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Research

# Molecular modeling investigation of 2-, 3-, and 4-aminobenzoic acids in a- and β-cyclodextrins

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**CONFLICTS OF INTEREST**
There are no conflicts of interest for any of the authors.

**ABSTRACT:**
Geometry optimizations of neutral, monocation and monoanion of 2-aminobenzoic acid (2ABA), 3-aminobenzoic acid (3ABA) and 4-aminobenzoic acid (4ABA) with a-, and β-cyclodextrins (a-CD, and β-CD) were carried out using semi-empirical PM3 method. PM3 calculations were performed upon the inclusion complexation of a-CD, β-CD with neutral, monoanion and monocation species of 2ABA, 3ABA and 4ABA. The negative Gibbs energy and enthalpy changes for the inclusion complexes indicated that the formation of these complexes is spontaneous and exothermic. Hydrogen bonding interactions played a major role in the ABA:CD inclusion process. The dipole moment values for guests increased when they entered into the CD cavity which is an indication of the increase of the polarity and the formation of complex. The computational results indicated that the formation of all the inclusion complexes were enthalpy driven process.

**KEY WORDS:** Cyclodextrin, Aminobenzoic acid, inclusion complex, PM3, molecular modeling.

## INTRODUCTION

Cyclodextrins are powerful carriers for improving the therapeutic efficacy of drugs with poor solubility and/or stability problems, owing to their ability to amend these unfavorable properties through the formation of inclusion complexes [1–3]. However, the exploitation cyclodextrin properties in the pharmaceutical area is hindered by problems such as high molecular weight, rather high cost, relatively low water solubility, potential toxicity, etc. [4]. Strengthening the complexation and solubilization efficacy of cyclodextrins is a possible tool to reduce their workable amount in pharmaceutical formulations. Among the strategies proposed toward this aim, the addition of suitable auxiliary substances can be a valuable approach to increase the cyclodextrin solubilizing capacity [4–6]. It has been shown for example that certain low molecular weight acids or hydroxyacids can strongly enhance the cyclodextrin solubilizing power toward basic drugs, as a result of the combined effect of salt formation and inclusion complexation [7–11]. Likewise, the positive effects on drug solubility of ternary complexation involving an acidic drug, a basic additive and a cyclodextrin have been reported [12–14].

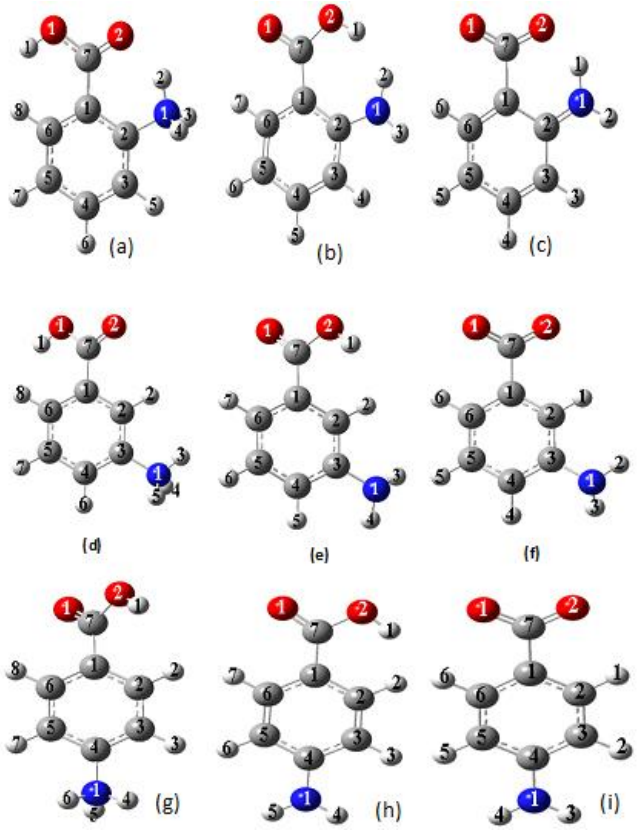
Encapsulation is a method, which has been used extensively during the last decades in the cosmetics and drug industry. In the food industry it is being used for many purposes, such as a flavor carrier and to impart some degree of protection against evaporation, reaction or migration in a food [15,16]. During recent years nutraceuticals are considered as health-promoting ingredients in food and encapsulation can provide the necessary protection for these active compounds against oxidation. It also provides an enhancement of the solubility of active compounds and thus these encapsulated ingredients may be used for preparation of several fortified foods and functional foods [17].

In our previous work, we have investigated the molecular modeling studies of the complexation of cyclodextrin with various neutral organic molecules [18-23]. In this paper, we aim to investigate the various anionic species of organic molecules with cyclodextrins.

## Experimental

The initial structure of a-CD, β-CD [24] and all the species of 2ABA, 3ABA, and 4ABA were built with Spartan (version 8.0) and fully optimized by PM3 method without imposing any symmetrical restrictions (Figure 1). Since the semiempirical PM3 method has been proved to be a powerful tool in the conformational study of cyclodextrin complexes and has high computational efficiency in calculating the CDs systems [25-27], it is selected to study the inclusion process of the CD with the above ABAs in this paper.

**Figure 1.** The optimized structure of (a) 2ABA-MC, (b) 2ABA-N, (c) 2ABA-MA, (d) 3ABA-MC, (e) 3ABA-N, (f) 3ABA-MA, (g) 4ABA-MC, (h) 4ABA-N and (i) 4ABA-MA.

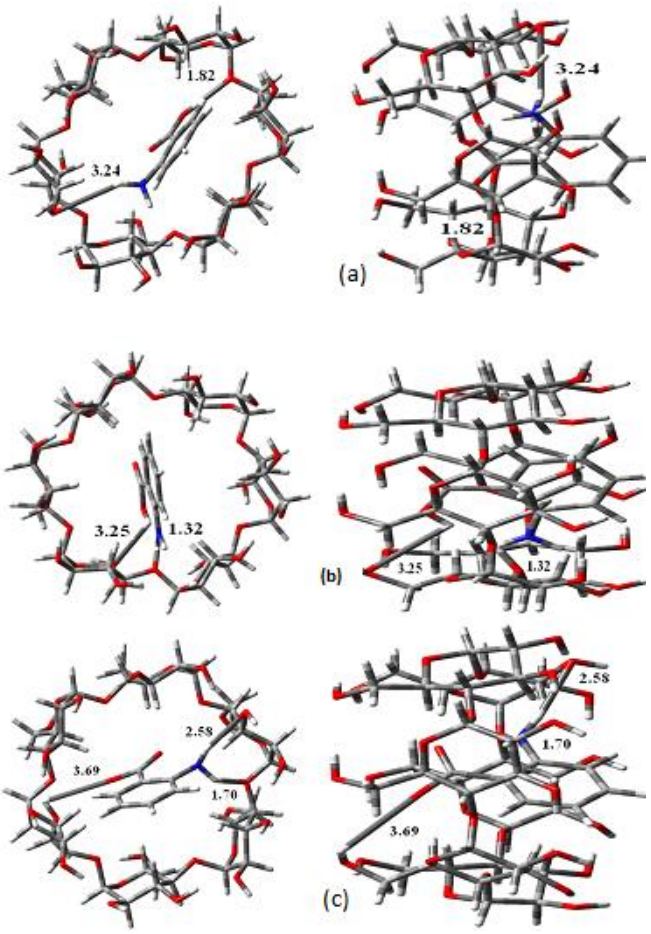



The glycosidic oxygen atoms of the a-CD and β-CD were placed onto the XY plane and their center was defined as the center of the coordination system. The primary hydroxyl groups were placed pointing toward the positive Z axis. The inclusion complexes were constructed from the PM3-optimized CD and guest molecules. The functional groups were always located pointing to the primary hydroxyls of CD according to the experimental observation [28,29]. The longer dimension of the guest molecule was initially placed onto the Z axis. The position of the guest was determined by the Z coordinate of one selected atom of the guest. The inclusion process was simulated by putting the guest in one end of CD and then letting it pass through the CD cavity by steps. In every step, the geometry of the host guest complex was completely optimized by PM3 without any restriction. Frequency calculations using PM3 are also performed, and no negative eigen value was found for the final structures.

**RESULT AND DISCUSSION**

Tables 1 to 3 and Figures 2 to 7 shows the inclusion models of ABA with a-CD and β-CD. For the construction of ABA/CD complexes, the glycosidic oxygen atoms of the CD molecules were placed on the XY plane and their center were defined as the center of the coordinate system. The secondary hydroxyl groups of the CDs were placed pointing toward the positive Z axis. The hydroxyl groups of the guest molecules were initially placed along the Z axis. Two possible orientations of the guest molecules in the complexes were considered. The orientation in which the COOH group of the guests points toward secondary hydroxyl of CDs was called the "A orientation", the other, in which the amino group of the guest points toward the primary hydroxyl of CD was called the "B orientation". The inclusion processes emulation was then achieved along the Z axis from 5 to −5 Å with a step of 1 Å.

**Figure 2.** The inclusion complex structure of (a) 2ABA-MC, (b) 2ABA-N, (c) 2ABA-MA with a-CD.

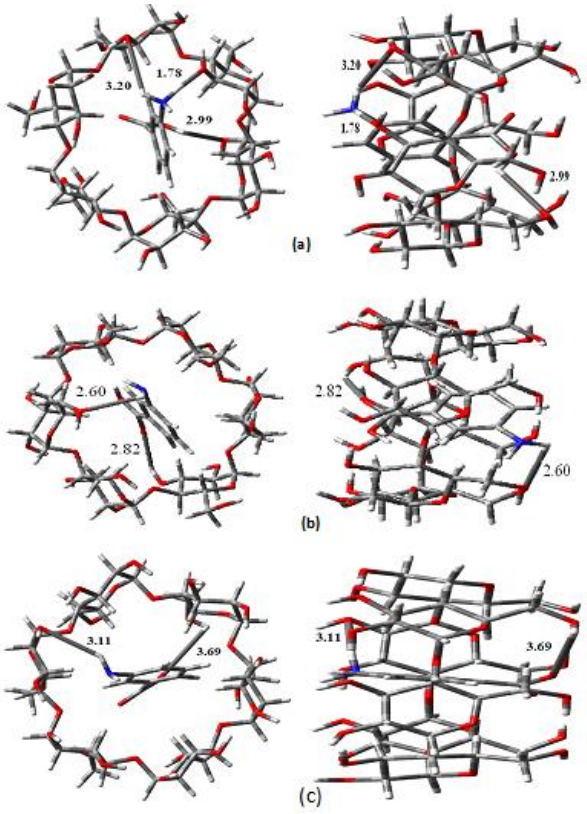



The generated structures at each step were optimized by PM3 methods without imposing any symmetrical restrictions. Complexation energy upon complexation between the guests and the CDs was calculated for the minimum energy structure according to Eqn. 1.

$$\Delta E_{complexaton} = E_{complex} - (E_{CD} + E_{guest}) \quad (1)$$

where $E_{complex}$, $E_{CD}$ and $E_{guest}$ represent the total energy of the complex, the free optimized CD and the free optimized drug respectively.

**Figure 3.** The inclusion complex structure of (a) 3ABA-MC, (b) 3ABA-N, (c) 3ABA-MA with a-CD.




In this study we have considered only the inclusion complexes in molar proportion 1:1 formed between one molecule of the both CDs and the guests. All the complexation energies are negative which show that the inclusion processes of the ABAs in both CDs are thermodynamically favorable.

HOMO as ionization energy (IE) and LUMO as electron affinity (EA) were used for calculating the electronic chemical potential (μ), which is half of the energy of the HOMO and LUMO:

$$\mu = (E_{HOMO} + E_{LUMO}) /2 \quad (2)$$

The hardness (η) as half of the energy gap between HOMO and LUMO was calculated using the following expression:

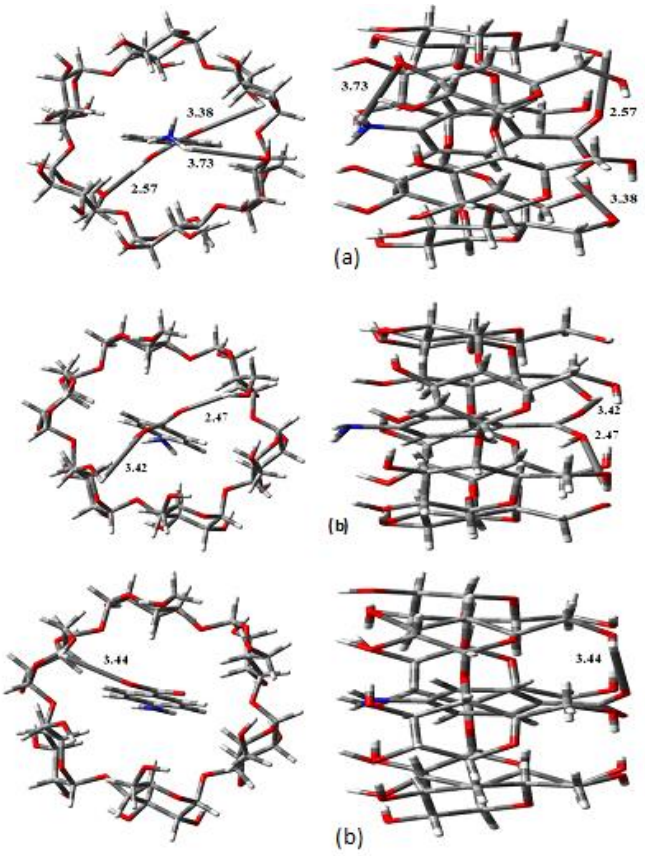
$$Gap = E_{HOMO} - E_{LUMO} \quad (3)$$

$$\eta = E_{LUMO} - E_{HOMO} /2 \quad (4)$$

The electrophilicity (ω) of the components are calculated in semiempirical method using the following eqn. (5):

$$\omega = \mu^2/2\eta \quad (5)$$

**Figure 4.** The inclusion complex structure of (a) 4ABA-MC, (b) 4ABA-N, (c) 4ABA-MA with a-CD.




Complexation energies, HOMO, LUMO, thermodynamic parameters (enthalpy, entropy, free energy) and dipole moment (D) of the guests (2ABA, 3ABA and 4ABA), hosts (α-CD and β-CD) and the inclusion complexes for the most stable structures obtained by PM3 method were summarized in Tables 1 to 3. It is clear that in CD complexation with neutral (N), monocation (MC) and monoanion (MA) species, the complexation energy is more in favor of monoanion species of the guests than others. Among the nine inclusion complexes, monoanion of the ABA/β-CD had the lowest energy when compared to other complexes. The above results show that monoanion in ABAs and β-CD formed a more stable inclusion complex than the other complexes (because high negative value leads to greater stability).

**Table 1:** Binding energies and HOMO, LUMO energy of monocation (MC), neutral (N) and monoanion (MA) of 2ABA before and after inclusion complexation by PM3 method.

| Properties | MC | N | MA | MC : α-CD | N :α-CD | MA :α-CD | M :β-CD | N : β-CD | MA : β-CD |
|---|---|---|---|---|---|---|---|---|---|
| $E_{HOMO}$ (eV) | -14.74 | -8.76 | -13.86 | -12.72 | -12.36 | -6.50 | -12.12 | -9.82 | -12.25 |
| $E_{LUMO}$ (eV) | -5.32 | -0.13 | -8.88 | -4.22 | -0.45 | 2.37 | -4.06 | -0.37 | -7.35 |
| $E_{HOMO}$ – $E_{LUMO}$ (eV) | -9.41 | -8.27 | -4.97 | -8.50 | -11.90 | -8.87 | -8.06 | -9.45 | -4.89 |
| Dipole (D) | 5.92 | 5.37 | 12.87 | 14.79 | 9.54 | 13.40 | 11.76 | 13.13 | 14.88 |
| ΔD | | | | -2.47 | -7.17 | -10.81 | -6.45 | -4.53 | -10.28 |
| E* | 86.98 | -56.93 | 212.66 | -1170.55 | -1318.9 | -1374.73 | -1435.87 | -1529.90 | -1286.17 |
| ΔE* | | | | -10.01 | -14.45 | -339.87 | -65.22 | -15.34 | -384.12 |
| H* | 158.73 | 24.08 | 264.37 | -394.16 | -551.72 | -615.81 | -415.76 | -648.48 | -415.3 |
| ΔH* | | | | -18.32 | -24.59 | -308.97 | -93.06 | -5.01 | -12.12 |
| G* | 185.81 | 30.49 | 291.74 | -511.61 | -670.90 | -729.87 | -657.08 | -780.86 | -545.62 |
| ΔG* | | | | -20.69 | -24.66 | -344.88 | -53.37 | -21.83 | -47.84 |
| S* | -0.090 | -0.088 | -0.091 | -0.393 | -0.399 | -0.382 | -0.412 | -0.444 | -0.437 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ΔS* | | | | 0.05 | 0.042 | 0.062 | 0.087 | 0.053 | 0.063 |
| Zero point energy | 92.89 | 81.78 | 73.22 | 728.64 | 719.02 | 756.13 | 728.64 | 826.66 | 816.56 |
| Mulliken charges | 1.00 | 0.00 | 0.00 | 1.00 | 0.00 | -1.00 | 1.00 | 0.00 | 1.00 |

**Unit *=**Kcalmol$^{-1}$, ** = cal/mol-Kelvin

From Tables 1 to 3, it is found that, (i) in all the three ABAs, the difference in energy of MA:β-CD inclusion complexes is more negative than the other complexes, (ii) all the MC species HOMO are more negative than neutral and MA species, (iii) HOMO-LUMO gap for MC:a-CD inclusion complexes of ABAs is more negative than the other complexes, (iv) for all the ABAs, energy, enthalpy, entropy and free energy values are negative, (v) in 2ABA, MA:a-CD has more negative enthalpy and free energy than neutral and MC inclusion complexes, (vi) in 3ABA, energy and enthalpy of MA:β-CD has higher negative value, whereas MA:a-CD free energy has more negative than other complexes and (vii) in 4ABA, energy, enthalpy and free energy of MA:β-CD has higher negative value than other complexes.

**HOMO–LUMO parameters**

$E_{HOMO}$- $E_{LUMO}$ gap is an important scale of stability and molecules with large ($E_{HOMO}$- $E_{LUMO}$) values tend to have higher stability. LUMO as an electron acceptor represents the ability to obtain an electron and HOMO represents the ability to donate electron. Moreover, a lower HOMO–LUMO energy gap explained the eventual stability of the complex, i.e., the isolated molecule had lower stability than the complex molecule. HOMO and LUMO energies of the guest species (neutral, monoanion and dianion) and their inclusion complexes were shown in Tables 1 to 3 and Figure 8 and 9**.** The $E_{HOMO}$- $E_{LUMO}$ gap for the monoanion of ABA/a-CD inclusion complex was more negative, leading one to conclude that this complex is more stable than the other inclusion complexes addressed above. This result is in good agreement with the complexation energy.

**Table 2:** Binding energies and HOMO, LUMO energy of monocation (MC), neutral (N) and monoanion (MA) of 3ABA before and after inclusion complexation by PM3 method.

| Properties | MC | N | MA | MC :α-CD | N : α-CD | M : α-CD | MC : β-CD | N : β-CD | MA : β-CD |
|---|---|---|---|---|---|---|---|---|---|
| $E_{HOMO}$ (eV) | -14.41 | -9.10 | -4.49 | -12.68 | -8.65 | -5.12 | -12.86 | -8.97 | -5.60 |
| $E_{LUMO}$ (eV) | -5.182 | -0.44 | 3.82 | -3.90 | -0.40 | 2.78 | -4.65 | -0.30 | 1.98 |
| $E_{HOMO}$ – $E_{LUMO}$ (eV) | -9.22 | -8.65 | -8.31 | -8.78 | -8.24 | -7.90 | -8.21 | -8.67 | -7.58 |
| Dipole (D) | 13.3 | 4.78 | 11.20 | 16.38 | 4.50 | 13.40 | 12.45 | 10.94 | 10.12 |
| ΔD | | | | -8.26 | -18.04 | -10.81 | -13.14 | -6.13 | -13.37 |
| E* | 93.96 | -67.03 | -91.84 | -1176.24 | -1325.48 | -1374.73 | -1489.13 | -1565.11 | -1345.44 |
| ΔE* | | | | -22.68 | -10.93 | -35.37 | -125.46 | -40.45 | -204.03 |
| H* | 163.11 | -5.65 | -10.94 | -400.09 | -673.48 | -615.81 | -456.00 | -665.18 | -515.45 |
| ΔH* | | | | -8.01 | -96.62 | -33.66 | -48.44 | -80.02 | -163.04 |
| G* | 192.57 | 22.15 | -38.89 | -517.47 | -557.29 | -729.87 | -698.76 | -796.06 | -655.22 |
| ΔG* | | | | -33.31 | -97.29 | -114.25 | -10.81 | -28.69 | -73.19 |
| S** | -0.098 | -0.093 | -0.093 | -0.393 | -0.388 | -0.382 | -0.445 | -0.476 | -0.456 |
| ΔS** | | | | 0.058 | 0.058 | 0.064 | 0.062 | 0.026 | 0.046 |
| Zero point energy | 92.10 | 83.00 | 74.83 | 729.16 | 720.03 | 756.13 | 767.04 | 812.00 | 843.56 |
| Mulliken charges | 1.00 | 0.00 | -1.00 | 1.00 | 0.00 | -1.00 | 1.00 | 0.00 | -1.00 |

**Table 3:** Binding energies and HOMO, LUMO energy of monocation (MC), neutral (N) and monoanion (MA) of 4ABA before and after inclusion complexation by PM3 method.

| Properties | MC | N | MA | MC: α-CD | N: α-CD | M: α-CD | MC: β-CD | N: β-CD | MA: β-CD |
|---|---|---|---|---|---|---|---|---|---|
| $E_{HOMO}$ (eV) | -14.28 | -8.65 | -4.32 | -12.47 | -9.09 | -4.23 | -12.62 | -8.984 | -12.69 |
| $E_{LUMO}$ (eV) | -5.29 | 0.34 | 4.03 | -3.65 | -0.28 | 2.56 | -3.90 | -0.246 | -5.14 |
| $E_{HOMO}$ – $E_{LUMO}$ (eV) | -8.99 | -8.99 | -8.36 | -8.82 | -8.80 | -6.79 | -8.72 | -8.738 | -7.55 |
| Dipole (D) | 16.25 | 6.74 | 13.22 | 11.1 | 10.96 | 9.99 | 9.87 | 14.93 | 9.56 |
| ΔD | | | | -16.58 | -6.74 | -14.57 | -18.67 | -4.10 | -15.95 |
| E* | 95.23 | -64.71 | -85.01 | -1275.18 | -1322.67 | -1369.45 | -1392.32 | -1530.0 | -1308.12 |
| ΔE* | | | | -122.89 | -10.41 | -206.94 | -29.92 | -7.66 | -234.52 |
| H* | 193.80 | -3.82 | -31.34 | -523.55 | -672.03 | -698.11 | -502.48 | -649.9 | -436.09 |
| ΔH* | | | | -146.14 | -97.00 | -95.56 | -28.73 | -21.47 | -262.80 |
| G* | 164.32 | 23.47 | -6.13 | -423.54 | -554.75 | -579.00 | -635.21 | -787.0 | -569.65 |
| ΔG* | | | | -88.87 | -98.51 | -103.86 | -10.01 | -20.95 | -226.00 |
| S** | -0.098 | -0.091 | -0.084 | -0.332 | -0.393 | -0.432 | -0.445 | -0.459 | -0.447 |
| ΔS** | | | | 0.119 | 0.051 | 0.005 | 0.062 | 0.041 | 0.046 |
| Zero point energy | 92.03 | 82.26 | 73.55 | 678.15 | 719.97 | 776.07 | 834.83 | 824.51 | 817.10 |
| Mulliken charges | 1.00 | 0.00 | -1.00 | 1.00 | 0.00 | -1.00 | 1.00 | 0.00 | -1.00 |

The dipole moment of the neutral, monoanion and dianion species of the ABAs and the inclusion complexes are presented in Tables 1 to 3. All the inclusion complexes showed higher dipole moment values than the corresponding isolated ABAs, whereas compared to both CDs, the values were low or high. This indicates that the polarity of the CDs cavity changed after the guest entered into the CDs cavity. From these results it can be concluded that the dipole moment values show a strong correlation with the complexation behavior of the molecules.

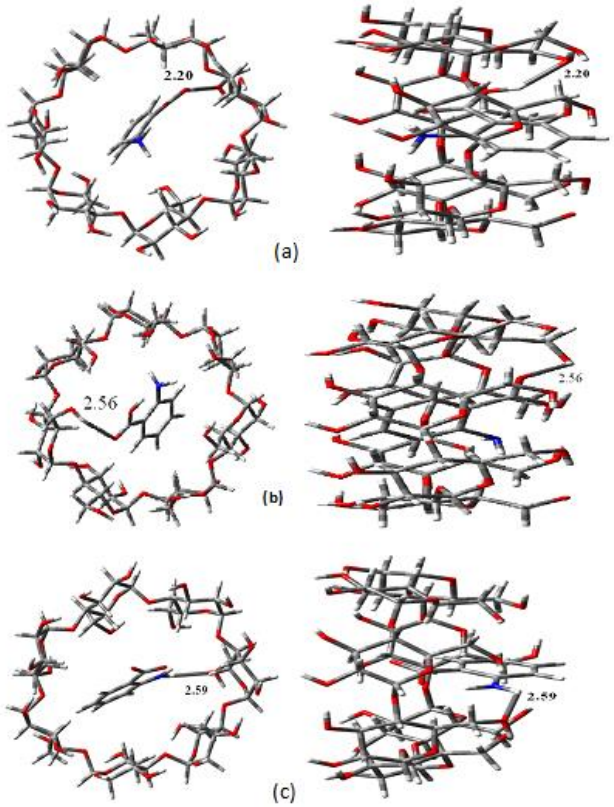



**Figure 5.** The inclusion complex structure of (a) 2ABA-MC, (b) 2ABA-N, (c) 2ABA-MA with β-CD.

**Thermodynamics parameters**

To investigate the thermodynamic parameters of the complexation process, the statistical

thermodynamic calculation was carried out at 1 atm pressure and 298.15 K temperature. The thermodynamic quantities, enthalpy changes (ΔH), Gibbs free energy changes (ΔG) and entropy changes (ΔS) are depicted in Tables 1 to 3. The difference in free energy (ΔG), enthalpy (ΔH) and entropy (ΔS) for the all the inclusion complexes are more negative than the corresponding isolated species. The negative free energy change (ΔG) of the inclusion complexes implies that the inclusion should proceed spontaneously at room temperature. The high negative ΔG values noticed for monoanion/a-CD inclusion complex specify that this inclusion process is more spontaneous than that of the other three species.

**Figure 6.** The inclusion complex structure of (a) 3ABA-MC, (b) 3ABA-N, (c) 3ABA-MA with β-CD.

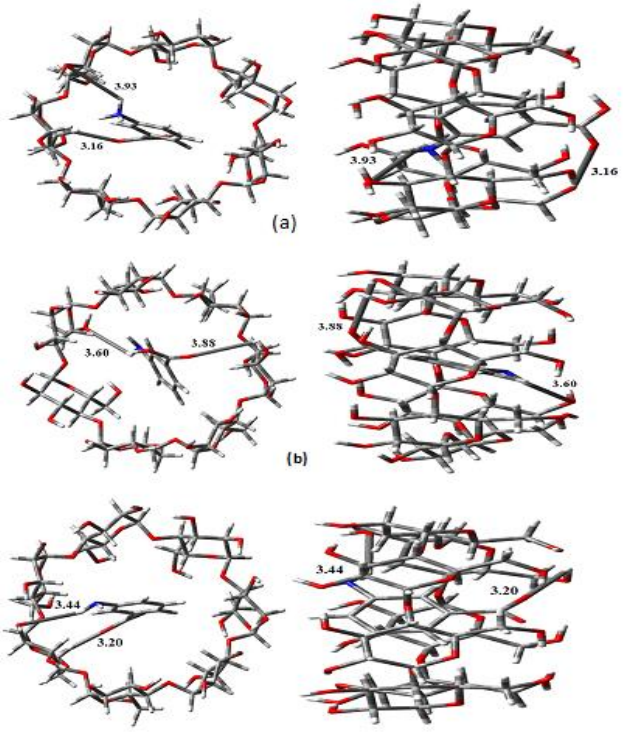



**Figure 7.** The inclusion complex structure of (a) 4ABA-MC, (b) 4ABA-N, (c) 4ABA-MA with β-CD.

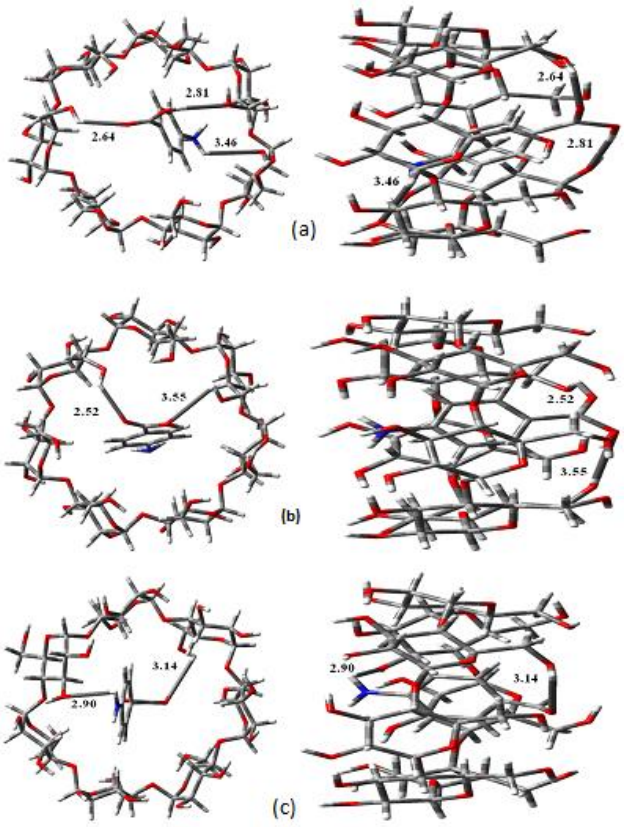



**Figure 8.** HOMO-LUMO energy structure of (a) 2ABA-MC, (b) 2ABA-N, (c) 2ABA-MA.

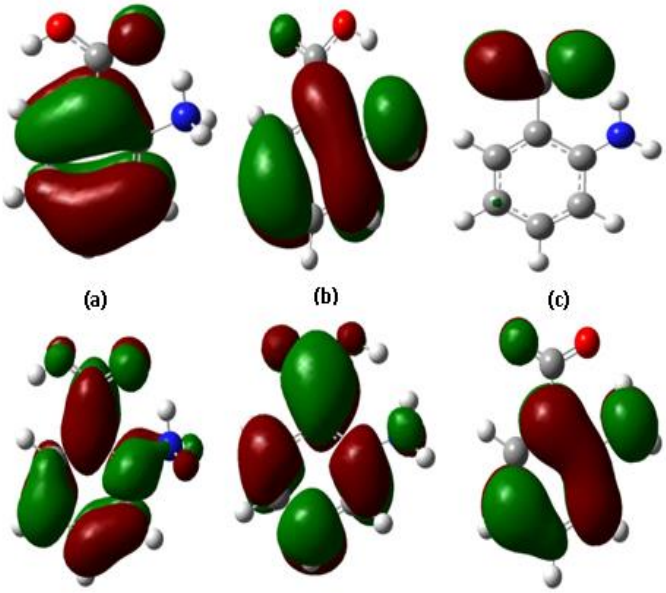
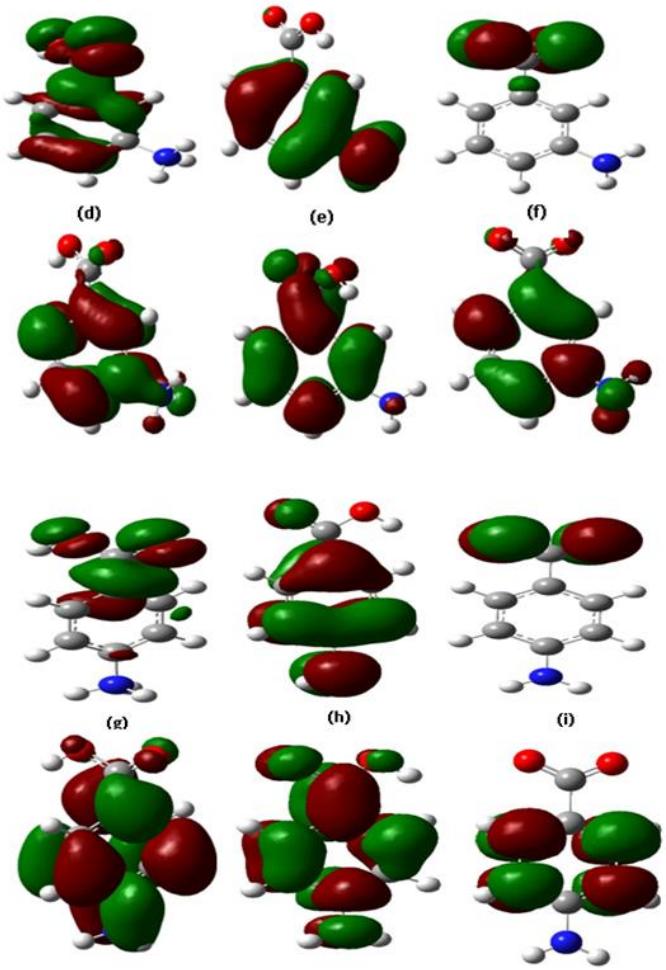



**Figure 9.** HOMO-LUMO energy structure of (d) 3ABA-MC, (e) 3ABA-N, (f) 3ABA-MA, (g) 4ABA-MC, (h) 4ABA-N and (i) 4ABA-MA.




The negative ΔH values indicated that the inclusion formations of guest with CDs are exothermic and enthalpy-driven. ΔH for MA/β-CD is more negative than the other complexes. Probably geometric factor plays a considerable role in complexation process. The negative enthalpy change (ΔH) arose from the van der Waal's interaction, while the negative entropy change (ΔS) is the steric barrier caused by molecular geometrical shape and the limit of CDs cavities to the freedom of shift and rotation of guest molecule. The calculated results indicated that the inclusion reaction of CD with neutral and dianion species of the guests were an exothermic reaction accompanied with negative ΔS.

The difference in Δ*E* and Δ*G* can be explained by the solvent effect. The experiments were conducted in aqueous medium and the computational work was done in vacuum phase. We were unable to do the computational work at the aqueous medium due to system limitations. Unfortunately because of limitations in the calculation ability of the computer and the large molecular size of CDs, calculations for these systems could not be performed for aqueous solutions and excited state. However, it is observed that the solvent effect on the host-guest interactions easily changes the inclusion reaction from a non-spontaneous process in the gas phase to a spontaneous one in the aqueous phase. The host-guest interaction causes an enthalpy-entropy compensating process in the gas phase whereas the same interaction causes an enthalpy-entropy co-driven process in aqueous solution, due to release of number of water molecules from the cavity of CD in inclusion complexation.

**Charge transfer**

The charge transfer interactions play a relevant role in the stabilization of their inclusion complexes. The Mullikan charges of the heavy atoms of all the species, charge transfer of complexes of all the species with α-CD and β-CD are summarized in Tables 1 to 3. The data show that both the CD molecules accept the electron from guests and the charge transfer of MA/α-CD is the largest of all complexes.

**The structure parameters of inclusion complexes**

All the inclusion complexes structures are shown in Figures 2 to 7. We could notice that several intermolecular H-bonds present in the guest/CD structure. Here, the H-bond is defined as C-H-O or O-H-O and the N-O-H bond length shorter than 3 Å which is close to the reported data [30]. Obviously, the hydrogen bonds of neutral/β-CD are more than that of the other complexes. This explains why the complexation energy of the inclusion neutral/β-CD is lower than the other complexes.

**Table 4:** Geometrical parameters of monocation (MC), neutral (N) and monoanion (MA) of 2ABA before and after inclusion in α- and β-CD for the most stable inclusion complexes.

| Properties | MC | | MC :α-CD | MC:β-CD | N | | N:α-CD | N:β-CD | MA | | MA: α-CD | MA:β-CD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bond length (Å) | H1-H6 | 5.89 | 5.92 | 5.91 | H1-H5 | 5.77 | 5.80 | 5.79 | H6-H2 | 5.49 | 5.51 | 5.49 |
| | H8-H3 | 5.24 | 5.26 | 5.28 | H7-H3 | 5.12 | 5.15 | 5.14 | H6-H1 | 4.65 | 4.65 | 4.65 |
| | H7-H5 | 4.30 | 4.31 | 4.33 | H6-H4 | 4.32 | 4.36 | 4.38 | H5-H3 | 4.28 | 4.28 | 4.28 |
| | O1-N1 | 4.26 | 4.24 | 4.27 | O1-N1 | 4.23 | 4.24 | 4.22 | O1-N1 | 4.22 | 4.22 | 4.22 |
| Bond angle (°) | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | O1-C4 | 5.15 | 5.13 | 5.16 | O1-C4 | 5.19 | 5.21 | 5.20 | C7-C4 | 4.34 | 4.34 | 4.34 |
| Dihedral angle (°) | O1-C7-O2 | 112 | 114 | 116 | O1-C7-O2 | 114 | 115 | 118 | O1-C7-O2 | 124 | 125 | 128 |
| | O1-C7-C1 | 124 | 125 | 122 | O1-C7-C1 | 122 | 121 | 122 | O1-C7-C1 | 117 | 119 | 120 |
| | O2-C7-C1 | 123 | 125 | 121 | O2-C7-C1 | 120 | 122 | 123 | O2-C7-C1 | 118 | 119 | 123 |
| | N1-C2-C3 | 118 | 120 | 119 | N1-C2-C3 | 119 | 121 | 118 | N1-C2-C3 | 119 | 120 | 122 |
| | O1-C7-C1-C6 | -0.00 | -0.11 | -0.15 | O1-C7-C1-C6 | -0.00 | -0.10 | -0.12 | O1-C7-C1-C6 | 0.00 | -0.10 | -0.12 |
| | O2-C7-C1-C2 | -0.01 | -0.05 | -0.08 | O2-C7-C1-C2 | -0.01 | -0.06 | -0.10 | O2-C7-C1-C2 | 0.01 | -0.06 | -0.10 |
| | N1-C2-C3-C4 | 179 | 181 | 178 | N1-C2-C3-C4 | 177 | 180 | 179 | N1-C2-C3-C4 | 180 | 181 | 179 |

**Table 5** Geometrical parameters of monocation (MC), neutral (N) and monoanion (MA) of 3ABA before and after inclusion in α- and β-CD for the most stable inclusion complexes.

| Properties | MC | | MC: α-CD | MC:β-CD | N | | N:α-CD | N:β-CD | MA | | MA:α-CD | MA:β-CD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bond length (Å) | H1-H5 | 5.79 | 5.81 | 5.83 | H1-H5 | 5.54 | 5.56 | 5.58 | H1-H6 | 4.28 | 4.29 | 4.28 |
| | H8-H2 | 4.31 | 4.32 | 4.30 | H7-H2 | 4.31 | 4.33 | 4.30 | H5-H3 | 4.68 | 4.70 | 4.72 |
| | H7-H4 | 5.01 | 5.00 | 4.98 | H6-H3 | 5.40 | 5.45 | 5.43 | O1-H4 | 6.13 | 6.16 | 6.19 |
| | O1-N1 | 6.01 | 6.03 | 6.05 | O1-N1 | 5.93 | 5.91 | 5.95 | O1-N1 | 6.02 | 6.11 | 6.14 |
| | C7-C4 | 4.27 | 4.29 | 4.30 | C5-N1 | 3.70 | 3.73 | 3.72 | C7-C4 | 4.34 | 4.36 | 4.33 |
| Bond angle (°) | O1-C7-O2 | 123 | 126 | 125 | O1-C7-O2 | 123 | 120 | 121 | O1-C7-O2 | 123 | 124 | 126 |
| | O1-C7-C1 | 125 | 127 | 120 | O1-C7-C1 | 123 | 125 | 127 | O1-C7-C1 | 118 | 120 | 122 |
| | O2-C7-C1 | 120 | 118 | 122 | O2-C7-C1 | 112 | 121 | 122 | O2-C7-C1 | 118 | 119 | 120 |
| | N1-C3-C4 | 119 | 120 | 122 | N1-C3-C4 | 120 | 119 | 122 | N1-C3-C4 | 119 | 120 | 121 |
| Dihedral angle (°) | O1-C7-C1-C6 | -32 | -30 | -28 | O1-C7-C1-C6 | -45 | -52 | -54 | O1-C7-C1-C6 | 33 | 36 | 40 |
| | O2-C7-C1-C2 | -26 | -20 | -24 | O2-C7-C1-C2 | -42 | -48 | -52 | O2-C7-C1-C2 | 33 | 35 | 36 |
| | N1-C3-C2-C1 | -179 | -0.00 | -0.02 | N1-C3-C2-C1 | -173 | -175 | -178 | N1-C3-C2-C1 | -176 | -180 | -183 |
| | N1-C3-C4-C5 | 178 | 180 | 181 | N1-C3-C4-C5 | 174 | 176 | 176 | N1-C3-C4-C5 | 176 | 178 | 178 |

**Table 6:** Geometrical parameters of monocation (MC), neutral (N) and monoanion (MA) of 4ABA before and after inclusion in α- and β-CD for the most stable inclusion complexes.

| Properties | MC | | MC :α-CD | MC :β-CD | N | | N:α-CD | N:β-CD | MA | | MA:α-CD | MA :β-CD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bond length (Å) | H1-H5 | 6.81 | 6.83 | 6.85 | H1-H4 | 6.40 | 6.42 | 6.44 | H1-H6 | 4.28 | 4.30 | 4.34 |
| | H2-H8 | 4.32 | 4.30 | 4.34 | H7-H2 | 4.31 | 4.34 | 4.37 | H5-H2 | 4.33 | 4.34 | 4.37 |
| | H3-H7 | 4.36 | 4.37 | 4.39 | H6-H3 | 4.34 | 4.36 | 4.39 | O1-N1 | 6.45 | 6.47 | 6.50 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | O1-N1 | 6.49 | 6.52 | 6.54 | O1-N1 | 6.48 | 6.50 | 6.53 | C7-C4 | 4.33 | 4.34 | 4.32 |
| | C7-C4 | 4.27 | 4.28 | 4.28 | C7-C4 | 4.27 | 4.29 | 4.30 | C1-C4 | 2.80 | 2.84 | 2.84 |
| Bond angle (°) | O1-C7-O2 | 112 | 116 | 117 | O1-C7-O2 | 110 | 112 | 115 | O1-C7-O2 | 110 | 113 | 114 |
| | O1-C7-C1 | 125 | 126 | 129 | O1-C7-C1 | 121 | 122 | 124 | O1-C7-C1 | 121 | 123 | 126 |
| | N1-C4-C5 | 119 | 121 | 124 | N1-C4-C5 | 120 | 118 | 119 | N1-C4-C5 | 120 | 120 | 120 |
| | N1-C4-C3 | 119 | 120 | 124 | N1-C4-C3 | 120 | 122 | 124 | N1-C4-C3 | 120 | 123 | 124 |
| Dihedral angle (°) | O1-C7-C1-C6 | -51 | -54 | -57 | O1-C7-C1-C6 | -51 | -54 | -56 | O1-C7-C1-C6 | -51 | -60 | -65 |
| | O2-C7-C1-C2 | -53 | -58 | -61 | O2-C7-C1-C2 | -53 | -50 | -55 | O2-C7-C1-C2 | -53 | -56 | -61 |
| | N1-C4-C3-C2 | 179 | 180 | 182 | N1-C4-C3-C2 | 179 | 181 | 183 | N1-C4-C3-C2 | 179 | 182 | 182 |
| | N1-C4-C5-C6 | -178 | -179 | -179 | N1-C4-C5-C6 | -178 | -182 | -185 | N1-C4-C5-C6 | -178 | -180 | -181 |

Tables 4 to 6 present the most interesting bond distances, bond angles and dihedral angles of the both guests before and after complexation in a-CD and β-CD obtained from PM3 calculations for the most stable structure. It was evident that after complexation, the geometry of the guests was completely altered. The alterations were significant in dihedral angles, which indicated that the guests adopted a specific conformation to form a stable complex. According to the results obtained in Tables, we can see that no significant correlation observed in the inclusion complexes confirmed that the structure of all the ABAs inclusion complex species in the CDs cavities was different from others.

## Conclusion

The stable structures and the inclusion process for neutral, monoanion and dianion species of 2ABA, 3ABA, and 4-ABA with a-CD and β-CD inclusion complexes were studied by PM3 method. From the computational study we find that (i) all the three ABAs were fully encapsulated into the CDs cavities, (ii) the negative Gibbs energy and enthalpy changes for the inclusion complexes indicated that the formation of these complexes is spontaneous and exothermic, (iii) hydrogen bonding interactions played a major role in the ABA:CD inclusion process, (iv) the dipole moment values for drugs increased when they entered into the CDs cavities which is an indication of the increase of the polarity and the formation of complex, (v) the computational results indicated that the formation of all the inclusion complexes were enthalpy driven process and (vi) the structure of all the ABAs inclusion complex species in the CD cavities was different from others.

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**REFERENCES**


1. L. Szente, J. Szejtli, Adv. Drug Deliv. Rev. 36 (1999) 17.
2. D.O. Thompson, Critical Reviews in Therapeutic Drug Carrier Systems, 14 (1997) 1.
3. K. Uekama, F. Hirayama, T. Irie, Chem. Rev. 98 (1998) 2045.
4. T. Loftsson, M. Brewster, J. Pharm. Sci. 85 (1996) 1017.
5. T. Loftsson, H. Fridriksdo´ttir, A.M. Sigurdardo´ttir, H. Ueda, Int. J. Pharm. 110 (1994) 169.
6. G. Ganzerli, L. van Santvliet, E. Verschuren, A. Ludwig, Pharmazie 51 (1996) 357.
7. E. Fenyvesi, M. Vikmon, J. Szeman, J. Szejtli, P. Ventura, M. Pasini, in: T. Osa (Ed.), Proceedings of Seventh International Symposium on Cyclodextrins, Academic Society of Japan, (1994) 414.
8. M. Vikmon, J. Szeman, J. Szejtli, M. Pasini, E. Redenti, P. Ventura, in: T. Osa (Ed.), Proceedings of Seventh International Symposium on Cyclodextrins, Academic Society of Japan, (1994) 480.
9. M.T. Esclusa-Diaz, M. Gayo-Otero, M.B. Pe´rez-Marcos, J.L. Vila-Jato, J.J. Torres-Labandeira, Int. J. Pharm. 142 (1996) 183.
10. P. Mura, M.T. Faucci, A. Manderioli, G. Bramanti, J. Incl. Phenom. 39 (2001) 131.
11. E. Redenti, L. Szente, J. Szejtli, J. Pharm. Sci. 89 (2000) 1.
12. G. Piel, B. Pirotte, I. Delneuville, P. Neven, G. Llabres, J. Elargı`, L. Delatore, J. Pharm. Sci. 86 (1997) 475.
13. M. Vikmon, I. Kolbe, J. Szejtli, E. Redenti, P. Ventura, in: J.J. Torres Labandeira, J.L. Vila Jato (Eds.), Proceedings of Ninth International Symposium on Cyclodextrins, Kluwer, Dordecht, (1999) 281.
14. E. Redenti, L. Szente, J. Szejtli, J. Pharm. Sci. 90 (2001) 979.
15. S. Gouin, Trends in Food Science and Technology, 15 (2004) 330.
16. B.L. Zeller, F.Z. Saleeb, R.D. Ludescher, Trends in Food Science and Technology, 9 (1999) 389.
17. P.M.M. Schrooyen, R. van der Meer, C.G. De Kruif, Proceedings of the Nutrition Society, 60 (2001) 475. Antony Muthu Prabhu, and N. Rajendiran, J. Indian Chem Soc. 90 (2013) 1127.
18. G. Venkatesh, T. Sivasankar, M. Karthick, N. Rajendiran, J Incl Phenom Macrocycl Chem., 77 (2013) 309.
19. M. Jude Jenita, A. Antony Muthu Prabhu & N. Rajendiran, Ind. J. Chem. 51A (2012) 1686.
20. N. Rajendiran, G. Venkatesh, Supramolecular Chemistry, 26(2014) 783. Antony Muthu Prabhu & N. Rajendiran, J Fluoresc, 22 (2012) 1461.
21. T. Sivasankar, A. Antony Muthu Prabhu, N. Rajendiran, J Mol Struc., 1028 (2012) 57.
22. R.K. Sankaranarayanan and N. Rajendiran, J. Experimental Nanoscience, 10 (2015) 407
23. L. Liu, Q.X. Guo, J. Incl. Phenom. Macrocycl. Chem. 50 (2004) 95.
24. A.A. Rafati, S.M. Hashemianzadeh, Z.B. Nojini, M.A. Safarpour, J. Mol. Liqs. 135 (2007) 153.
25. R. Castro, M.J. Berardi, E. Cordova, M.O. de Olza, A.E. Kaifer, J.D. Evanseck, J. Am. Chem. Soc. 118 (1996) 10257. Antony Muthu Prabhu, G. Venkatesh, N. Rajendiran, J Fluoresc, 20 (2010) 1199.
26. R.K. Sankaranarayanan, A. Antony Muthu Prabhu, N. Rajendiran, J. Mol. Liqs. 161 (2011) 107.