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Impact of Inclusion Complex Formation on Absorption and Emission Characteristics of Some 4-Arylidenamino-5-phenyl-4*H*-1,2,4-triazole-3-thiols

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The inclusion complexes of a series of 4-arylidenamino-5-phenyl-4*H*-1,2,4-triazole-3-thiols have been synthesized with β-cyclodextrin. The compounds and their inclusion complexes have been characterized by studying their physical and spectral properties. The thermodynamic stability constant and free energy of activation have been determined to know the stability of inclusion complexes and type of host-guest relation. Finally, the absorption, excitation and emission spectra of the compounds and their inclusion complexes have been taken to examine whether the inclusion complex formation has any impact on absoption and emission characteristics of 4-arylidenamino-5-phenyl-4*H*-1,2,4-triazole-3-thiols. It is found that inclusion complex formation brings about a drastic change in absorption, excitation and emission spectra of newly synthesized compounds.

Keywords: Triazole-3-thiol, Inclusion complex, Absorption spectra, Excitation spectra, Emission spectra.

INTRODUCTION

The drugs containing 1,2,4-triazole nucleus are reported to exhibit a wide spectrum of pharmacological activities like antimicrobial [1-5], anticancer [6,7], antiviral [8], antiinflammatory [9], analgesic [10], anticonvulsant [11] *etc*. It is known that the formation of inclusion complex of variety of drug molecules with β-cyclodextrin improves their solubility, stability as well as bioavailability [12-16]. But transference of drug molecules which are usually non-polar in nature, into hydrophobic core of β-cyclodextrin causes a drastic change in its microenvironment. Since the spectral chacteristics of molecules depend upon the molecular structure and its microenvironment [17-23] such a transference will definitely have some impact on absorption and emission characteristics of the molecules.

In view of these facts, an attempt has been made to synthesize some 4-arylidenamino-5-phenyl-4*H*-1,2,4-triazole-3-thiol (Schiff bases) in their purest forms and prepare their inclusion complexes with β-cyclodextrin. The absorption, excitation and emission spectra of the compounds and their inclusion complexes are taken to examine whether the inclusion complex formation has any impact on absoption and emission characteristics of 4-arylidenamino-5-phenyl-4*H*-1,2,4-triazole-3-thiols.

EXPERIMENTAL

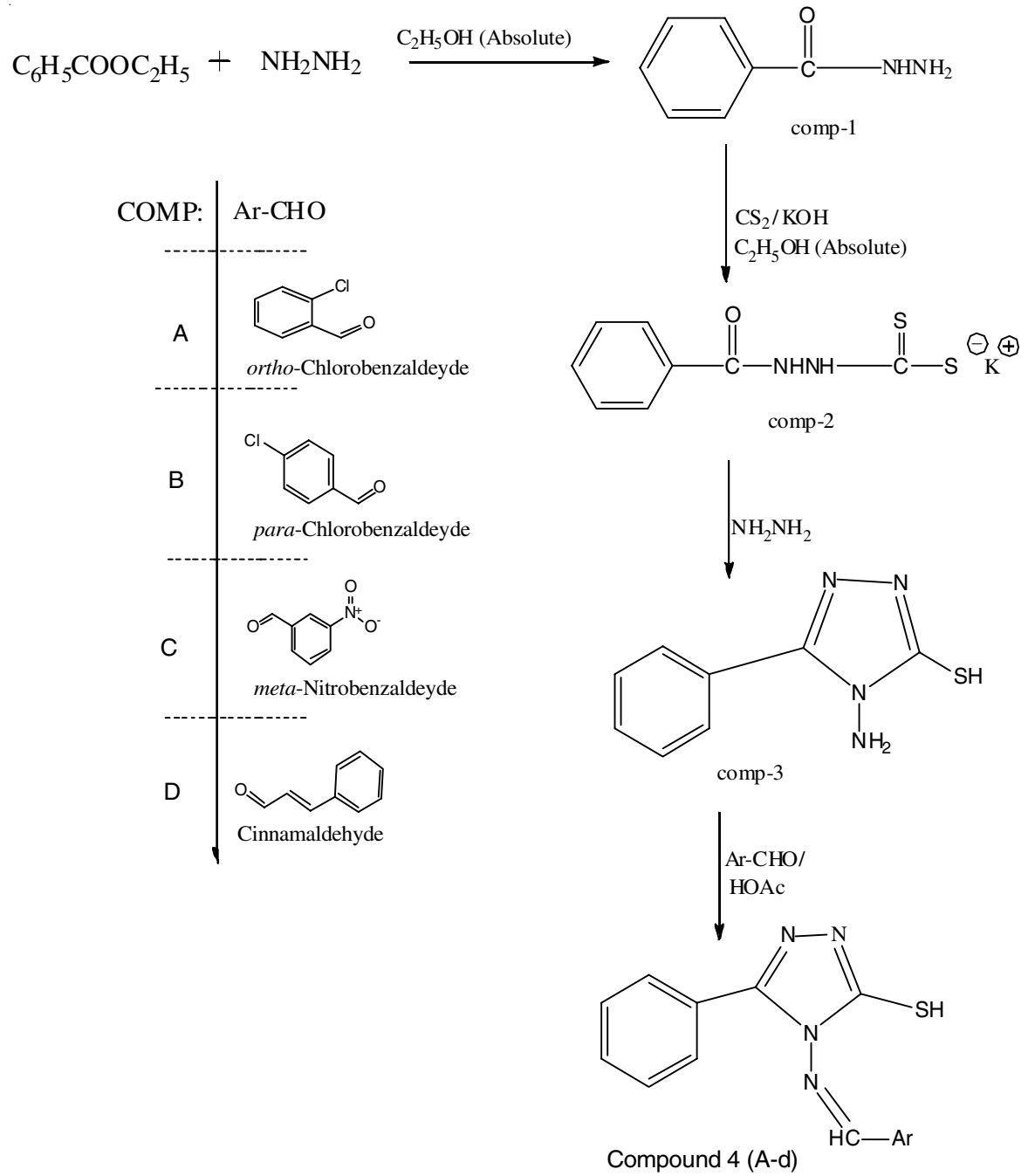
All the chemicals used in the present work were procured from local market. Double distilled water was used as solvent. The elemental analysis was performed in a CHN analyzer. Melting points were recorded by open capillary method. Electronic spectra were recorded in Shimadzu UV-1800 spectrophotometer and IR spectra were recorded in KBr pellets in Shimadzu 8400 FT-IR spectrophotometer. ^{1}H NMR spectra were obtained with Brukers spectrophotometer model ultrashield at 300 MHz in DMSO-d_6 solution with TMS as internal standard. The purity of the newly synthesized compounds were checked by TLC. Fluorescence spectra and intensity measurements were made on a Shimadzu RF-1501 spectrofluorimeter equipped with a150 W xenon lamp.

The synthesis of the titled compounds A, B, C and D were carried out as per Panda *et al.* [24] as shown in **Scheme-I**.

Phase solubility measurements: The aqueous phase solubility of the compounds at various concentrations of β-cyclodextrin (0-10 mM) was studied by Higuchi-Conner method [25].

Synthesis of inclusion complexes: Co-precipitation method was used for the preparation of inclusion complexes of the compounds with β-cyclodextrin [15,26].

Study of thermodynamic properties: The stability constants of the complexes (K) were calculated from plot of



A = 4-[2-Chlorobenzilidenamino]-5-phenyl-4*H*-1,2,4-triazole-3-thiol; B = 4-[4-Chlorobenzilidenamino]-5-phenyl-4*H*-1,2,4-triazole-3-thiol; C = 4-[3-Nitrobenzilidenamino]-5-phenyl-4*H*-1,2,4-triazole-3-thiol; D = 4-[(*E*)-3-phenylallylideneamino]-5-phenyl-4*H*-1,2,4-triazole-3-thiol

Scheme-I

inverse of change in absorbance *versus* inverse concentration of β-cyclodextrin using Benesi-Hilderband relation [27].

$$1/\Delta A = 1/\Delta\varepsilon + 1/K\,[Guest]_o\cdot[\beta\text{-CD}]$$

where ΔA is change in absorbance, Δε is change in absorption coefficient, K stability constant, $[Guest]_o$ is the concentration of compound and [β-CD] is the concentration of β-cyclodextrin. The values of K for all the complexes are calculated using the relation.

$$K = \text{Intercept/Slope}$$

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

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

RESULTS AND DISCUSSION

Four different 4-arylidenamino-5-phenyl-4*H*-1,2,4-triazole-3-thiols (A, B, C and D) have been synthesized as shown in **Scheme-I** in their purest forms. The inclusion complexes of A, B,C and D have been prepared with β-cyclodextrin after determining the optimum concentration of host and guest through aqueous phase solubility study (Fig. 1). The structures of the compounds (A, B, C and D) and their inclusion complexes have been confirmed from the study of their physical properties, elemental composition, IR and ^{1}H NMR data (Tables 1 and 2). The elemental composition of the compounds matches with theoretical data (Table-2). The IR and ^{1}H NMR

TABLE-1
SOME PHYSICAL PROPERTIES OF SYNTHESIZED COMPOUNDS AND THEIR COMPLEXES

S. No.	Compound/Complex	m.f.	m.w.	Colour	m.p. (°C)	Yield (%)
1	Compound-A	$C_{15}H_{11}N_4SCl$	314.79	Yellow	148-150	77
	Inclusion complex A			White	280	77
2	Compound-B	$C_{15}H_{11}N_4SCl$	314.79	Light yellow	165-170	63
	Inclusion complex B			White	273-275	76
3	Compound-C	$C_{15}H_{11}N_5O_2S$	325.35	Yellowish white	185-190	70
	Inclusion complex C			Dull white	282-284	75
4	Compound-D	$C_{17}H_{14}N_4S$	306. 38	Brown	95	70
	Inclusion complex D			White	282-285	72

TABLE-2
SPECTRAL DATA AND ELEMENTAL COMPOSITION OF THE COMPOUNDS AND THEIR INCLUSION COMPLEXES

S. No.	Compound/ Complex	IR (KBr, ν_{max}, cm^{-1})	NMR (DMSO-d_6)	Elemental analysis (%): Calcd. (Found)		
				C	H	N
1	A	941.26 (N-C-S str), 3072.60, 3132.70 (Ar-H str), 1502.56 (C=C str), 696.30 (C-S str), 1350.17 (C-N str), 769.60 (C-Cl str), 1610.56 (C=N str)	7.49-7.88 (m, 9H, Ar-H), 14.30 (s, 1H, SH), 10.43 (s, 1H, N=CH)	57.23 (57.07)	3.52 (3.42)	11.26 (11.22)
	Inclusion complex A	937.40 (N-C-S str), 2931.80, (Ar-H str), 1408.04 (C=C str), 1656.85 (C=N str), 756.10 (C-S str), 1332.81, (C-N str), 792.74 (C-Cl str), 3363.86 (OH str, β-CD), 2931.80 (C-H str, β-CD)	7.94-7.96 (m, 9H, Ar-H), 3.34 (s, 1H, β-CD), 3.37 (s, 1H, β-CD), 3.54 (s, 1H, β-CD), 3.60 (s, 1H, β-CD), 3.62 (s, 1H, β-CD)			
2	B	941.26 (N-C-S str), 3034.03, 3099.61 (Ar-H str), 1502.55 (C=C str), 696.30 (C-S str), 1350.17 (C-N str), 769.60 (C-Cl str). 1610.56 (C=N str)	7.52-7.92 (m, 9H, Ar-H), 14.243 (s, 1H, SH), 9.7 65 (s, 1H, N=CH).	57.23 (57.09)	3.52 (3.45)	11.26 (11.13)
	Inclusion complex B	937.40 (N-C-S str), 2931.80 (Ar-H str), 1409.96 (C=C str), 705.95 (C-S str), 1348.24 (C-N str), 792.74 (C-Cl str), 1658.78 (C=N str), 3367.71 (OH str, β-CD), 2931.80 (C-H str, β-CD)	7.95-7.98 (m, 9H, Ar-H), 3.58 (s, 1H, β-CD), 3.61 (s, 1H, β-CD), 3.63 (s, 1H, β-CD), 3.65 (s, 1H, β-CD), 3.66 (s, 1H, β-CD),			
3	C	943.19 (N-C-S str), 3032.10, 3088.03 (Ar-H str), 1508.33 (C=C str), 675.09 (C-S str), 1350.17 (C-N str), 1537.27, 1350.17 (NO_2), 1608.63 (C=N str)	7.52-8.33 (m, 9H, Ar-H), 14.34 (s, 1H, SH), 10.023 (s, 1H, N=CH).	55.37 55.47)	3.41 (3.32)	21.53 (21.42)
	Inclusion complex C	937.40 (N-C-S str), 2933.73 (Ar-H str), 1660.71 (C=C str), 705.95 (C-S str), 1361.74 (C-N str), 1409.96 (NO_2), 1660.71 (C=N str), 3367.71 (OH str, β-CD), 2933.73 (C-H str, β-CD)	7.94-8.23 (m, 9H, Ar-H), 3.37 (s, 1H, β-CD), 3.54 (s, 1H, β-CD), 3.61 (s, 1H, β-CD), 3.62 (s, 1H, β-CD), 3.65 (s, 1H, β-CD),			
4	D	941.26 (N-C-S str), 3143.97 (Ar-H str), 696.30 (C-S str), 1573.91 (C=C str), 1350.17 (C-N str). 1610 (C=N str), 1649.14 (C=C unsaturated)	6.93-7.87 (m, 8H, Ar-H),	66.64 (66.69)	4.61 (4.66)	18.29 (18.24)
	Inclusion complex D	937.40 (N-C-S str), 2933.73 (Ar-H str), 1409.96 (C=C str), 705.95 (C-S str), 1361.74 (C-N str), 1658.78 (C=N str), 3356.14 (OH str, β-CD), 2914.44 (C-H str, β-CD)	7.94-8.28 (m, 9H, Ar-H), 3.27 (s, 1H, β-CD), 3.29 (s, 1H, β-CD), 3.37 (s, 1H, β-CD), 3.61 (s, 1H, β-CD), 3.65 (s, 1H, β-CD),			

data of the compounds confirm the expected structures. The synthesis of inclusion complexes of the compounds have been confirmed from the changes in melting point,colour and IR and ^1H NMR spectral characteristics (Tables 1 and 2). The higher melting point of the inclusion complexes than their corresponding compounds may be attributed to the fact that extra amount of thermal energy is required for the latter to bring it out of β-cyclodextrin cavity [15]. The IR-stretching frequencies due to different bonds undergo downward shift towards lower energy and the peaks become broader, weaker and smoother which may be attributed to the restriction on the compounds for undergoing vibration due to the development of weak interaction like H-bonding, vander-Waal forces and hydrophobic interactions, *etc*. within the cavity. This observation clearly demonstrates transference of the compound from a more protic environment (aqueous media) to a less protic environment (cavity of β-cyclodextrin). The compound and β-cyclodextrin interaction leading to inclusion complex formation is further supported by NMR data (Table-2). It is seen that the NMR signals due to different protons undergo smaller shifts (small shift towards down field in case of all the compounds) after their inclusion complex formations which may be due to changes in the microenvironment of the compound after encapsulation.

The aqueous phase-solubility diagrams of the compounds with β-cyclodextrin are shown in Fig. 1. It is seen that aqueous solubility of the compounds increase linearly as a function of the concentration of β-cyclodextrin up to 5^{th} point followed by a decline. This clearly indicates that the concentration at 5^{th} point is the optimum concentration for inclusion complex formation. The plot of inverse absorbance against inverse concentration of β-cyclodextrin gives straight lines with definite slope and intercept for different compounds (Fig. 2).The equilibrium constants (K) have been calculated from the slope

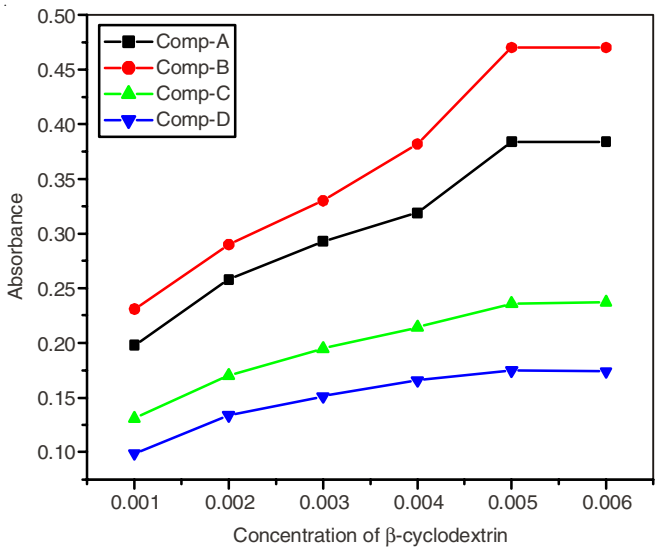


Fig. 1. Phase solubility study of the synthesized compounds in aqueous solution of β-cyclodextrin

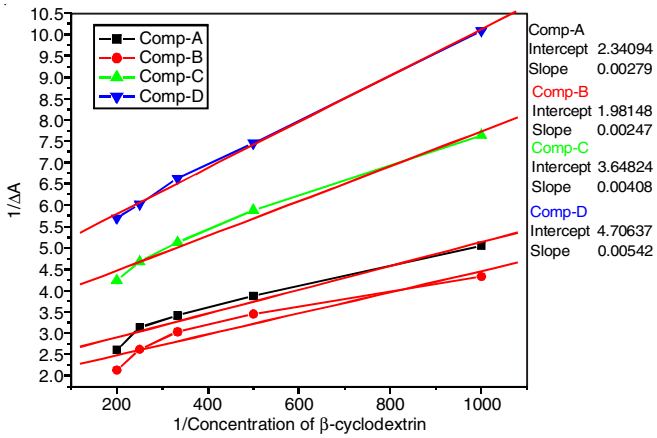


Fig. 2. Plot of inverse absorbance against inverse concentration of β-cyclodextrin

and intercept [27] and are found to be in the range of 457.07 to 893.58 (Table-3). Since all the values are remaining within ideal range [28], complexes formed are quite stable. Further, it is found that the values of all the slopes are less than one indicating the inclusion complexes to have 1:1 stoichiometry [14-16]. Negative values of free energy changes for all the inclusion complexes (Table-3) further suggest that the process of inclusion complex formation is spontaneous and thermodynamically allowed.

TABLE-3
THERMODYNAMIC STABILITY CONSTANT AND FREE ENERGY CHANGE OF INCLUSION COMPLEXES

S. No.	Inclusion complex of compound	Equilibrium constant (K) in M^{-1}	ΔG (kJ/mol)
1	Inclusion complex A	839.04	-16.679
2	Inclusion complex B	802.21	-16.568
3	Inclusion complex C	894.17	-16.837
4	Inclusion complex D	868.33	-16.764

It is interesting to note that the absorption and emission characterestics of all the compounds (A, B, C and D) undergo drastic changes after their inclusion complex formation. The absorption maxima shifts towards lower wavelength (Table-4) and the intensity of the peaks becomes higher (Figs. 3-6) after their inclusion complex formation. However, although the excitation and emission peaks shift towards lower wavelength, the intensity of the peaks becomes lower after their inclusion complex formation (Figs. 7-10). The shifting of absorption and excitation peak positions may be due to the fact that more amount of energy is required for the compounds for their excitation after encapsulation because the molecules get stabilized within the cavity of β-cyclodextrin through some weak intermolecular forces.

TABLE-4
ABSORPTION, EXCITATION AND EMISSION PEAK POSITION OF THE COMPOUNDS AND THEIR INCLUSION COMPLEXES

S. No.	Compound/ Complex	Absorption maximum λ_{max} (nm)	Exitation peak position λ (nm)	Emission peak position λ (nm)
1	Compound-A	290	318	453
	Inclusion complex A	278	303	442
2	Compound-B	288	325	450
	Inclusion complex B	270	307	439
3	Compound-C	280	308	453
	Inclusion complex C	266	285	435
4	Compound-D	274	310	442
	Inclusion complex D	261	290	427

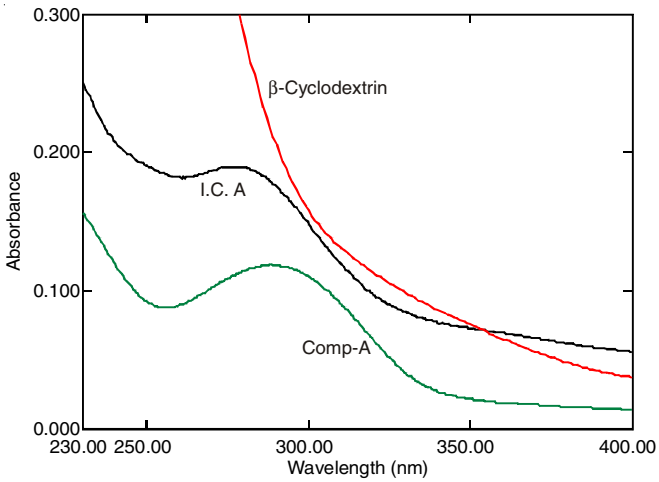


Fig. 3. UV spectrum of β-cyclodextrin, compound A and its inclusion complex

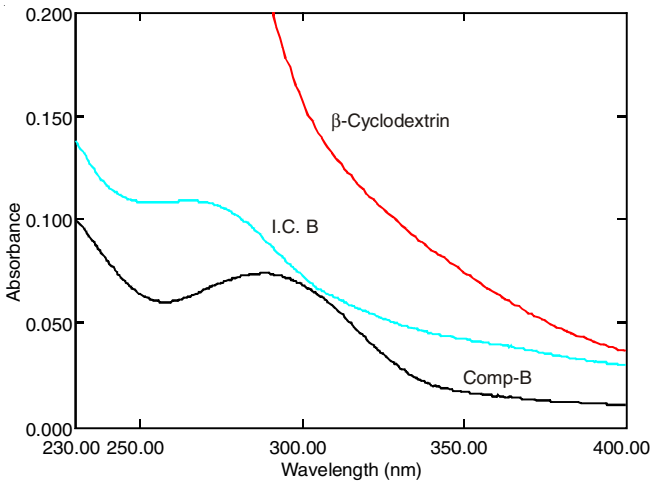


Fig. 4. UV spectrum of β-cyclodextrin, compound B and its inclusion complex

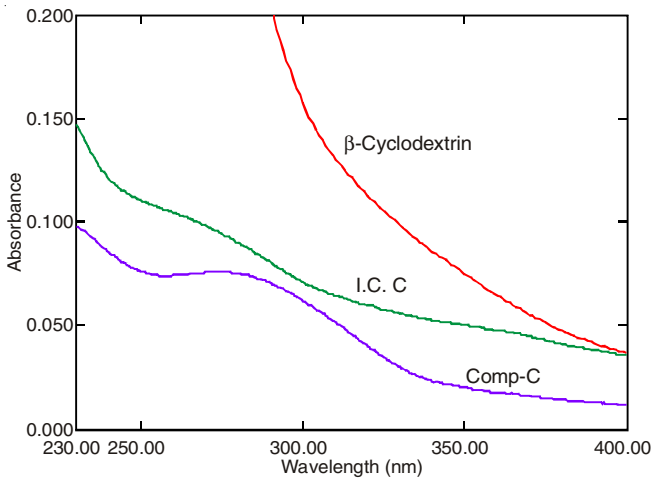


Fig. 5. UV spectrum of β-cyclodextrin, compound C and its inclusion complex

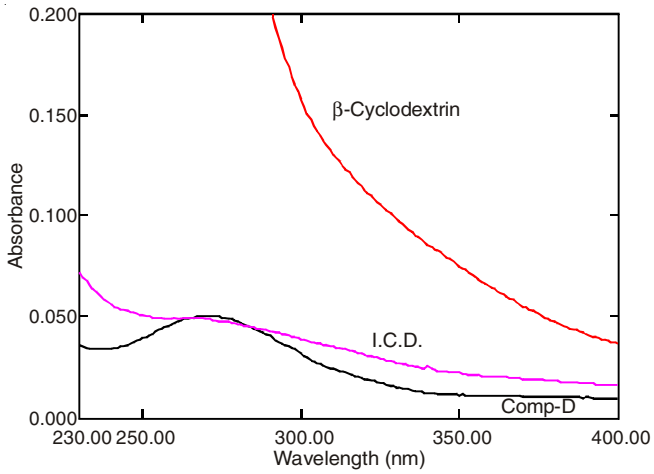


Fig. 6. UV spectrum of β-cyclodextrin, compound D and its inclusion complex

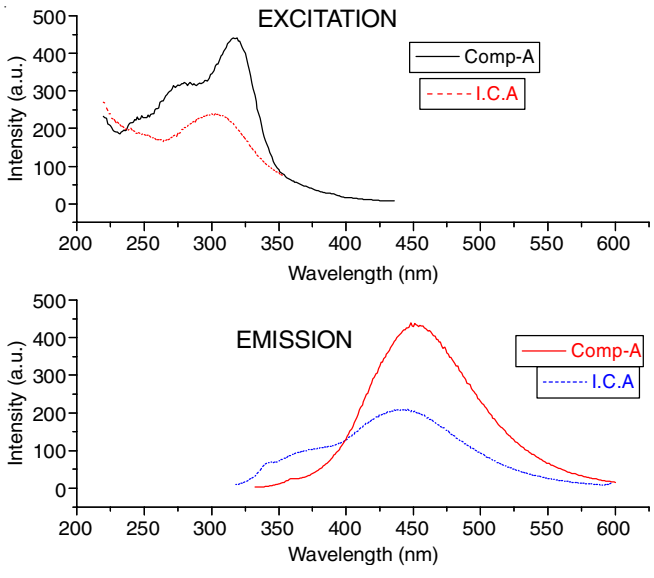


Fig. 7. Excitation and emission spectra of compound A and its inclusion complex

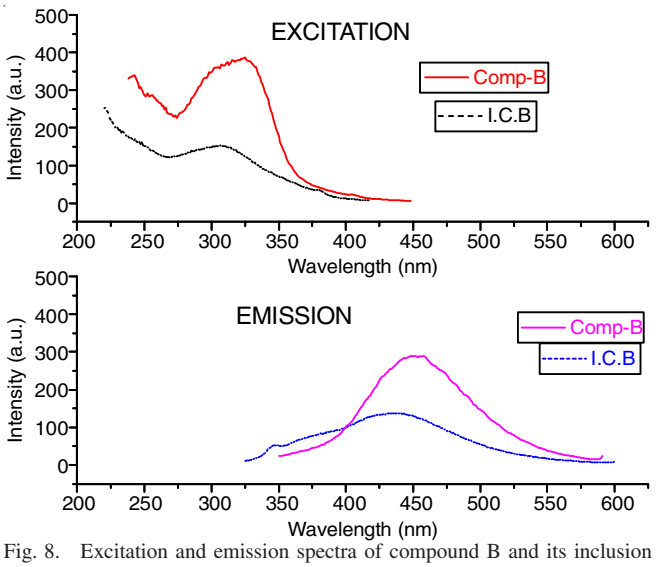


Fig. 8. Excitation and emission spectra of compound B and its inclusion complex

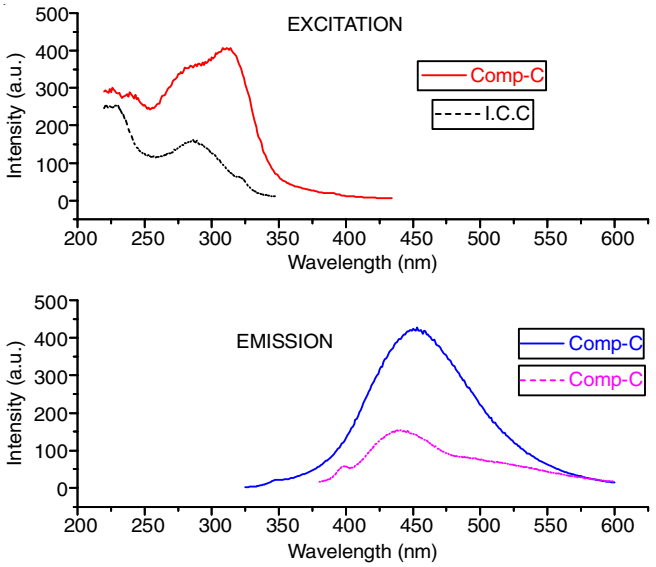


Fig. 9. Excitation and emission spectra of compound C and its inclusion complex

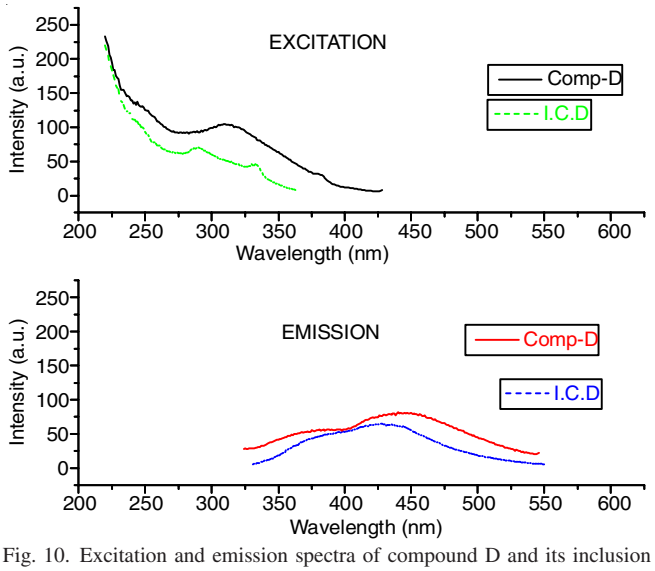


Fig. 10. Excitation and emission spectra of compound D and its inclusion complex

Conclusion

The above results established the fact that inclusion complexes of the synthesized compounds alter the absorption and emission characteristics of molecules.

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