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HOST- GUEST INTERACTION OF 3-(4-CHLOROPHENYL)-1-CYCLOPROPYL-2-(2-FLUOROPHENYL)-5-(4-FLUOROPHENYL) PENTANE-1, 5-DIONE: B-CYCLODEXTRIN INCLUSION COMPLEX

T. R. Ragi*, H. Manikandan & K. Sivakumar***
* Department of Chemistry, Faculty of Science, Sri Chandrasekharendra Saraswathi Viswa Mahavidyalaya University Enathur, Kanchipuram, Tamilnadu
** Department of Chemistry, Annamalai University, Annamalainagar, Tamilnadu

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Abstract:
The inclusion complex of 3-(4-chlorophenyl)-1-cyclopropyl-2-(2-fluorophenyl)-5-(4-fluorophenyl) pentane-1, 5-dione (CFPD) and β-Cyclodextrin (β-CD) has been investigated using UV and fluorescence spectroscopic techniques. The binding constant and 1:1 stoichiometry of the inclusion complex were determined using Benesi- Hildebrand plots. 1:1 stoichiometry for CFPD: β-CD has been confirmed by Job's plot. The thermodynamic parameter (ΔG) of inclusion process was determined. The formation of the inclusion complex between CFPD and β-CD, was further confirmed by molecular docking studies are in good relationship with the results obtained through experimental methods.

Key Words: Benesi-Hildebrand Plot, Beta-Cyclodextrin, Inclusion Complex, Supramolecular Chemistry, 3-(4-Chlorophenyl)-1-Cyclopropyl-2-(2-Fluorophenyl)-5-(4-Fluorophenyl) Pentane-1 & 5-Dione.

1. Introduction:

Cyclodextrins are cyclic glucose oligosaccharides. It mainlyconsists of α-D-glucopyranose units. In number of fields, β-CD is used than α and γ CDs. Cyclodextrin have ability to complexes with hydrophobic compounds, becauseinner part ofis hydrophobic and outer is hydrophilic. The solubility of hydrophobic compounds is increased by this binding with cyclodextrin. Due to the ability of cyclodextrins to form host-guest complexes with hydrophobic molecules, they have to be used in different industries. They are used in food industry [1], pharmaceuticl field [2], biomedical [3], textile [4] field etc.

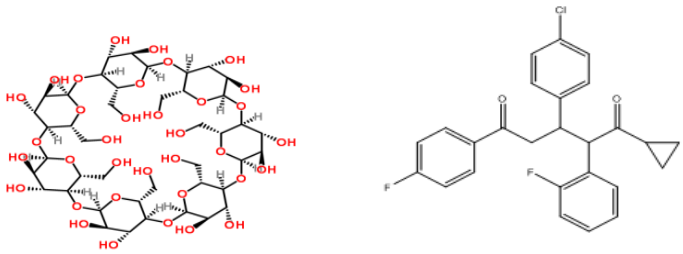

Figure 1: Chemical structure of (a) β-Cyclodextrin and (b) CFPD

CFPD is a diketone. Diketonesare mainly used in organic synthesis. Also they exhibit antioxidants, antitumor and antibacterial activities [5]. For the preparation of various heterocyclic compounds dike tones are key intermediate [6].In this paper, we report the complexation of CFPD and β-CD in liquid state and virtual state.

2. Materials and Methods:

2.1 Reagents: β-Cyclodextrin (β-CD) was obtained from HiMedia Laboratories Pvt. Ltd. and used without further purification. Triply distilled water was used to prepare all solutions. CFPD was obtained by stirring acetophenone, 4-chlorobenzaldehyde, cyclopropyl 2-fluorobenzyl ketone and sodium hydroxide solution in ethanol for 3 hrs at room temperature[7].

2.2 β-Cyclodextrins Solution Preparation: 1×10^{-4} mol dm^{-3} concentration of stock solution of CFPD was prepared using methanol and 0.2 ml of this stock solution were added into 10 ml volumetric flasks and made up to the mark using following concentration of β-CD solutions 0, 2, 4, 6, 8, 10, 12, 14 and 16×10^{-3} mol dm^{-3} respectively and shaken thoroughly. All the spectra were recorded at 30±1°C.

2.3 Determination of Stoichiometry of Inclusion Complex by Job's Method: One of the first methods used for the determination of the stoichiometry of inclusion complex was Job's method also known as the continuous variation method [8].The experiment was carried out using stock solutions with equimolecular concentrations of β-CD and CFPD. The samples were prepared by mixing different volume of these two solutions in such a way that the total concentration of [CFPD] and [β -CD] remains constant and the molar fraction of the guest X_{CFPD} varies in the range of 0-1. The variation of the experimental measurement properties, ΔA and ΔI in presence of the host with respect to the value of free guest is plotted against X_{CFPD}. Absorbance was recorded at different molar ratios by using UV and fluorescence spectrophotometer.

2.4 Instruments: The UV spectra were recorded with Specord 200 plus, Germany. The Fluorescence spectra were recorded using Spectrofluorometer, Perkin Elmer, USA. The absorbance and fluorescence were measured in 1 cm path length quartz cells. The measurements were taken 1–2 min after preparing the solution at 30±1 °C.

2.5 Molecular Docking Study: The most probable structure of the CFPD: β-CD inclusion complex was determined also by molecular docking studies using the Patch Dock server [9] and Cyclo Predict server [10]. The 3D structural data of β-CD and were obtained from crystallographic databases.

3. Results and Discussions:

3.1 Effect of β-CD: The absorbance intensity of increases regularly upon raise in the β-CD concentration from 0 to 16 x 10^{-3}M [Fig.2]. In general, the consistent variation in the intensity of UV spectra on increase in the concentration of β-CD is assigned to the enhanced dissolution and inclusion of molecule into the non-polar cavity of β-CD through hydrophobic interaction. In the inclusion complex formed between host and guest (CFPD: β-CD), the equilibrium can be written as,

$$CFPD + \beta - \mathrm{CD} \overset{K}{\longleftrightarrow} CFPD.....\beta - \mathrm{CD} \qquad (1)$$

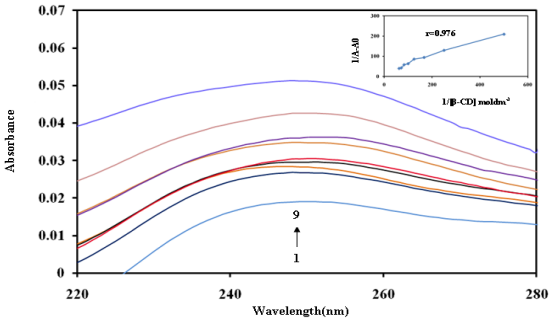

Figure 2: The absorption spectra of CFPD (10^{-4} M) in different β-CD (M): (1) 0.0; (2) 0.002;(3)0.004; (4) 0.006; (5) 0.008; (6) 0.010; (7) 0.012;(8)0.014 and (9)0.016M. Inset: Benesi Hildebrand plot of 1/A-A0 VS. 1/ [β-CD] for CFPD in distilled water.

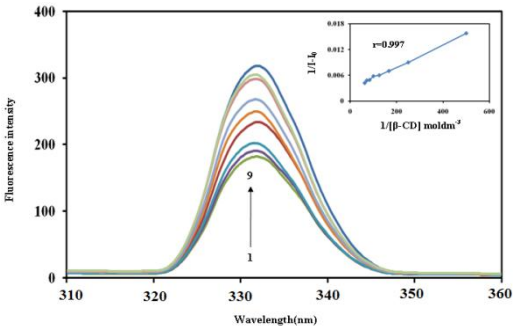

Figure 3: The fluorescence spectra of CFPD (10^{-4} M) in different β-CD concentrations (M):(1) 0.0; (2) 0.002; (3) 0.004; (4)0.006; (5) 0.008; (6) 0.010; (7)0.012; (8)0.014M and (9)0.016M. Inset: Benesi Hildebrand plot of1/ I-I0 VS. 1/ [β-CD] for CFPD in distilled water.

The binding constant '*K'* and stoichiometric ratios of the inclusion complex of can be determined according to the Benesi–Hildebrand [11] relation assuming the formation of a 1:1 host–guest complex.

$$\frac{1}{\mathrm{A}-\mathrm{A}_0} = \frac{1}{\Delta\varepsilon} + \frac{1}{K[CFPD]_0 \Delta\varepsilon[\beta - \mathrm{CD}]_0} \qquad (2)$$

Where, A and $A_0$is the difference between the absorbance of in the presence and absence of β-CD, $\Delta\varepsilon$ is the difference between the molar absorption coefficient of CFPD and the inclusion complex, $[\mathrm{CFPD}]_0$and $[\beta\text{-CD}]_0$ are the initial concentration of CFPD and β-CD respectively. The inset of Fig.2 depicts the plot of $1/A\text{-}A_0$ vs 1/ [β-CD] for, in which a good linear correlation was obtained, confirming the formation of a 1:1 inclusion complex. From the intercept and slope values of the plot, the binding constant '*K'* evaluated as 226.26 M^{-1}. The interaction of β-CD on the fluorescence spectra of CFPD also analyzed. In the emission spectra of CFPD, [Fig.3] the fluorescence intensity increases for the variation of β-CD concentration from 0 to 16 x 10^{-3}M. These results indicate that CFPD is entrapped into the β-CD cavity to form: β-CD inclusion complex. The binding constant for the formation of complex has been determined by analyzing the changes in the intensity of emission maxima with the β-CD concentration using the Benesi- Hildebrand [11] relation assuming the formation of a 1:1 host –guest complex.

$$\frac{1}{\mathrm{I} - \mathrm{I}_0} = \frac{1}{\mathrm{I}' - \mathrm{I}_0} + \frac{1}{K\,[\mathrm{I}' - \mathrm{I}_0]\,[\beta - \mathrm{CD}]_0} \qquad (3)$$

Where, $[\beta\text{-CD}]_0$represents the initial concentration of β-CD, "I_0"and "I" are the fluorescence intensities in the absence and presence β-CD respectively, and I' is the limiting intensity of florescence. The '*K*' value was estimated from the slope and intercept of the Benesi–Hildebrand plot (inset of Fig. 3) which shows a good linear correlation supporting the assumption of 1:1CFPD: β-CD incusion complex. The binding constant '*K*' is evaluated as 244.39 M^{-1}.

Table 1: Absorption and fluorescence maxima (nm) of CFPD (1x10^{-4} M) at different concentrations of β-CD in water

S.No	Concentration of β-Cyclodextrin (M)	UV		Fluorescence	
		$\lambda_{max(nm)}$	log ε	$\lambda_{Flu\ (nm)}$	Flu. Intensity
1	0	251	2.28	334	182.17

2	0.002	250	2.44	334	190.9
3	0.004	250	2.42	333.5	202.55
4	0.006	250	2.47	333.5	234.16
5	0.008	251	2.48	333.5	249.91
6	0.010	251	2.54	333.5	268.34
7	0.012	251	2.55	333.5	298.86
8	0.014	251	2.62	333.5	305.34
9	0.016	251	2.78	333.5	318.56
Binding constant ($M^{1)}$		226.26		244.39	
ΔG (kJ mol^{-1})		-13.52		-13.71	

3.2 The Thermodynamics of Inclusion Process: The thermodynamic parameter ΔG, for the binding of guest molecule CFPD to β-CD cavity can be calculated from the binding constant '*K*' by using the following equation,

$$\Delta G = -RT \ln K$$

The thermodynamic parameter ΔG for the binding of guest molecule to β-CD cavity is given in Table 1. The negative value of ΔG suggests that the inclusion process proceeded spontaneously at 303K.

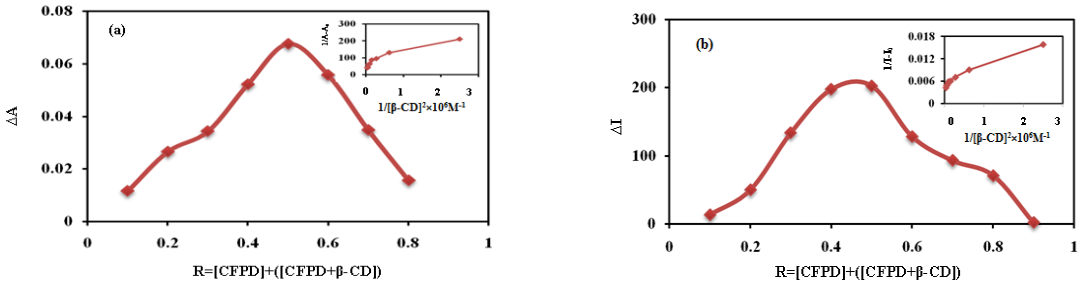

Figure 4: (a) Job's plot ΔA vs. mole fraction of CFPD with β-CD (inset:Benensi-Hildebrand fluorescence plot of 1/ [A-A_0] against 1/ [β- CD] ^{2}for CFPD). (b) Job's plot ΔI vs. molefraction of CFPD with β-CD (inset:Benensi-Hildebrand fluorescence plot of 1/ [I-I_0] against 1/ [β- CD] ^{2}for CFPD).

3.3 Job's Plot: The stoichiometry of the inclusion complex of CFPD and β-CD is further confirmed by Job's continuous variation method. Figure 4 shows the change in absorbance and fluorescence against mole fraction of CFPD. In the case of 1:1 inclusion complex the maximum deviation will be observed for mole fraction 0.5 [12]. As shown in Job's plot, the peak maximum is obtained at mole fraction 0.5 which indicates that the inclusion complex between CFPD and β-CD has 1:1stoichiometry.The plot of 1/ [A-Ao] and 1/ [I-Io] Vs 1/ [β-CD] ^{2} reveal a non-linear correlation as shown in Fig. 4(inset) indicating that CFPD: β-CD complex does not possess 1:2 stoichiometries.

3.4 Molecular Docking Study of Inclusion Process: The 3D structure of β-CD and CFPD obtained from crystallographic databases are shown in Scheme 1a and 1b. The guest molecule, CFPD was docked into the cavity of β-CD using Patch Dock server. The Patch Dock server program gave several possible docked models for the most probable structure based on the energetic parameters; geometric shape complementarity score [13], approximate interface area size and atomic contact energy [14] of the CFPD: β-CD inclusion complex. The docked CFPD: β-CD 1:1 model Scheme 1 with the highest geometric shape complementarity score 4622, approximate interface area size of the complex 566.2 Å^{2}and atomic contact energy -353.38 kcal/mol was the highly probable and energetically favorable model as shown in Scheme 1.

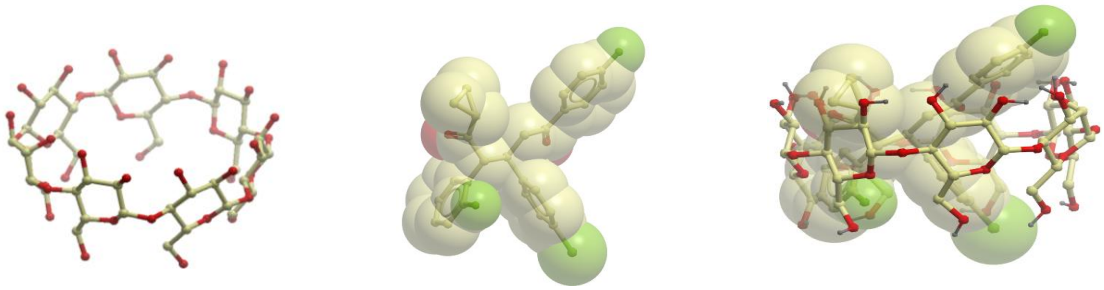

Figure 5: Ball and stick representation of (a) β-CD (b) CFPD (c) CFPD: β-CD inclusion complex.

4. Conclusion:

The inclusion complex formation between CFPD and β-cyclodextrin was investigated in liquid and virtual states. The binding constants of the complex were estimated using UV-Visible and fluorescence spectral

analysis. The 1:1 stoichiometry of the complex was determined by Benesi- Hildebrand plots and further confirmed by Job's plot. Molecular docking was used as supporting evidences for the results observed from the experimental analysis.

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