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Thermodynamic and Spectral Studies of Inclusion Complexes of Substituted Indole Derivatives with β-Cyclodextrin

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Indole and its analogous are very good pharmacophores for designing several chemotherapeutic reagents which exhibit wide spectrum of antimicrobial activities. The poor solubility of these compounds in polar medium is one of the limiting factors for better bioaccessibility of these compounds. In this work, some arylidenamino-1,3,4-thiadiazino[6,5b]indoles have been synthesized in their pure form. In order to increase the solubility of these compounds in polar medium for better pharmacological activities, inclusion complexes of arylidenamino-1,3,4-thiadiazino[6,5b]indoles with β-cyclodextrin have been prepared and their spectral and thermodynamic properties have been studied.

Key Words: Indole, Substituted indole, β-Cyclodextrin, Inclusion complex.

INTRODUCTION

Indole and its derivatives are well known for their antidepressive, antiinflammatory, antifungicidial, antibactericidial and antituberculostatic activities[1-4]. Further, azediones and thiazolidinones also show good antimicrobial activities[5-8]. Since the bio-accessibility of a compound depends upon its solubility, the poor solubility of these compounds in polar medium (in water) may be a limiting factor reducing pharmacological activities of these compounds[9]. One of the ways of enhancing solubility and bio-accessibility of the compounds is to form inclusion complexes with β-cyclodextrin that is easily available and cheaper form of cyclodextrins. β-Cyclodextrin also shows higher stability towards heat and oxidation[10-12]. In the present work an attempt has been made to synthesize some 2-[arylidenamino]-1,3,4-thiadiazino[6,5b]indoles in pure forms and then prepare their respective inclusion complexes with β-cyclodextrin. The formation of compounds and their inclusion complexes have been ascertained from elemental analysis, melting point data and study of spectral characteristics. Thermodynamics properties of the inclusion complexes are also studied to know thermodynamic stability of inclusion complexes and the type of interaction in between the host and guest.

EXPERIMENTAL

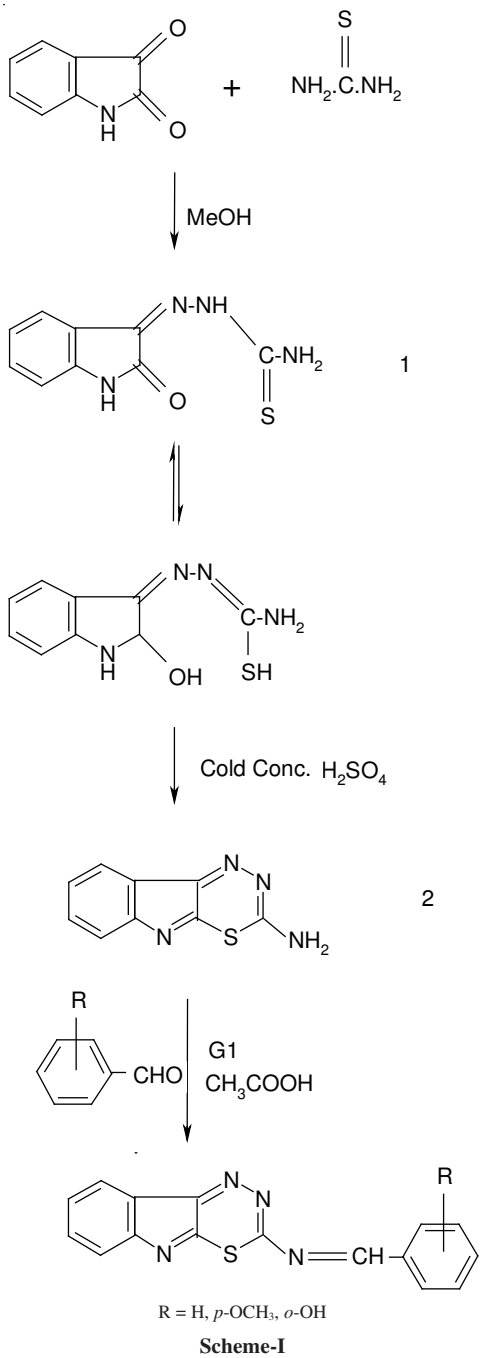
All the chemicals of acceptable standards were procured from local market. Double distilled water to be used as solvent was prepared in the laboratory. Electronic spectra were recorded on Shimadzu UV-1700 spectrophotometer and IR spectra were recorded in KBr pellets in Shimadzu 8400 FTIR spectrophotometer. Melting points were recorded by open capillary method.

Synthesis of 2-[arylidenamino]-1,3,4-thiadiazino[6,5b]-indoles: Three different 2-[arylidenamino]-1,3,4-thiadiazino-[6,5b]indoles were synthesized starting from indole -2,3-dione (**Scheme-I**) through the following intermediate steps[12].

(i) Synthesis of 3-thiosemicarbazideindole-2-one: A mixture of 2 g of indole-2,3-dione and 1.23 g of thiosemicarbazide in 50 mL of methanol was refluxed for 1 h. The completion of the reaction was checked by TLC. The excess of methanol was distilled out. The content was cooled and poured into ice cold water. It was filtered, washed with water, dried and recrystallised from ethanol to obtain 3-thiosemicarbazide-indole-2-one[13].

(ii) Synthesis of 2-amino-1,3,4-thiadiazino[6,5-b]-indole: 3 g of 3-thiosemicarbazideindole-2-one was mixed with small quantity of cold and concentrated H_2SO_4. The reaction mixture was left at room temperature for 16 h. The reaction mixture was then poured into ice-cold water and neutralized with liquid NH_3 to obtain a solid mass. The solid mass was filtered by using Whatmann-42 filter paper. It was washed with water, dried and recrystallized from ethanol to yield 2-amino-1,3,4-thiadiazino[6,5-b]indole.

Synthesis of benzylidenamino-1,3, 4-thiadiazino[6,5b]-indole (compound I): 1.06 g of benzaldehyde and 2.02 g of 2-amino-1,3,4-thiadiazino[6,5-b]indole were taken in 50 mL of methanol. The mixture was refluxed for 6 h in presence of glacial acetic acid. The completion of the reaction was checked



Scheme-I

by TLC and excess of methanol was distilled off. The refluxed mixture was poured into ice-cold water, filtered , washed with water and dried. The dried mass was recrystallized from ethanol.

Synthesis of 2-[4-methoxy benzylidenamino]-1,3,4-thiadiazino[6,5b]indole (compound II): 1.36 g of anisaldehyde and 2.02 g of 2-amino-1,3,4-thiadiazino[6,5-b] indole were taken in 50 mL of methanol. The mixture was refluxed for 6 h in presence of glacial acetic acid. The completion of the reaction was checked by TLC and excess of methanol was distilled off. The refluxed mixture was poured into ice-cold water, filtered and washed with water and dried. The dried mass was crystallized from ethanol.

Synthesis of 2-[2-hydroxy benzylidenamino]-1,3,4-thiadiazino[6,5b]indole (compound III): 1.22 g of salicylaldehyde and 2.02 g of 2-amino-1,3,4-thiadiazino[6,5-b]indole were taken in 50 mL of methanol. The mixture was refluxed for 6 h in presence of glacial acetic acid. The completion of the reaction was checked by TLC and excess of methanol was distilled off. The refluxed mixture was poured into ice-cold water, filtered and washed with water and dried. The dried mass was crystallized from ethanol.

Phase solubility measurements: The aqueous phase solubility of the compound at various concentration of β-cyclodextrin (0-10 mmL) was studied by Higuchi-Corner method[13]. Accurately weighed sample of these compounds was shaken in rotary flash shaker at room temperature in a series of conical flask for a period of 48 h till the attainment of equilibrium. The solutions were filtered through Whatmann-42 filter paper and were analyzed in a UV-visible spectrophotometer. The various values of absorbance at λ_{max} were plotted against different concentrations of β-cyclodextrin.

Synthesis of inclusion complexes: The inclusion complexes of the compounds (**I**, **II** and **III**) with β-cyclodextrin were prepared as per co-precipitation method[14]. The solutions of these compounds in required concentrations were added drop by drop to β-cyclodextrin solution of the required concentration. The mixtures were stirred for a period of 48 h and filtered. The filtrate was cooled for 24 h in refrigerators. The precipitate obtained was filtered through G-4 crucible, washed with water and dried in air for 24 h.

Study of thermodynamic properties: The thermodynamic stability constant of the complexes was calculated using Benesi-Hilderband relation[15]. The stability constant K of each complex was calculated with increasing temperature. From the slope of the linear plot of ln K *versus* 1/T, ΔH was calculated. Then ΔS was calculated from vant Hoff's equation

$$\ln K = \frac{\Delta H}{RT} + \frac{\Delta S}{R}$$

The value of ΔG was calculated at 298 K using the equation:

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

RESULTS AND DISCUSSION

The synthesis of compound **I** (benzylidenamino-1,3,4-thiadiazino[6,5b]indole), compound **II** (2-[4-methoxy benzylidenamino]-1,3,4-thiadiazino[6,5b] indole) and compound **III** (2-[2-hydroxy benzylidenamino]-1,3,4-thiadiazino[6,5b]indole) have been confirmed from elemental analysis and IR data as shown in Table-1. The elemental composition matches with theoretical data. IR data of the compound **I** show characteristic absorption at 672, 1296, 1611, 1682 and 3141 cm^{-1} due to (C-S), (C-C), (N-N), (C=N) stretching. IR data of the compound **II** show characteristic absorptions at 677, 1213, 1466, 1575, 1707 and 3133 cm^{-1} due to (C-S), (C-C), (C-N), (N-N), (C=N) stretching. Similarly, the IR-data of the compound **III** show characteristic absorptions at 672, 1294, 1611, 1683 and 3142 cm^{-1} due to (C-S), (C-C), (N-N), (C=N) stretching.

The synthesis of inclusion complexes of compound **I** (benzylidenamino-1,3,4-thiadiazino[6,5b]indole), compound **II** (2-[4-methoxy benzylidenamino]-1,3,4-thiadiazino[6,5b]-

TABLE-1
ANALYTICAL DATA OF COMPOUNDS WITH AND WITHOUT INCLUSION COMPLEX

Compound/ complex	m.p. (ºC)	Colour	Elemental analysis (first line indicates finding value and second line indicates calculated value)				λ_{max} (Å)	IR (KBr, ν_{max}, cm^{-1})
			C	H	N	S		
Compound **I**	224	Yellow	66.40 66.20	3.45 3.44	19.40 19.30	1.00 1.03	3550	672 (C-S), 1296 (C-C), 1611 (N-N), 1682 (-C=N), 3141 (ring)
Compound **I**-β-CD	228	Whitish yellow	–	–	–	–	3542	670 (C-S), 1290 (C-C), 1605 (N-N), 1679 (C=N), 3130 (ring)
Compound **II**	232	Yellow	63.80 63.75	3.80 3.75	17.70 17.50	10.10 10.00	3556	677 (C-S), 1213 (C-C), 1466 (C-N), 1575 (N-N), 1707 (-C=N), 3133 (ring)
Compound **II**-β-CD	237	Pale yellow	–	–	–	–	3550	673 (C-S), 1210 (C-C), 1464 (C-N), 1570 (N-N), 1698 (-C=N), 3118 (ring)
Compound **III**	239	Yellow	62.80 62.70	3.30 3.26	18.40 18.30	10.50 10.40	3540	672 (C-S), 1294 (C-C), 1611 (N-N), 1683 (C=N), 3142 (ring)
Compound **III**-β-CD	246	Whitish yellow	–	–	–	–	3530	669 (C-S), 1290 (C-C), 1610 (N-N), 1679 (C=N), 3130 (ring)

indole) and compound **III** (2-[2-hydroxy benzylidenamino]-1,3,4-thiadiazino[6,5b]indole) were confirmed from changes in melting point, colour and spectral characteristics (UV-vis and IR). The melting point of compound **I**, **II** and **III** are found to be 224, 232 and 239 ºC, respectively but their inclusion complexes have melting points 228, 237 and 246 ºC, respectively (Table-1). The colour of the compound **I**, **II** and **III** are found to be yellow but their inclusion complexes have colours whitish yellow, pale yellow and whitish yellow, respectively. The absorption maximum of the compounds **I**, **II** and **III** are found at 3550, 3556 and 3540 Å, respectively but their inclusion complexes have absorption maximum at 3542, 3550 and 3530 Å. The higher melting point of inclusion complexes than the compounds is due to the fact that extra amount of thermal energy is required for the latter to bring it out of β-cyclodextrin cavity.

It is quite interesting to note that the absorption maxima undergo a shift towards lower wavelength after the formation of inclusion complex (Table-1). This may be attributed to the transference of the compound from a more protic environment to a less protic environment with in the cavity of β-cyclodextrin. This is further supported by the IR stretching frequencies due to different bonds undergo a downward shift towards low energy and the peaks become broader, weaker and smoother. Such changes in spectral characteristics due to inclusion complex formation may be due to the weak interaction like H-bonding, van der Waal's forces, hydrophobic interactions *etc*., between the guest compound and the host β-cyclodextrin[16,17].

The phase solubility plots of the compounds in β-cyclodextrin solution are shown in Fig. 1(A-C). In all the cases, it is seen that there is a linear increase in solubility of these compounds with increasing concentration of β-cyclodextrin. Since the slopes of all the plots are less than unity the stochiometry of these complexes may be 1:1[18].

The thermodynamic stability constants (K_T) of inclusion complexes were determined by using Benesi-Hilderband relation

$$\frac{1}{\Delta A} = \frac{1}{\Delta E} + \frac{1}{K_T[Guest]_o[\beta - CD]_o}$$

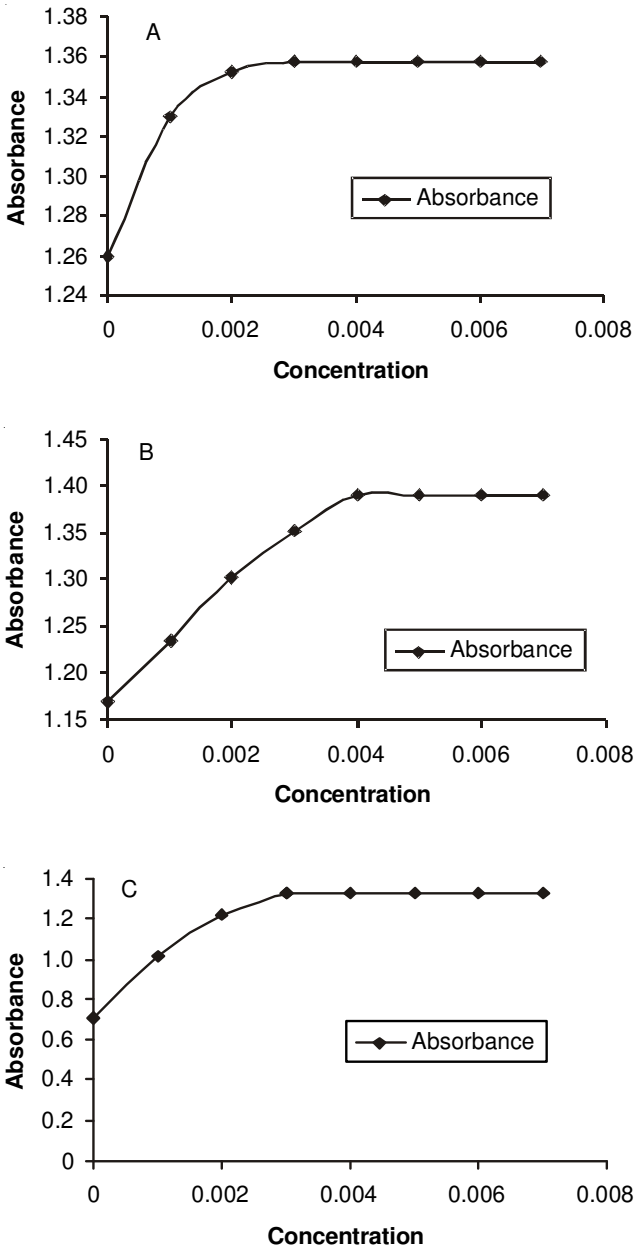


Fig. 1. Phase solubility of compounds **I**, **II**, **III**

Good linear correlations were obtained for a plot of 1/ΔA *verses* $[\beta\text{-CD}]_o$ for compounds (Fig. 2A-C). The values of K_T for all the complexes were calculated using the relation:

$$K_T = \frac{\text{Intercept}}{\text{Slope}}$$

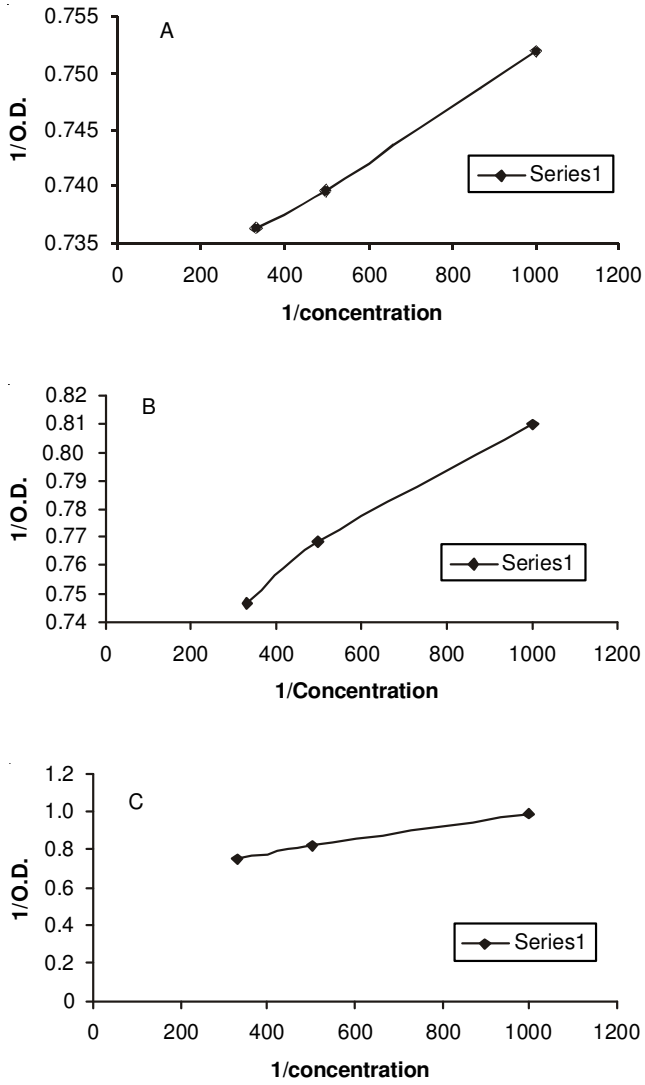


Fig. 2. Plot of 1/OD *versus* 1/concentration of β-cyclodextrin of compounds **I**, **II**, **III**

The K_T values of the inclusion complexes of compounds **I**, **II** and **III** with β-cyclodextrin are found to be 420.9, 718.5, 231.3 M^{-1}, respectively (Table-2). The data obtained are within 100-1000 M^{-1} (ideal values) indicating appreciable stabilities for the inclusion complexes[19].

The thermodynamic parameters associated with the interaction of the compound with β-cyclodextrin for 1:1 stochiometry have also been calculated by determining stability constant (K-values) at different temperatures. The K-values are to found to decrease with rise in temperature as expected for an exothermic process (deencapsulation)[20,21]. The plots of ln K *versus* inverse absolute temperature produce linear plots (Fig. 3A-C). From the slopes of the curves, van't Hoff's reaction isotherm and van't Hoff equation, the values of ΔG (change in free energy), ΔH (change in enthalpy) and ΔS (change in entropy) have been calculated (Table-2). In Table-2, it is found that ΔG values are negative for all the inclusion complexes. These data clearly demonstrates that formation of inclusion complexes of compounds **I**, **II** and **III** with β-cyclodextrin is a spontaneous process. Further it is found that in case of all three inclusion complexes, ΔH values are negative and ΔS values are positive (Table-2). The negative value of enthalpy change (ΔH) and positive value of entropy change (ΔS) indicate that all the three inclusion complex formations are allowed by both energy factor and entropy factor. That is, the compounds are getting stabilized within the cavity of β-cyclodextrin by weak intermolecular forces as suggested earlier[22,23].

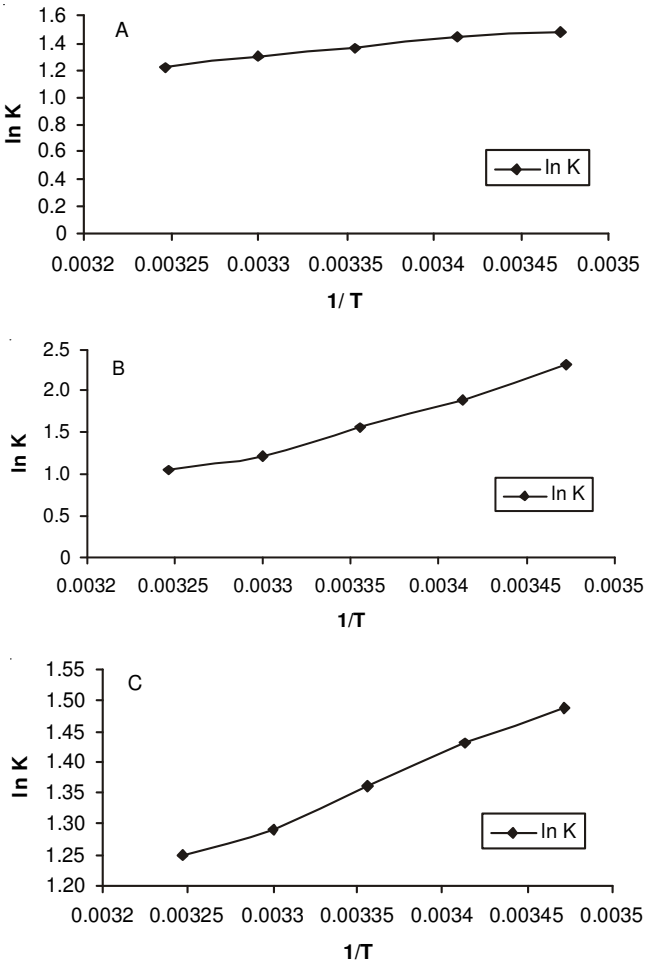


Fig. 3. Plot of ln K *versus* 1/T of compounds **I**, **II**, **III**-β-cyclodextrin complex

TABLE-2
THERMODYNAMIC DATA OF INCLUSION COMPLEXES AT 298 K

Complexes	K (M^{-1})	ΔG (KJ/mol)	ΔH (KJ/mol)	ΔS (KJ/mol)
Compound **I**-β-CD	420.9	-14.9800	-12.105	0.00965
Compound **II**-β-CD	718.5	-16.2987	-14.470	0.00615
Compound **III**-β-CD	231.3	-13.4890	-10.360	0.01050

Conclusion

From the above results and discussion, it is clear that the formation of inclusion complexes of compound **I**, **II** and **III** is thermodynamically allowed which can be a very good analytical tool for enhancing the bioaccessibility of the drugs. The study further reveals that non-covalent intermolecular forces bind the host β-cyclodextrin and guest molecules. The ΔG, ΔS and ΔH values support the formation of such complexes[24].

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