Schiff base – Cyclodextrins inclusion complexes

Jabbar Saleh Hadi and Ayat Abdul-Kadhim

Department of Chemistry, College of Education for Pure Science, University of Basrah, Basrah, Iraq

E-mail: jshalkabi2@gmail.com

Abstract. A Schiff base derived from the condensation of indole-3-carboxaldehyde with sulfathiazole was prepared, and used to prepare three inclusion complexes with -CD, 2HP-CD and 2HP-CD by freeze drying method, the formation of Schiff base and the nature of interaction with CDs were confirmed by IR, HNMR and XRD. The phase solubility of Schiff base in -CD and 2HP-CD were studied following Higuchi and Connors method, the stability constant value of complexes and the solubilization efficiency were estimated.

Keywords: Schiff base, Inclusion complex, XRD, Phase solubility

1. Introduction

Cyclodextrins are cyclic oligosaccharides consist of -D-glucopyranose units which are connected via 1 and 4 carbon atom. One of the most CDs that are used to inclusion complexes formation are , and . These three type of CDs are widely used as a host for a wide range of drugs as well as other chemical compounds as a guest molecules . The inclusion complexes or host-guest systems formed without covalent bond, the derivad forces between guest molecules and the hydrophopic cavity of CDs are vander weals forces electrostatic interaction and hydrogen bonding most of physical properties of the guest molecules will be modified and in most cases often improve and helps in many application.

2. Materials and Methods

Materials: Sulfathiazole was obtained from sigma company, indole-3-carboxaldehyde was obtained from Himedia company, 2HP-CD and 2HP-CD were purchased from Synonym, HGC company. -CD was purchased from Across organic chemical company. All starting material employed in synthesis used as received. All solvent employed in synthesis were of extra –pure grade and used as received without further purification.

Instrument and spectral measurements: Melting point was recorded by Thermo fisher instrument and uncorrected using open capillary tube. TLC plant type Silicagel 60 F254 (Aluminum) was to monitor the reaction. FT-IR spectra were recorded by using Shimadzu FTIR-8300 spectrophotometer in the region 4000–400 cm⁻¹ in KBr disc. HNMR spectra were scanned on a zzzzBrucher (400 MHz) in DMSO-d₆ as a solvent and TMS as internal reference. XRD patterns were record on Philips X, Pertrpo diffractometer.
using Cu K radiation (λ=1.54060 Å) and analyzed from 2θ (5-50°). Uv-visible spectra were recorded by T × 80, uv-vis spectrophotometer in the range 190–900 nm.

3. Synthesis of 4-((1H-indol-3-yl)methylene amino)-N-(thiazol-2-yl) benzene sulfonamide (A2)

![Image of the title Schiff base]

The title Schiff base was prepared from the condensation of indole-3-carboxaldehyde and sulfathiazole. 1.25g (5mmole) of sulfathiazole in 50 ml of absolute ethanol was gently heated until totally dissolved, then 0.725 gm of aldehyde was dissolved in 10ml of ethanol and drop wise, and 2 drops of conc H₂SO₄ added to the mixture, the mixture was refluxed, the reaction mixture was monitored by TLC using ethylacetate :Chloroform (7:3) as eluent until the reaction complete (1-8 hrs), then the yellow precipitate which formed filtered with cold ethanol, and dried, m.p 257°Gd yield 70% (Rf =0.54).

Preparation of inclusion complexes: The general procedure were following to prepare to the inclusion complexes of Schiff base with three type of cyclodextrins namely -CD, 2HP- -CD and 2HP- -CD.

A solutions of Schiff base with CD (1:1 molar ratio ) were transferred to conical flask containing 25 ml deionized water. The resulting solutions were stirred at room temperature for 3 days, then the solution were filtered freezing and then lyophilized in a freeze drying (CHRIST, model alpha 1-2 LD plus). The resulting powder were kept in disecator over silica gel.

4. Results and discussion

(Fig 1a) show the FT-IR spectrum of Schiff base (A2) where the characteristic strong band at 1656.85 cm⁻¹ which attributed to azomethine group C= N, and another strong band at 1585.49 cm⁻¹ which attributed to stretching vibration of C=N of thaizole moiety (8). The bands at 1541.2, 1533.41, 1521 and 1494.83 cm⁻¹ which attributed to skeleton C= C of aromatic ring, another two very bands at 1350.17 cm⁻¹ and 1145.72 cm⁻¹ attributed to asym and sym stretching vibration of O=S=O group, the very strong band at 923.9 cm⁻¹ attributed to S-N and medium at 848.6 cm⁻¹ attributed to C-S (9,8).

(Fig 1 b,c,d) shows the FT-IR spectra of prepared inclusion complexes, it can be seen a significant changed in the position and intensity of the band attributed to the functional groups as shown in (Table 1,2,4), where the band of azomethine shifted to lower frequency in all complexes spectra. The other position and intensity of aromatic C=C, O=S=O, S-N and C-S are significantly changed, this result indicated the totally incapsulated of Schiff base in the hydrophobic cavity of all CDs (3,4,10).
(Fig 1) FT-IR spectra of

a: A2  b: A2+ CD  c: A2+2HP- CD  d: A2+2HP- CD
### (Table 1) IR data and the changes in wavenumber in cm$^{-1}$ (A2-CD)

| band                  | B-CD (cm$^{-1}$) | A$_2$ free (cm$^{-1}$) | Complex$_{A2+β-CD}$ (cm$^{-1}$) | Δυ (cm$^{-1}$) |
|-----------------------|------------------|------------------------|----------------------------------|---------------|
| OH                    | 3365.78          | 3352.28                | 3352.28                          | -13.52        |
| N-H                   | 3442.94          |                        |                                  |               |
| C=N azomethine        | 1656.85          | 1639.49                | 1639.49                          | -17.36        |
| OH$_{bending}$        | 1639.49          | 2931.80                | 2929.87                          | -1.93         |
| C-H                   | 2931.80          | 2929.87                |                                  |               |
| O=S=O asy             | 1350.17          | 1330.88                | 1330.88                          | -19.29        |
| O=S=O sym             | 1145.72          | 1153.43                | 1153.43                          | 7.71          |
| C=C                   | 1533.41          | 1523.76                | 1523.76                          | -9.65         |
| S-N                   | 1494.83          | 1425.40                | 1425.40                          | -69.43        |
| C=N thiazole          | 1585.49          | 1577.77                | 1577.77                          | -7.72         |
| S-N                   | 923.90           | 941.26                 | 941.26                           | 17.36         |

### (Table 2) IR data and the changes in wavenumber in cm$^{-1}$ (A2-2HP-CD)

| band                  | 2HP-γCD (cm$^{-1}$) | A$_2$ free (cm$^{-1}$) | Complex$_{A2+2HP-γCD}$ (cm$^{-1}$) | Δυ (cm$^{-1}$) |
|-----------------------|---------------------|------------------------|------------------------------------|---------------|
| OH                    | 3375.43             | 3394.72                | 3394.72                            | -19.28        |
| N-H                   | 3342.94             |                        |                                    |               |
| C=N azomethine        | 1656.85             | 1641.42                | 1641.42                            | -15.43        |
| OH$_{bending}$        | 1639.49             | 2931.80                | 2929.87                            | -1.93         |
| C-H                   | 2931.80             | 2929.87                |                                    |               |
| O=S=O asy             | 1350.17             | 1332.81                | 1332.81                            | -17.30        |
| O=S=O sym             | 1145.72             | 1151.50                | 1151.50                            | 5.78          |
| C=C                   | 1533.41             | 1529.55                | 1529.55                            | -7.86         |
| S-N                   | 1521.84             | 1421.54                | 1421.54                            | -100.30       |
| S-N                   | 1494.83             | 941.26                 | 941.26                             | 17.36         |

### (Table 3) IR data and the changes in wavenumber in cm$^{-1}$ (A2-2HP-βCD)

| band                  | 2HP-βCD (cm$^{-1}$) | A$_2$ free (cm$^{-1}$) | Complex$_{A2+2HP-βCD}$ (cm$^{-1}$) | Δυ (cm$^{-1}$) |
|-----------------------|---------------------|------------------------|------------------------------------|---------------|
| OH                    | 3363.86             | 3392.79                | 3392.79                            | -27.93        |
| N-H                   | 3442.94             |                        |                                    |               |
| C=N azomethine        | 1656.85             | 1637.56                | 1637.56                            | -19.29        |
| OH$_{bending}$        | 1637.56             | 2931.80                | 2931.80                            | -1.93         |
| C-H                   | 2931.80             | 2929.87                |                                    |               |
| O=S=O asy             | 1350.17             | 1330.88                | 1330.88                            | -19.29        |
| O=S=O sym             | 1145.72             | 1151.50                | 1151.50                            | 5.78          |
| C=C                   | 1533.41             | 1529.55                | 1529.55                            | -7.86         |
| C=N thiazole          | 1585.49             | 1577.77                | 1577.77                            | -7.72         |
| S-N                   | 923.90              | 935.48                 | 935.48                             | 11.58         |
The HNMR spectrum of A2 (Fig 2a) show a signal at 8.38 ppm attributed to azomethine proton which indicated the formation of Schiff base. Also a signals at 10.017 ppm attributed to NH indole moiety, a singlet at 12.229 ppm attributed to NH of SO$_2$NH and the aromatic protons are observed the rang 6.66 - 8.164 ppm.

Complexation of A2 (Fig 2b) with -CD resulted in the shifted of H3 and H5 located in the hydrophobic cavity of -CD to highfield ( -0.272 ppm) and -0.299 ppm respectively which indicated the complex formation.

While the complexation of A2 (Fig 2c) with 2HP- -CD the H3 and H5 shifted to down field +0.05 ppm and for H5 +0.07 ppm.

Also the signal were shifted to highfield ( -0.025, -0.027 and -0.01 ppm) respectively.

A remarkable highfield of these signal the spectrum of A2-2HP- -CD (Fig 2d) were observed where the azomethine signal shifted to highfield (-0.089), the SO$_2$NH proton signal shifted to highfield -0.073 and NH indole signal also shifted (-0.07).

Which may indicated that all these protons either deeply located into central cavity of 2HP- -CD or this protons are close to host atoms rich with electrons. All signal of A2 which attributed to aromatic protons are shifted in most cases to highfield the results are tabulated in (Table 4) which indicated the included in the cavity of CDs.
XRD

The formation of inclusion complexes between free Schiff base and cyclodextrin were confirmed by a comparative analysis of the diffractograms where the XRD pattern of free Schiff base (Figure 3a) shows an intense peak at 2θ =17.1, 18.75, 23.95 which indicated the crystallite structure of free Schiff base (A2). While the XRD of Schiff base-CD (Figure 3b) is characterized by diffraction peaks at 2θ = (8.45), (11.5), (11.55), (12.25), (17.75), (18.75) and intense peak at 17.7, which is not presented in free Schiff base and free-CD XRD patterns. This result confirms the formation of inclusion complexes. 

(Table 4) Chemical shift changes for aromatic region

|       | A2     | A2-CD  | A2-2HP-CD | A2-2HP-CD |
|-------|--------|--------|-----------|-----------|
| a     | 8.16   | 8.09   | 8.15      | 8.09      |
| b     | 6.95   | 6.75   | 6.94      | 6.75      |
| c     | 7.29   | 7.20   | 7.28      | 7.26      |
| d     | 7.38   | 7.29   | 7.30      | 7.29      |
| e     | 7.59   | 7.68   | 7.57      | 7.45      |
| f     | 7.35   | 7.46   | 7.51      | 7.51      |
| g     | 7.74   | 7.98   | 7.73      | 7.97      |
| h     | 6.83   | 6.88   | 6.82      | 6.88      |
| i     | 7.21   | 7.24   | 7.26      | 7.20      |

The formation of inclusion complexes between free Schiff base and cyclodextrin were confirmed by a comparative analysis of the diffractograms where the XRD pattern of free Schiff base (Figure 3a) shows an intense peak at \( \theta =17.1, 18.75, 23.95 \) which indicated the crystallite structure of free Schiff base (A2). While the XRD of Schiff base-CD (Figure 3b) is characterized by diffraction peaks at \( \theta = (8.45), (11.5), (11.55), (12.25), (17.75), (18.75) \) and intense peak at 17.7, which is not presented in free Schiff base and free-CD XRD patterns. This result confirms the formation of inclusion complexes. 

(Fig 2) ¹H NMR spectra of

(a) A2
(b) A2+ CD
(c) A2+2HP- CD
(d) A2+2HP- CD
The XRD patterns of Schiff base -2HP-CD (Fig 3c) and Schiff base -2HP-CD (Fig 3d) shows a broad diffraction peak, which indicated the amorphous (19,20,21).
Phase solubility studied

Phase solubility of A2 in cyclodextrins were carried out following Higuchi and Connors procedure \(^{(22)}\). Different concentration of CDs were prepared ranging (0, 1, 3, 6, 9, 12) \(\times 10^{-3}\) mM in deionized water. Excess of A2 (50 mg) were added to 50 ml of each concentration in a conical flask and the mixture the equilibrium solution were filtered (whatman N0.1) and the absorbance of each solution was measured after suitable dilution at \(\lambda_{\text{max}}\). The stability constant was calculated from the relation \(^{(6,23,24)}\).

\[
K_c = \frac{\text{slope}}{S_0(1 - \text{slope})}
\]

Where \(S_0\) is the solubility of A2 in water.

The solubility of A2 in -CD is shown in (Fig 4) it can be seen that the A2 solubility increase linearly with conc of -CD and classified as A\(_1\) type \(^{(25,22)}\). The value of \(K(379.8 \text{ M}^{-1})\) indicate the formation of 1:1 complex. The solubility increase by 4.5 folds, the same behavior was observed when 2HP- -CD used (Fig 5 and table 5) but the solubility of A2 increase by 11.4 folds and the stability constant was found to be 841.26 M\(^{-1}\) which confirm the high stability of the 2HP- -CD-A2 complex.

(Fig 4) : phase solubility diagram of A2- CD

(Fig 5) : Phase solubility diagram of A2 in 2HP- CD
(Fig 6): UV Spectra of A2 in different conc. of -CD

(Table 5): phase solubility data of A2

| CD          | S₀  | Sₘₐₓ | Kc  | Slope | Solubilization efficiency |
|-------------|-----|------|-----|-------|----------------------------|
| -CD         | 48  | 263  | 379.8 | 0.045 | 5.4                        |
| 2HP- -CD    | 48  | 549  | 841.26 | 0.091 | 11.4                       |

Conclusion

The totally encapsulation of Schiff base with CDs were confirmed from the IR and HNMR date. A remarkable changes of XRD patterns of the free Schiff base and CDs were observed and the nature of crystallinity were observed and in some case the complex show a morphous nature.

Schiff base increased linearly and classefied as A₁ type . and the value of stability constant indicate the 1:1 molar ratio .

References

[1] M.Rahouan and A.Raoudh : *Int.J.Advanced Research*, 3(2), 1030-1030 (2015).
[2] Ramnik Singh , Nitin Bharti , Jyotsana Madan and S. N. Hiremath : *J. of Pharmaceutical Science and Technology*, 2(3),pp171183,(2010).
[3] A.Farces , N.Jarroux , A-M.Farcas , V.Harabagiu and P.Guegan : *Digest Journal of Nanomaterials and Biostructures*, 1(2) , 55-60 (2006).
[4] P. S. Kavirajaa , M .Sharifah , M. S. Norazilawlati and N. A. Ismail : *Int. J. Mol. Sci* , 14 , 3671-3682 (2013).
[5] katageri Akshay R and Sheikh Mohsin A : *Int. Research Journal of Pharmacy*, 3(1) ,52-56 (2012).
[6] Sanjoy Kumar Das, Rajan Rajabalaya, Sheba David, Nasimul Gani, Jasmina Khanam and Arunabha Nanda: *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 4(2), 1694-1720 (2013).

[7] Zeynep Aytac, Huseyin Sener Sen, Engin Durgun and Tamer Uyar: *Colloids and Surfaces B: Biointerfaces*, 128, 331 – 338 (2015).

[8] 8-H. Ebrahimi, J. S. Hadi, A. A. Almayah, Z. Bolondnazar, A. G. Swadi and A. P. Ebrahimi: *Bioorganic and Medicinal Chemistry*, 24, 1121-1131 (2016).

[9] J. S. Hadi and H. M. Jarallah: *Res. J. of Pharmaceutical Biological and Chemical Sciences*, 4 (1), 292-301 (2013).

[10] Keith Gerald Flood: *Ph.D. Thesis*, Seton Hall University, (2000).

[11] H. M. Parekh and M. N. Patel: *Russian J. Coordination Chem*, Vol 32, pp 431 (2006).

[12] A. A. Jarrahpour and M. Zarei: *Molbank*, 376 (2004).

[13] J. S. Hadi and B. K. Alsalami: *National Journal Chemistry*, 184(2), (2008).

[14] Charles J. Pouchert: *The Aldrich Library of NMR Spectra*, edition II, Vol. ii, (1983).

[15] J. Turczan and T. Medwick: *J. of Pharm. Sci.*, 61(3), pp 434-443 (1972).

[16] J. Jablan, T. Weitner, M. Gabricevic and M. Jug: *Croat. Chem. Acta*, 84 (2), pp 169-178 (2011).

[17] M. A. S. Pires, R. A. S. dos Santos and R. D. Sinisterra: *Int. J. of ChemTech Research*, 16, 4482-4499 (2011).

[18] Zaibunnisa A.H., Siti Rashima R, and Nur Ain A.H: *International Conference on Biotechnology and Food Science*, Vol 7, (2011).

[19] 20-Shujing Li, Li Yuan, Yong Chen, Wei Zhou, and Xinrui Wang: *Molecules*, 22, 2183 (2017).

[20] V. Nikolic, L. Nikolic, S. Mihajlo, A. Kapor, M. Popsavin and C. Cvetkovic: *J. Serb. Chem. Soc.*, 72(8-9), 737-746 (2007).

[21] T. Higuchi and K.A. Connors: *Adv. Anal. Chem. Instrum.*, 4, pp 117-212 (1965).

[22] S. Budavari, The Merck index: *an encyclopedia of chemicals, drugs, and biologicals, Merck and Co. Inc, Rahway, NJ*, p1409 (1989).

[23] S. Zidane, A. Maiza, H. Bouleghlem, W. Herizi, and S. Dahmani: *Int. J. of Chemical Engineering and Applications*, 7(3), (2016).

[24] Arun Rasheed, Ashok Kumar C.K and Sravanthi V: *Scientia Pharmaceutica*, 76, 567-598 (2008).