by using UV–visible spectroscopy [25]. Job plots were generated by plotting $\Delta A \times R$ vs R, where ΔA is the difference in absorbance of NTs with and without *β*-CD and R = [NT]/([NT] + [CD]), through varying the mole fraction of the NTs in the range 0–1 (Tables S1–S3, supporting information) [26,27]. Absorbance values were measured at respective λ_{max} for a series of solutions at 298.15 K. The value of R at the maximum deviation provides the stoichiometry of the inclusion complex (IC) (*e.g.*, R = 0.5 for 1:1 complexes; R = 0.33 for 1:2 complexes; R = 0.66 for 2:1 complexes, etc.). Here, for each of the three plots maxima were found at R = 0.5, which clearly indicate 1:1 stoichiometry between the host and the guest (Fig. 1).

2.2. Surface tension study explains the inclusion as well as stoichiometric ratio of the inclusion complexes

Surface tension (γ) measurement provides significant indication about formation of IC as well as stoichiometry of the host–guest assembly [28–30]. *β*-CD, because of having lipophilic outer surface and hydrophilic rims, does not show any change in γ while dissolved in aqueous medium in a considerable range of concentration [31,32]. In the present work all the three guest NTs have a common feature in their structures, *i.e.*, they have a hydrophobic –CH_2–CH_2–Ph [–CH_2–CH(OH)–Ph for EH] group and



Scheme 1. Molecular structure of the three neurotransmitters and *β*-cyclodextrin.

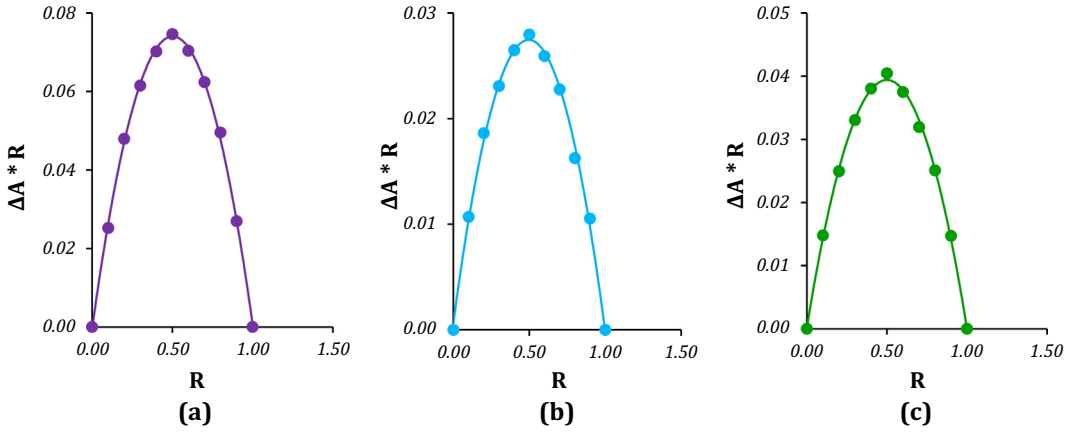


Fig. 1. Job plot of different neurotransmitter-*β*-CD systems at 298.15 K. (a) Dopamine hydrochloride at λ_{max} = 278 nm, (b) tyramine hydrochloride at λ_{max} = 275 nm and (c) (±)-epinephrine hydrochloride at λ_{max} = 278 nm. R = [NT]/([NT] + [*β*-CD]), ΔA = absorbance difference of the NTs without and with *β*-CD.

a terminal $-NH_3^+$ [$-NH_2^+-$ for EH] group (Scheme 1), which make them surfactant like activities, thus γ of aqueous solutions of each of the NTs are found to be lower than that of pure water. Here γ of aqueous NTs has been measured with increasing concentration of β-CD at 298.15 K (Tables S4–S6). DH, TH and EH showed increasing trend of γ with increasing concentration of β-CD (Fig. 2) may be because of removal of the NT molecules (surface active) from the surface of the solution into the hydrophobic cavity of β-CD forming host–guest inclusion complexes (Scheme 2).

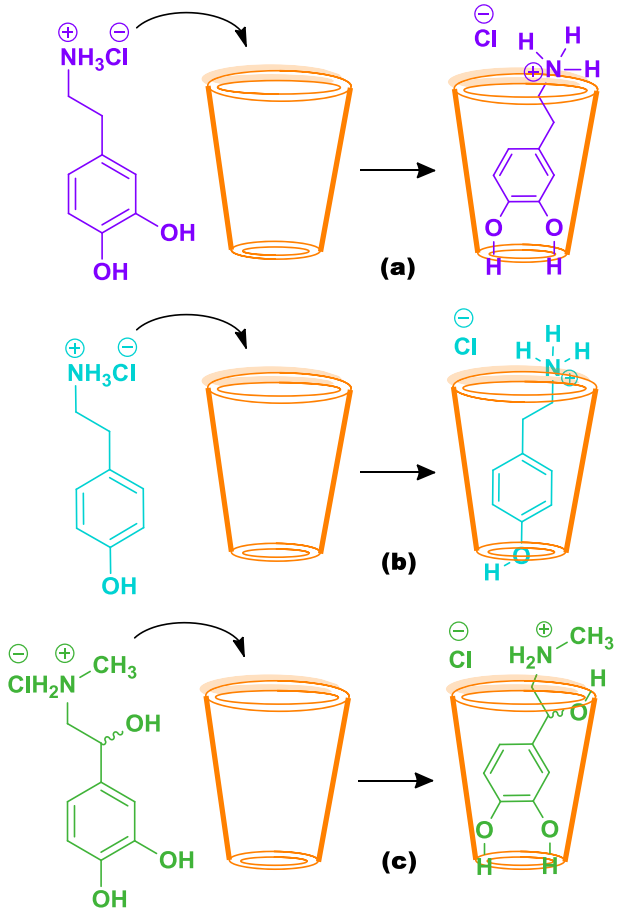
Each plot also indicates that there is a break point at certain concentrations after which the slops become less. Finding of break point in surface tension curve not only indicates formation of IC but also provides information about its stoichiometry, *i.e.*, appearance of single, double and so on break point in the plot indicates 1:1, 1:2 and so on stoichiometry of host:guest ICs (Scheme 3) [33].

The values of γ and corresponding concentrations of β-CD at each break have been listed in Table 1 and the overall variation have been listed in Tables S4–S6, which clearly point out that the breaks have been found at certain concentrations of NTs and β-CD where their concentration ratio in the solution was almost 1:1. Hence this study proves formation of 1:1 ICs between NTs and β-CD.

2.3. Conductivity study illustrates inclusion process and their stoichiometric ratio

Conductivity (κ) of aqueous solutions of the NTs has been measured to get clue whether ICs have been formed while β-CD being added to it [34,35]. The studied NTs show considerable κ because of having their charged structures. As β-CD was added to the aqueous solution of a NT (Tables S7–S9), the κ was observed to show decreasing trend probably because of encapsulation of the NT molecules inside into the cavity of β-CD (Scheme 2). After a certain concentration of β-CD a break was found in each of the conductivity curves (Fig. 3), indicating the formation of ICs. The values of κ and corresponding concentrations of β-CD at each break have been shown in Table 1, which reveal that the ratio of the concentrations of a NT and β-CD at the break point was found to be approximately 1:1, suggesting the host–guest ratio to be 1:1.

The break point is found at certain concentration where maximum inclusion takes place ever before, *i.e.*, though there is a dynamic equilibrium between the host and the guest, most of the guest molecules are encapsulated at the break point (1:1 M ratio of host & guest), beyond this point concentration of β-CD is higher than that of NT, thus shifting the equilibrium more toward the IC.



Scheme 2. Formation of inclusion complexes of (a) dopamine hydrochloride, (b) tyramine hydrochloride and (c) (±)-epinephrine hydrochloride with β-CD.

2.4. ^{1}H NMR study confirms inclusion phenomenon

Insertion of any guest molecule into the hydrophobic cavity of β-CD consequences in the chemical shift of the guest and β-CD in the NMR spectra, which is because of the interaction of the β-CD with the guest molecule [27].

In case of aromatic guest molecules the spectral changes that can be observed upon inclusion is the diamagnetic shielding of the aromatic moiety with the interacting atoms of β-CD [33]. In the structure of β-CD the H3 and H5 hydrogens are situated inside

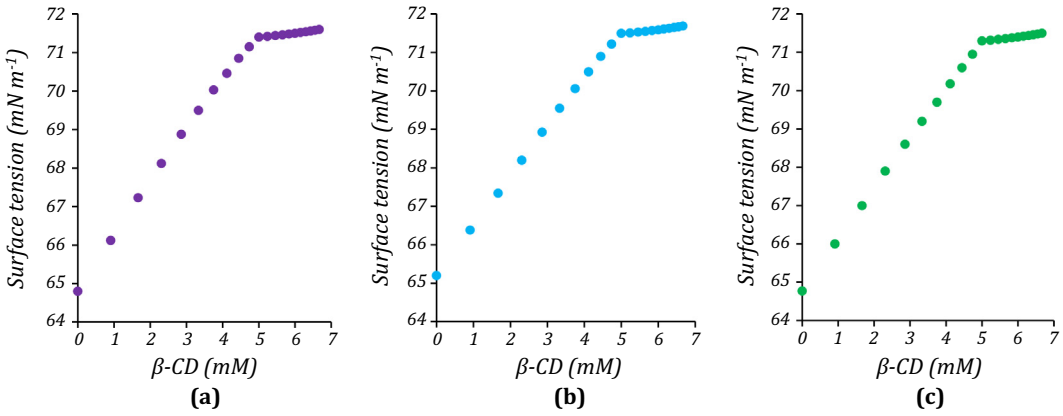
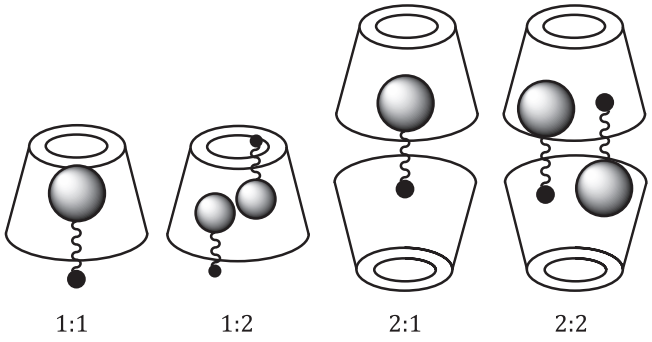


Fig. 2. Variation of surface tension of aqueous (a) dopamine hydrochloride solution, (b) tyramine hydrochloride solution and (c) (±)-epinephrine hydrochloride solution respectively with increasing concentration of β-cyclodextrin at 298.15 K.



Scheme 3. Different possibilities of host–guest ratio for inclusion complex.

the conical cavity, particularly, the H3 are placed near the wider rim while H5 are placed near the narrower rim, the other H1, H2 and H4 hydrogens are located at the exterior of the β-CD molecule (Scheme 4) [36,37]. In the present article the molecular interactions have been studied with the help of ^{1}H NMR spectra. The signals of interior H3 and H5 of β-CD as well as that of the interacting aromatic protons of the NTs showed considerable upfield shift in ^{1}H NMR spectra of 1:1 mixture of β-CD and each NT, confirming the ICs were formed (Figs. 4–6). As found from the chemical shifts, interaction of the H3 with the aromatic guest was much higher than that of the H5, proving the guest entered through the wider rim of β-CD (Scheme 5).

2.5. Association constants and thermodynamic parameters

Association constants (K_a) have been calculated for various NT-β-CD ICs by UV–visible spectroscopy as a result of changes in molar extinction coefficient ($\Delta\varepsilon$) of the NTs when complexed with β-CD molecule, which is owing to the changes in the polarity of the environment of the chromophore of the NTs when it goes from the polar aqueous environment to the apolar cavity of β-CD [38]. Changes in absorption intensity (ΔA) of DH (278 nm), TH (275 nm) and EH (278 nm) were studied as a function of concentration of β-CD to determine the value of K_a (Tables S11 and S12). The double reciprocal plots have been drawn on the basis of reliable Benesi–Hildebrand method for 1:1 host–guest ICs (Fig. S1, Eq. (1)) [27,39].

$$\frac{1}{\Delta A} = \frac{1}{\Delta\varepsilon[\mathrm{NT}]K_a}\cdot\frac{1}{[\beta\mathrm{CD}]} + \frac{1}{\Delta\varepsilon[\mathrm{NT}]} \quad (1)$$

The values of K_a for each of the ICs were evaluated by dividing the intercept by the slope of the straight line of the double reciprocal plot (Table 2) [40].

Various thermodynamic parameters for the formation of ICs can easily be derived basing upon the values of K_a found by the above method with the help of van't Hoff equation (Eq. (2)).

$$\ln K_a = -\frac{\Delta H^o}{RT} + \frac{\Delta S^o}{R} \quad (2)$$

There is a linear relationship between $\ln K_a$ and $1/T$ in the above equation (Fig. S2), on the basis of which the thermodynamic parameters ΔH^o, ΔS^o and ΔG^o for the formation of ICs may be obtained (Table S13) [41].

However, the above study has been performed in a short range of temperature in which ΔH^o and ΔS^o are considered to be non variable. Non-linear methods may be used for studies in wide range of temperatures. The magnitude of ΔH^o depends on the equilibrium constant of the inclusion complex at different temperatures and thus may have limitation compared to direct calorimetric methods [42]. On the other hand, in this study thermodynamic parameters have been calculated from K_a values, which in turn were determined from $\Delta\varepsilon$ of the NTs, which is owing to the changes in the environment of the chromophore of the NTs

Table 1
Values of surface tension (γ) and conductivity (κ) at the break point with corresponding concentration of aqueous β-cyclodextrin at 298.15 K.[a]

Dopamine hydrochloride		Tyramine hydrochloride		(±)-Epinephrine hydrochloride	
Surface tension					
Conc (mM)	γ (mN m^{-1})	Conc (mM)	γ (mN m^{-1})	Conc (mM)	γ (mN m^{-1})
4.83	71.37	4.89	71.47	4.96	71.28
Conductivity					
Conc (mM)	κ (mS m^{-1})	Conc (mM)	κ (mS m^{-1})	Conc (mM)	κ (mS m^{-1})
4.90	0.426	4.85	0.417	4.90	0.406

[a] Standard uncertainties (u): temperature: $u(T) = \pm 0.01$ K, surface tension: $u(\gamma) = \pm 0.1$ mN m^{-1}, conductivity: $u(\kappa) = \pm 0.001$ mS m^{-1}.

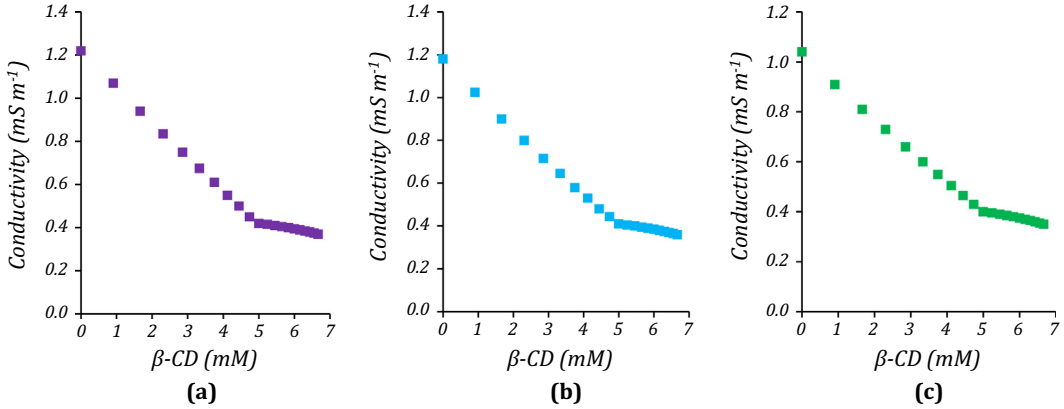
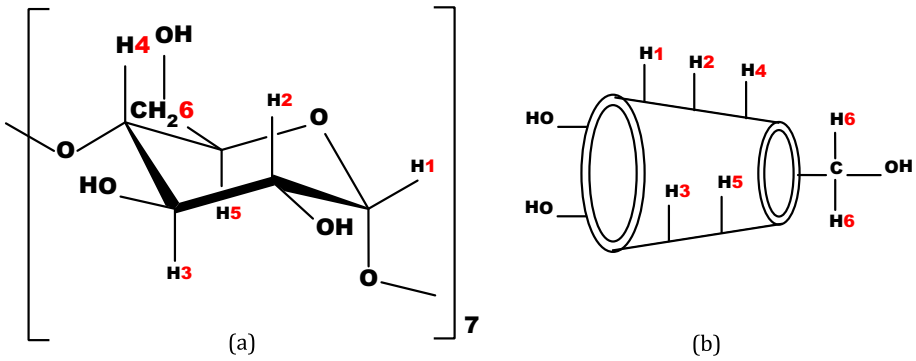


Fig. 3. Variation of conductivity of aqueous (a) dopamine hydrochloride solution, (b) tyramine hydrochloride solution and (c) (±)-epinephrine hydrochloride solution respectively with increasing concentration of β-cyclodextrin at 298.15 K.



Scheme 4. (a) Stereo-chemical configuration of β-cyclodextrin, (b) truncated conical structure of β-cyclodextrin with interior and exterior protons.

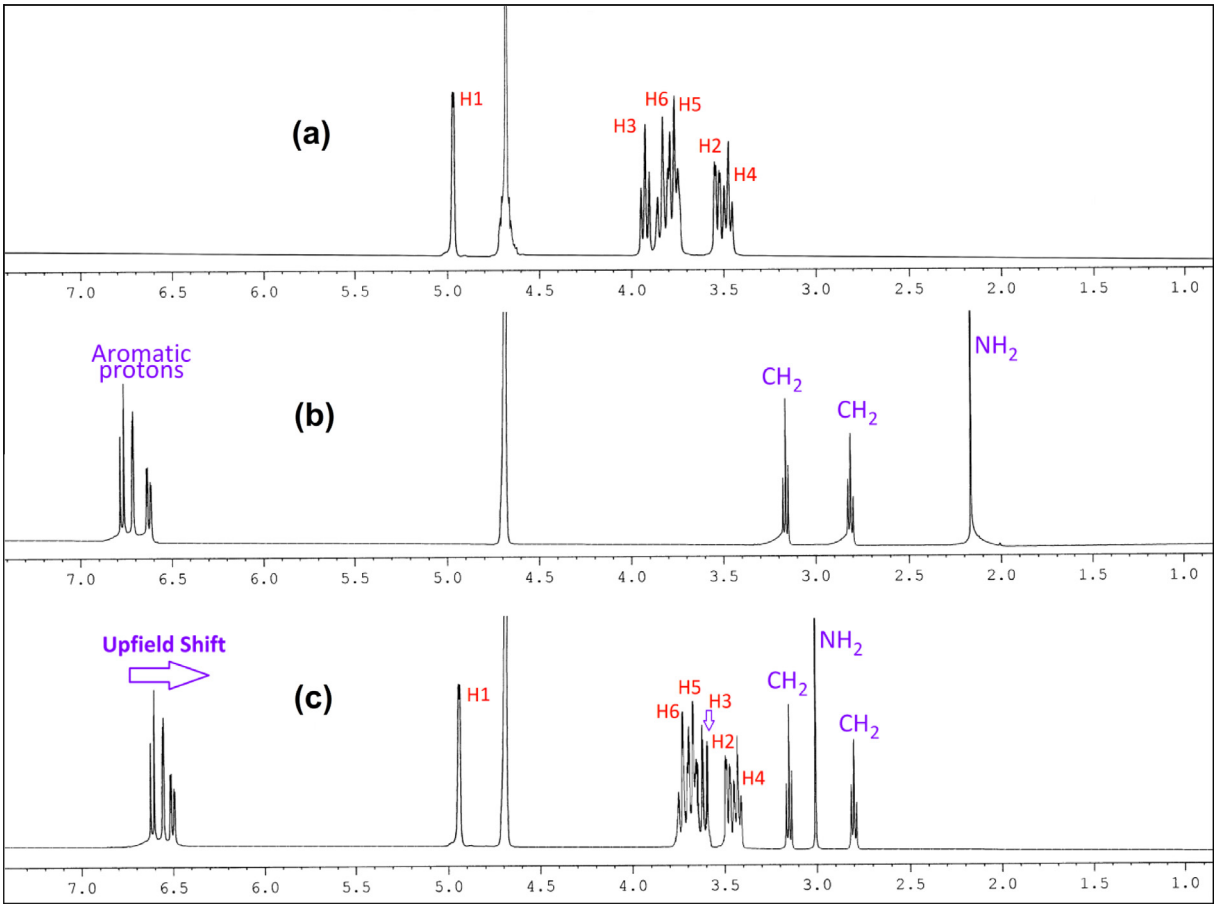


Fig. 4. ^{1}H NMR spectra of (a) β-CD, (b) dopamine hydrochloride and (c) 1:1 M ratio of β-CD & dopamine hydrochloride in D_2O at 298.15 K.

when it goes from the polar aqueous environment to the apolar cavity of β-CD. Hence, the ΔH^o and ΔS^o values presented here are exclusively for the formation of inclusion complex, not for the other solvent interactions taking place in the medium.

The values of ΔG^o for the formation of ICs were found negative suggesting that the inclusion process proceeds spontaneously, whereas negative values of ΔH^o and ΔS^o indicate that the inclusion process is exothermic and entropy controlled, but not entropy driven (Table 2). These consequences may be explained on the basis of molecular association that was taking place while IC was being formed between β-CD and each NT, resulting in a drop of entropy, which is unfavorable for the spontaneity of the inclusion complex formation, but this effect is overcome by higher negative value of ΔH^o, making the overall inclusion process thermodynamically favorable.

The data shown in Table 2 indicate that order of K_a for ICs with β-CD and the order of $-\Delta G^o$ is EH > DH > TH. This may be explained on account of the difference in the structures of three NTs, which have almost similar hydrophobic moiety, but EH can form H-bonds at both rims of β-CD because of having two phenolic and one alcoholic –OH groups, thus, it forms strongest IC among the three. Similarly, the results for DH and TH may be explained because of having two and one –OH groups in their structures respectively.

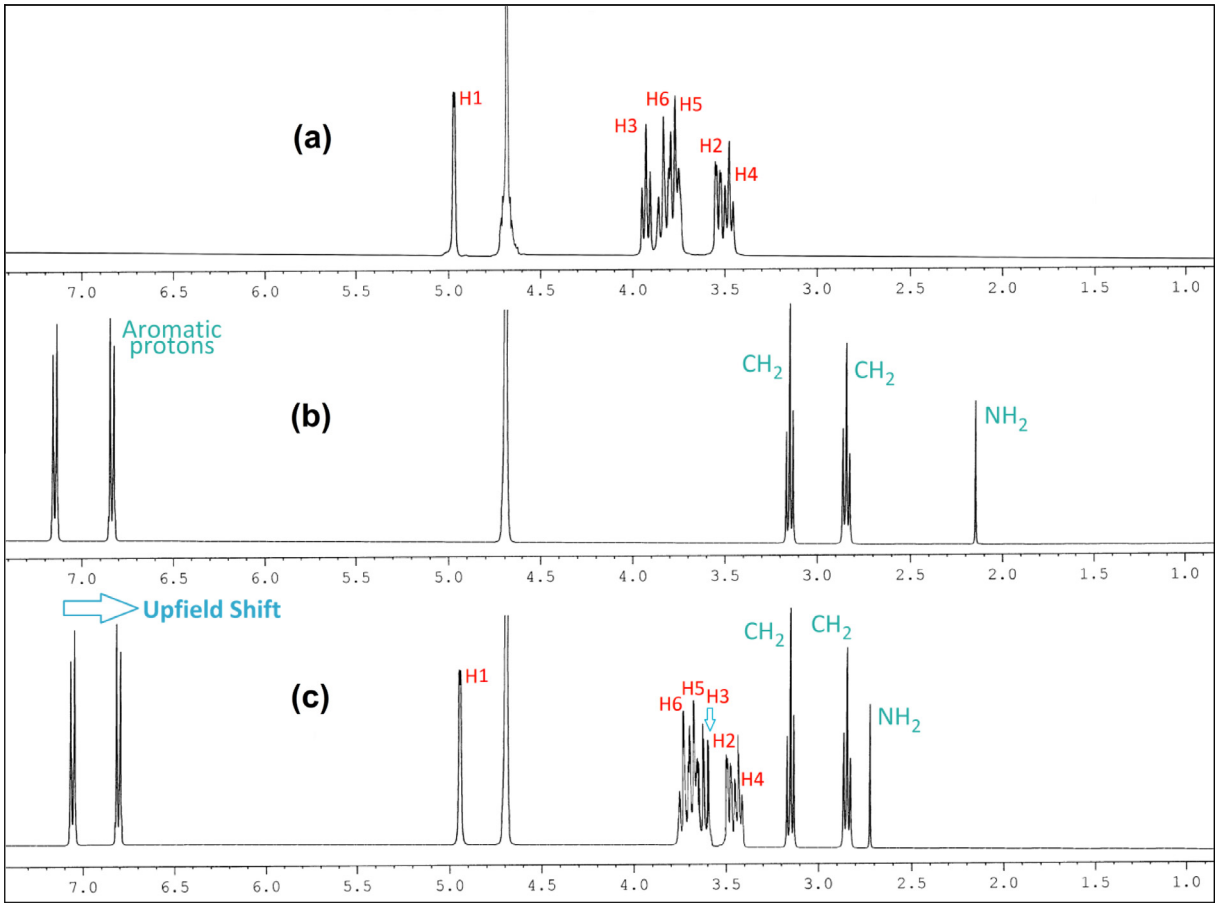


Fig. 5. ^{1}H NMR spectra of (a) β-CD, (b) tyramine hydrochloride and (c) 1:1 M ratio of β-CD & tyramine hydrochloride in D_2O at 298.15 K.

3. Conclusion

Molecular recognition of the three important NTs by β-CD has been shown, which may find its use as potential drug delivery system in pharmacological science. The molecular assemblies, *i.e.*, formation of ICs have been explained qualitatively as well as quantitatively so as to make it dependable in its field of application. β-CD has long been used as a carrier for its unique structural features, which is further explored in the present work, confirming that β-CD forms 1:1 ICs with DH, TH and EH, established by reliable physicochemical techniques. The association constants are found highest for EH, then DH and then TH for the ICs with β-CD. Hence, this exclusive study describes that the ICs in aqueous medium can be used as controlled delivery systems in the field of modern biomedical sciences.

4. Experimental section

4.1. Source and purity of samples

Dopamine hydrochloride, Tyramine hydrochloride, (±)-Epinephrine hydrochloride and β-cyclodextrin of puriss grade were purchased from Sigma–Aldrich, Germany and used as it was. The mass fraction purity of Dopamine hydrochloride, Tyramine hydrochloride, (±)-Epinephrine hydrochloride and β-cyclodextrin were ~1.00, ⩾0.98, ~1.00 and ⩾0.98 respectively.

4.2. Apparatus and procedure

Solubility of β-cyclodextrin and chosen neurotransmitters have been precisely checked in triply distilled and degassed water (with a specific conductance of 1×10^{-6} S cm^{-1}) and observed that the selected neurotransmitters were freely soluble in all proportion of aqueous β-cyclodextrin. All the stock solutions of the neurotransmitters were prepared by mass (weighed by Mettler Toledo AG-285 with uncertainty 0.0003*g*), and then the working solutions were obtained by mass dilution at 298.15 K. Sufficient precautions were made to decrease evaporation losses during mixing.

UV–visible spectra were recorded by JASCO V-530 UV/VIS Spectrophotometer, with an uncertainty of wavelength resolution of ±2 nm. The measuring temperature was held constant by an automated digital thermostat.

Surface tensions of the solutions were determined by platinum ring detachment technique using a Tensiometer (K9, KRŰSS; Germany) at 298.15 K. Accuracy of the study was ±0.1 mN m^{-1}. Temperature of the system was maintained by circulating thermostated water through a double-wall glass vessel holding the solution.

Conductivities of the solutions were studied by Mettler Toledo Seven Multi conductivity meter having uncertainty 1.0 μS m^{-1}. The study was carried out in a thermostated water bath at 298.15 K with uncertainty ±0.01 K. HPLC grade water was used with specific conductance 6.0 μS m^{-1}. The conductivity cell was calibrated using 0.01 M aqueous KCl solution.

NMR spectra were recorded in D_2O unless otherwise stated. ^{1}H NMR spectra were recorded at 400 MHz and 500 MHz using Bruker ADVANCE 400 MHz and Bruker ADVANCE 500 MHz instruments respectively. Signals are quoted as δ values in ppm using residual protonated solvent signals as internal standard (D_2O: δ 4.79 ppm). Data are reported as chemical shift.

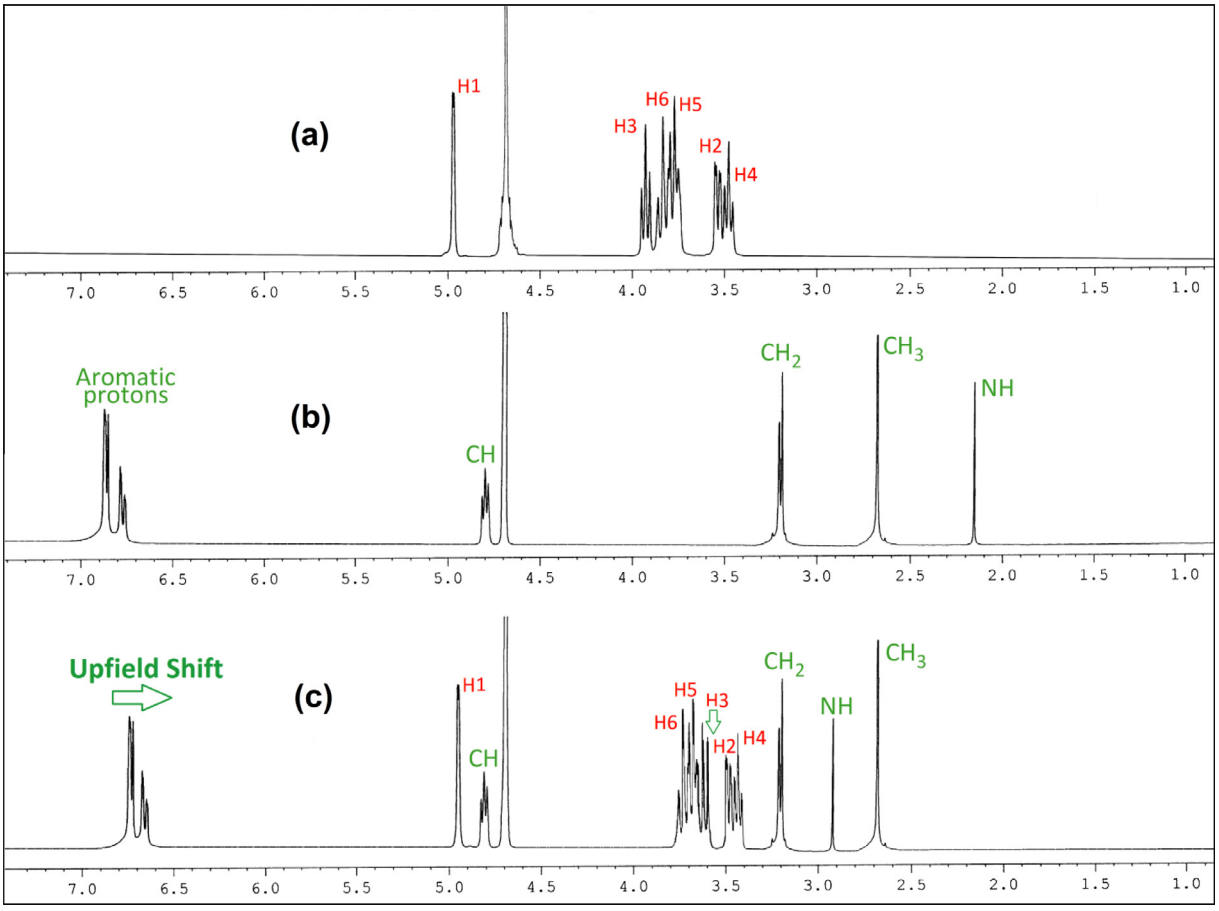
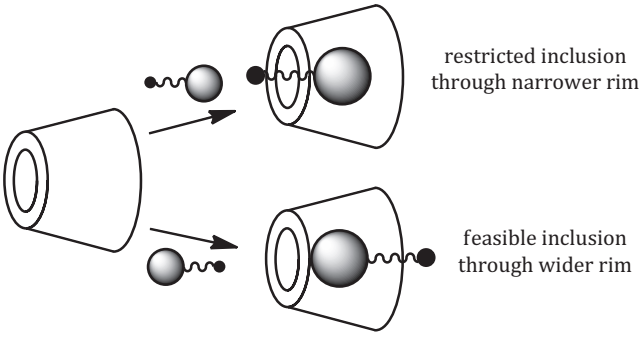


Fig. 6. ^{1}H NMR spectra of (a) β-CD, (b) (±)-epinephrine hydrochloride and (c) 1:1 M ratio of β-CD & (±)-epinephrine hydrochloride in D_2O at 298.15 K.



Scheme 5. Feasible and restricted inclusion of the guest into the host molecule.

4.3. ^{1}H NMR data

β-Cyclodextrin: ^{1}H NMR (400 MHz, D_2O): δ = 3.49–3.54 (6H, t, J = 9.2 Hz), 3.57–3.60 (6H, dd, J = 9.6, 3.2 Hz), 3.79–3.84 (18H, m), 3.87–3.92 (6H, t, J = 9.2 Hz), 5.00–5.01 (6H, d, J = 3.6 Hz).

Dopamine hydrochloride: ^{1}H NMR (400 MHz, D_2O): δ = 2.15 (–NH_2), 2.78–2.81 (2H, t, J = 7.2 Hz), 3.13–3.16 (2H, t, J = 7.2 Hz), 6.66–6.69 (1H, dd, J = 8.0, 1.6 Hz), 6.76–6.77 (1H, d, J = 2 Hz), 6.81–6.83 (1H, d, J = 8.4 Hz).

Tyramine hydrochloride: ^{1}H NMR (400 MHz, D_2O): δ = 2.14 (–NH_2), 2.82–2.86 (2H, t, J = 7.2 Hz), 3.14–3.17 (2H, t, J = 7.2 Hz), 6.81–6.83 (2H, dd, J = 6.8, 2.0 Hz), 7.12–7.14 (2H, d, J = 8.8 Hz).

Table 2
Association constant (K_a) and thermodynamic parameters ΔH^o, ΔS^o and ΔG^o of different neurotransmitter-β-cyclodextrin inclusion complexes.

	Temp (K)[a]	$K_a \times 10^{-3}$ (M^{-1})[b]	ΔH^o (kJ mol^{-1})[b]	ΔS^o (J mol^{-1} K^{-1}[b]	ΔG^o (298.15 K) (kJ mol^{-1})[b]
Dopamine hydrochloride + β-CD	293.15	1.48	−19.80	−6.83	−17.77
	298.15	1.31			
	303.15	1.13			
Tyramine hydrochloride + β-CD	293.15	1.24	−18.37	−3.38	−17.36
	298.15	1.11			
	303.15	0.97			
(±)-Epinephrine hydrochloride + β-CD	293.15	1.59	−20.30	−7.94	−17.93
	298.15	1.40			
	303.15	1.21			

[a] Standard uncertainties in temperature u are: $u(T)$ = ±0.01 K.
[b] Mean errors in K_a = ±0.02 × 10^{-3} M^{-1}; ΔH^o = ± 0.01 kJ mol^{-1}; ΔS^o = ±0.01 J mol^{-1} K^{-1}; ΔG^o = ± 0.01 kJ mol^{-1}.

(±)-Epinephrine hydrochloride: ^{1}H NMR (400 MHz, D_2O): δ = 2.14 (NH), 2.68 (3H, s), 3.18–3.20 (2H, d, J = 6.4 Hz), 4.81–4.84 (1H, t, J = 6.4 Hz), 6.77–6.79 (1H, d, J = 8.4 Hz), 6.85–6.87 (2H, m).

β-CD + DH: ^{1}H NMR (500 MHz, D_2O): δ = 2.77–2.80 (2H, t, J = 7.2 Hz), 3.01 (–NH_2), 3.12–3.15 (2H, t, J = 7.2 Hz), 3.45–3.50 (6H, t, J = 9.2 Hz), 3.53–3.56 (6H, dd, J = 9.6, 3.2 Hz), 3.59–3.64 (6H, t, J = 9.2 Hz), 3.69–3.77 (18H, m), 4.96–4.97 (6H, d, J = 3.6 Hz), 6.48–6.51 (1H, dd, J = 8.0, 1.6 Hz), 6.56–6.57 (1H, d, J = 2 Hz), 6.64–6.66 (1H, d, J = 8.4 Hz).

β-CD + TH: ^{1}H NMR (400 MHz, D_2O): δ = 2.72 (–NH_2), 2.81–2.85 (2H, t, J = 7.2 Hz), 3.13–3.16 (2H, t, J = 7.2 Hz), 3.46–3.51 (6H, t, J = 9.2 Hz), 3.54–3.57 (6H, dd, J = 9.6, 3.2 Hz), 3.62–3.68 (6H, t, J = 9.2 Hz), 3.71–3.79 (18H, m), 4.96–4.97 (6H, d, J = 3.6 Hz), 6.80–6.82 (2H, dd, J = 6.8, 2.0 Hz), 7.07–7.09 (2H, d, J = 8.8 Hz).

β-CD + EH: ^{1}H NMR (500 MHz, D_2O): δ = 2.68 (3H, s), 2.92 (NH), 3.17–3.19 (2H, d, J = 6.4 Hz), 3.44–3.49 (6H, t, J = 9.2 Hz), 3.52–3.56 (6H, dd, J = 9.6, 3.2 Hz), 3.57–3.63 (6H, t, J = 9.2 Hz), 3.68–3.76 (18H, m), 4.81–4.83 (1H, t, J = 6.4 Hz), 4.97–4.98 (6H, d, J = 3.6 Hz), 6.64–6.66 (1H, d, J = 8.4 Hz), 6.73–6.75 (2H, m).

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cplett.2016.05.031.

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