VISCOMETRIC INVESTIGATIONS AND MOLECULAR INTERACTIONS OF SOME DERIVATIVES OF 5-SUBSTITUTED INDOLE DIHYDROPYRIMIDINES IN MIXED ORGANIC SOLVENTS

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Abstract: Colloid chemical behavior of indole dihydropyrimidines in non-aqueous solvent mixture benzene-methanol of varying composition has been investigated by viscometric measurements at 303K± 0.1. The viscosity of the system increases with the increase in concentration. The Trend Change Point (TCP) values have been determined by intersection of two straight lines, which are found to be dependent on the composition of solvent mixtures. The study confirms that the nature of synthesized compounds agglomerate formed below and above 50% benzene concentration is quite different. The viscometric data have been analyzed in terms of Einstein, Vand, Moulik and Jones-Dole equations. These well known equations have been successfully applied to explain the results of viscosity measurements and the viscometric parameters show that the behavior of compound changes in the proximity of 50% benzene concentration.

Keywords: Substituted indoles, Dihydropyrimidines, Trend change point, viscosity, and Solute-Solvent interaction.

INTRODUCTION

In the family of heterocyclic compounds Nitrogen containing heterocycles are an important class of compounds in the medicinal chemistry and also contributed to the society from biological and industrial point which helps to understand life processes.[1] This seems to be because pyrimidines represents one of the most active class of compounds possessing wide spectrum of biological activity viz. significant in vitro activity against unrelated DNA and RNA, viruses including polio herpes viruses, diuretic, antitumor, anti HIV, cardiovascular.[2] Biginelli compounds show a diverse range of biological activities. The interest focused on Biginelli compounds leading to the development of Nitractin,[3] that has excellent activity against the virus of trachoma group, the same compounds also exhibit antibacterial activity. 4-Aryl dihydropyrimidines e.g. Nifedipine are the important and most studied class as Calcium channel modulars, in 1975 their introduction in clinical medicine for the treatment of cardiovascular diseases.[4] some of the analogues were screened as antitumor agents.

Pyrimidine –5-carboxamide of type was reported to possess anticarcinogenic activity, anti-inflammatory,[5] analgesic.[6] The topsentins, as antiviral and antitumor agents from marine sponge represents the emerging class of bis indole alkaloids. During the search of bioactive natural pro-

ducts act as cytotoxic and antifungal compounds belongs to class noprtopsentins.[7] The presence of highly substituted indole and indolines in a variety of bioactive molecular targets has inspired a number of groups including ours to develop new and improved routes to their synthesis.[8] Recently there is a much interest in the synthesis of small molecules for chemist in accelerating drug discovery.[9]

In the view of the potential applications of these compounds, present work has been undertaken to explain colloid chemical behavior in mixed solvents. Benzene and methanol has been chosen as the co solvents in the title study. The mixed solvents have a tendency to interact with compounds, which affect the aggregation of molecules. The viscosity data based on various equations has been extensively used to furnish information concerning the structural changes in solution trend change point (TCP) and nature of molecule-solvent interaction. This vital information plays an important role in their selection for various industrial and biological applications.

EXPERIMENTAL

The most obvious approach for carrying out the synthesis of substituted indole dihydropyrimidines is due to potent biological activity of indoles as well as dihydropyrimidines. The synthesis begins from the commercially available indole; we were able to synthesize 5-substituted indoles in three steps using known protocol.[10] The further formylation with DMF/POCl$_3$ by Wismeyer – Hack method to obtain Indole 3-carboxaldehyde in good yields.[11]

In cyclocondensation reaction of indole carboxaldehyde, thiourea and ethylacetoacetate in the presence of acid catalyst by refluxing in ethanol to afford indole dihydropyrimidines **(1)**.[12]
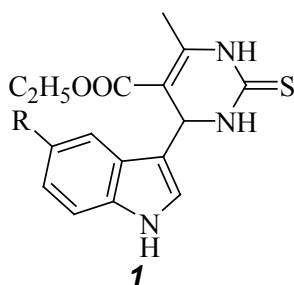
Compound	R
A	H
B	Br
C	Cl
D	I

Correlating 1H NMR and IR data with data for corresponding compounds made the structural assignments for indole 3-carboxaldehydes and indole dihydropyrimidines. Solubility of compounds in benzene and methanol was determined by preparing solutions of compounds in solvents. The viscosity of the solutions was measured by Ostwald's viscometer in thermostat bath. The viscometer was calibrated frequently with distilled water.

RESULTS AND DISCUSSION

The flow of characterization of solutions in terms of viscometric measurements has been employed as a tool to find out the TCP of molecule in benzene - methanol mixtures. The viscosity of solutions of varying composition of benzene- methanol mixtures increases with the increase in the concentration.

Table – 1.Viscosity, η, of compound A in benzene-methanol at 303K ± 0.1 in poise

	Volume % of methanol			
Conc	40%	60%	80%	100%
0.0002	0.589	0.566	0.549	0.529
0.0004	0.604	0.581	0.561	0.541
0.0006	0.616	0.593	0.570	0.551
0.0008	0.620	0.599	0.574	0.553
0.0010	0.627	0.604	0.580	0.557
0.0012	0.634	0.612	0.585	0.561
0.0014	0.643	0.619	0.589	0.564

Table – 2. Viscosity, η, of compound B in benzene- methanol at 303K ± 0.1 in poise

	Volume % of methanol			
Conc	40%	60%	80%	100%
0.0002	0.592	0.568	0.549	0.529
0.0004	0.607	0.585	0.565	0.542
0.0006	0.619	0.596	0.575	0.551
0.0008	0.624	0.601	0.577	0.555
0.0010	0.630	0.607	0.582	0.559
0.0012	0.638	0.616	0.588	0.564
0.0014	0.647	0.624	0.593	0.567

Table – 3. Viscosity, η, of compound C in benzene- methanol at 303K ± 0.1 in poise

	Volume % of methanol			
Conc	40%	60%	80%	100%
0.0002	0.591	0.571	0.551	0.533
0.0004	0.614	0.593	0.569	0.546
0.0006	0.627	0.606	0.581	0.559
0.0008	0.632	0.610	0.586	0.565
0.0010	0.639	0.616	0.593	0.570
0.0012	0.646	0.620	0.596	0.573
0.0014	0.651	0.629	0.600	0.576

Table – 4. Viscosity, η, of compound D in benzene-methanol at 303K ± 0.1 in poise

	Volume % of methanol			
Conc	40%	60%	80%	100%
0.0002	0.596	0.573	0.553	0.535
0.0004	0.621	0.595	0.573	0.551
0.0006	0.635	0.609	0.587	0.564
0.0008	0.641	0.615	0.592	0.568
0.0010	0.647	0.621	0.596	0.571
0.0012	0.652	0.627	0.599	0.573
0.0014	0.658	0.634	0.602	0.578

The increase in viscosity with the increase in concentration may be due to the increasing tendency of molecules to associate in the form of clustering entity in the solvent system. The numbers of workers have reported the molecular interaction and characterizing aspects of physico-chemical behavior of binary liquid mixtures and mixed solvent.[13] The difference in the viscosities of solutions in varying composition of benzene-methanol mixtures is mainly due to the difference in the viscosities of the solvent mixtures. The plots of viscosity (η) against concentration (C) are characterized by an intersection of two straight lines at a definite concentration corresponding to TCP of the molecule (Fig.1-4).
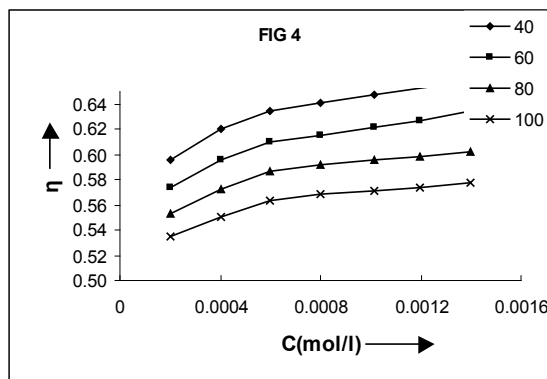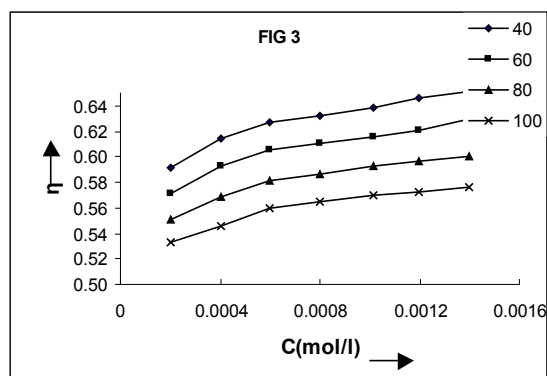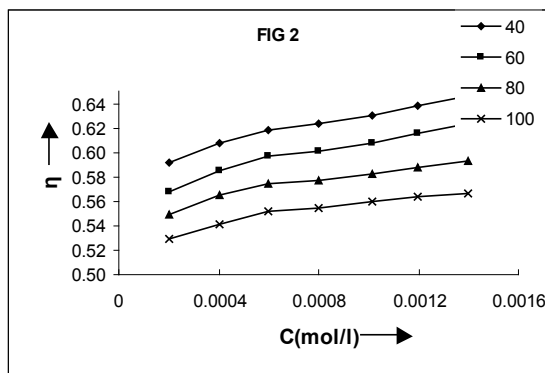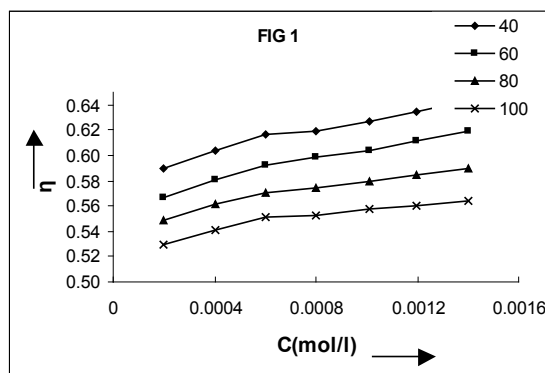

Fig. 1-4 Plot of η versus C for compound A-D in benzene-methanol.

Of course this is the maximum concentration of molecular dispersion where balancing of the internal forces causes the formation of aggregates. It is apparent from the data that the values of TCP are dependent on the composition of solvent mixtures. The values of TCP in the solution containing benzene below 50% are lower as compared to those containing higher volume percent of benzene. This may be attributed to the change in the mobility of the molecules due to change in the dielectric constant of the solvent mixture having different composition of benzene-methanol. Further it is suggested that predominance of lipophilic character in the solvent mixture plays a pertinent role in the clustering alignment of the solute molecules. Thus there is delay in the aggregation due to increase in the interaction between lipophilic solvent and solute molecules. The viscosity of solutions as well as those of the solvent mixtures increases as the volume percent

of benzene increases which may be attributed to the cumulative effect of the variation of dielectric constant, degree of aggregation and the nature of the agglomerate.

The values of specific viscosity (η_{sp}) of solutions in varying compositions of benzene-methanol mixtures also increase with the increase in the concentration.
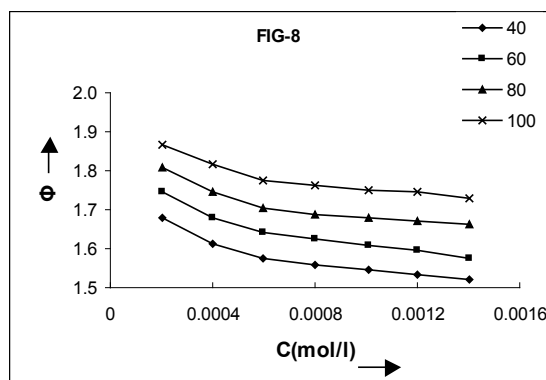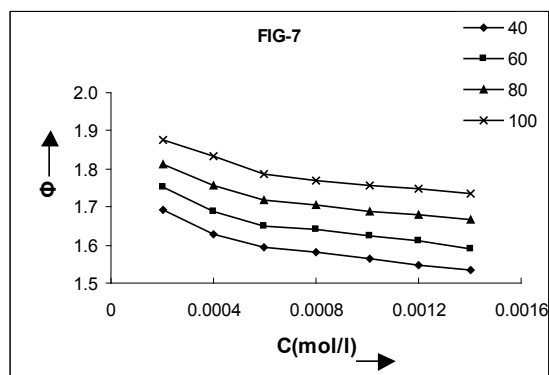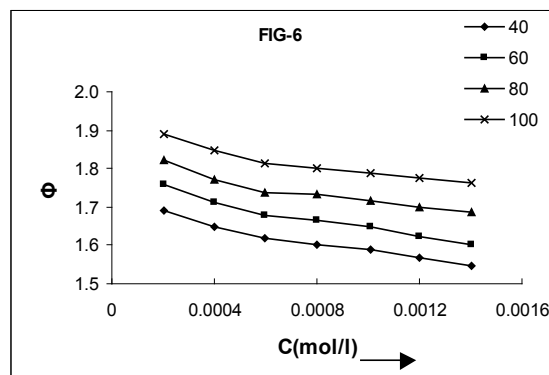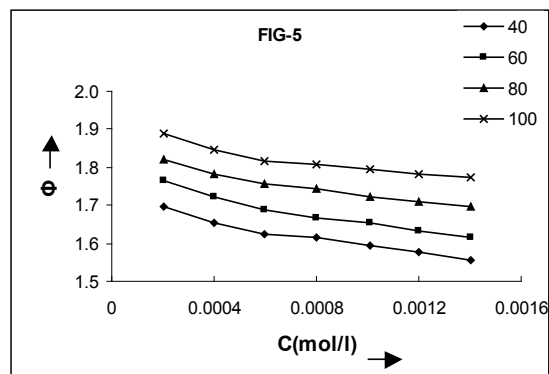

Fig. 5-8 Plots of ϕ versus C for vompound A-D in benzene-methanol.

The nature of curves and TCP values are in good agreement with those observed for viscosity data. The fluidity of solutions in benzene-methanol mixtures decreases with the increase in the concentration as well as with the increase in volume percent of benzene (Fig. 3). A perusal of Table-2 indicates that TCP values are in good agreement with those derived from viscosity and specific viscosity curves and are dependent on the solvent composition.

The viscosity results have been explained in terms of equations proposed by Einstein[14] and Vand. [15]

Einstein: $\eta_{sp} = 2.5\ V\ C$
Vand: $1/C = (0.921/V) \times [1/\log (\eta/\eta_0)] + QV$

Where V, C, Q, η, η_0 and η_{sp} are molar volume, concentration, interaction coefficient, viscosity of the solution, viscosity of solvent and specific viscosity respectively. The plots of specific viscosity (η_{sp}) against concentration (C) are characterized by an intersection of two straight lines at a definite concentration, which corresponds to the TCP. The plots with intercept almost equal to zero are linear below TCP, which shows that the equation proposed by Einstein are applicable to dilute solutions. [16] It is observed that the values of molar volume V obtained from the plots of Einstein equation and Vand equation.

Table – 5. Values of molar volume (V) in benzene – methanol derived from Einstein and Vand equations compound %of methanol Einstein equation Vand equation

		Einstein equation		Vand equation	
		V_1	V_2	V_1	V_2
compound A	40%	47.6600	27.7372	80.3960	53.9520
	60%	48.2680	24.8596	68.5360	59.0760
	80%	38.7288	19.1484	74.9440	51.6160
	100%	42.0640	14.0272	55.5680	48.3600
compound B	40%	46.7800	26.7800	93.2760	59.1720
	60%	51.7280	28.4644	75.4320	56.8120
	80%	48.3360	19.5212	72.6560	55.5640
	100%	42.8600	15.5160	56.5880	50.6400
compound C	40%	63.7520	22.6224	92.9160	77.2280
	60%	63.7520	22.6224	84.0840	75.8240
	80%	56.4240	16.6068	80.4800	71.1320
	100%	51.2000	14.3560	71.6560	66.2600
compound D	40%	68.5840	19.0068	106.9400	88.4320
	60%	65.9360	23.5528	96.2720	82.1600
	80%	63.5680	11.9428	86.6320	81.6600
	100%	55.4640	12.4064	83.2640	71.3760

It is interesting to note that the values of molar volume enumerated from these equations are almost equal and the trend remains unaltered irrespective of the type of equation applied.
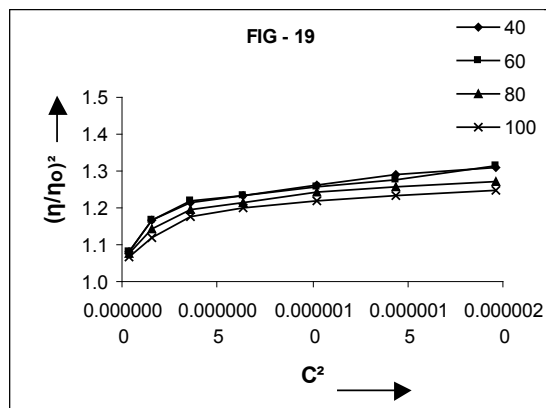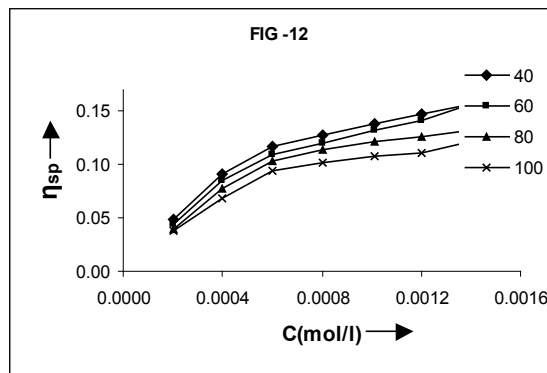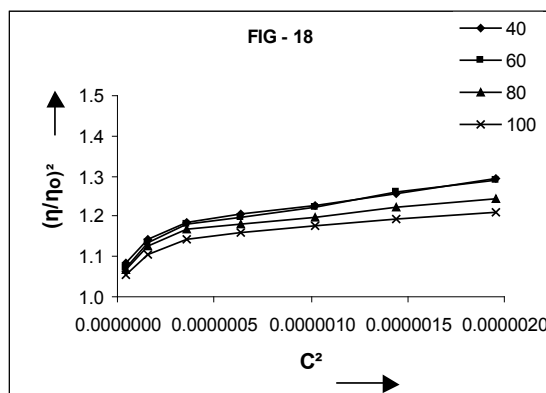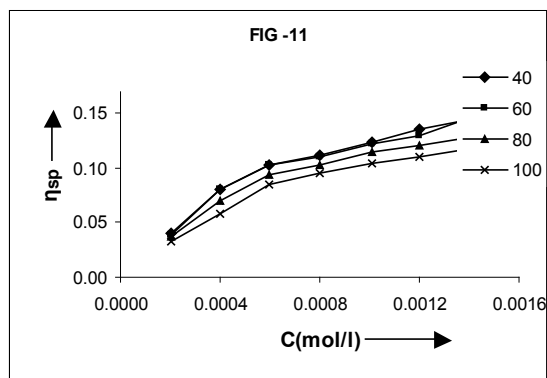
FIG -9

FIG -10
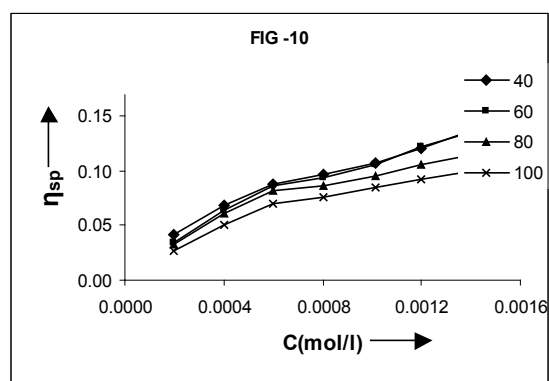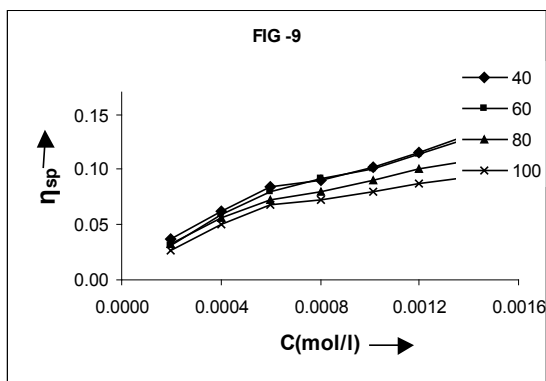
Fig. 9-12 Plot of η_{sp} versus C for compound A-D in benzene-methanol.

The Moulik equation.[17] also fits well to the solutions, as the plots $(\eta/\eta_0)^2$ vs. C^2 are almost linear.

$$(\eta/\eta_0)^2 = M + KC^2$$

Where M and K are constants.

The values of M and K have been calculated from the intercepts and slopes of the $(\eta/\eta_0)^2$ vs. C^2 plots and are recorded in Table-6.
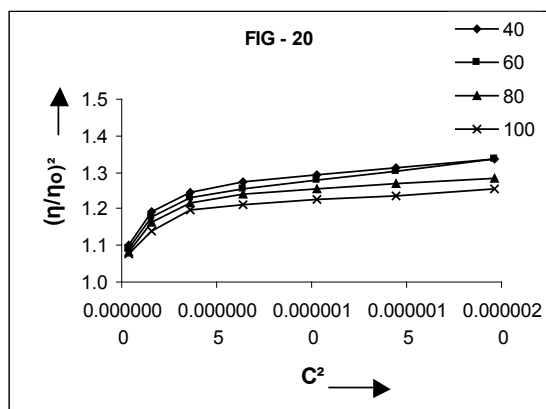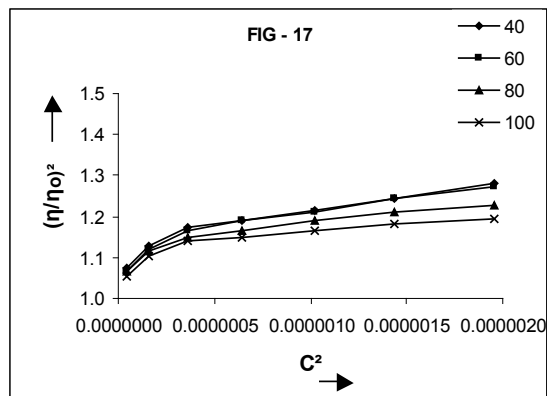

Fig.17-20 Plot of $[\eta/\eta_0]^2$ versus C^2 for compound A-D in benzene-methanol.

The viscosity data have also been interpreted in the light of Jones-Dole equation.[18]

$$(\eta/\eta_0-1)/\sqrt{C} = A + B\sqrt{C}$$

For convenience, the equation may be expressed as

$$\psi/\sqrt{C} = A + B\sqrt{C}$$

Where the coefficient A and B refer to solute-solute and solute-solvent interactions respectively. The plots $\psi / \sqrt{C}$ vs. $\sqrt{C}$
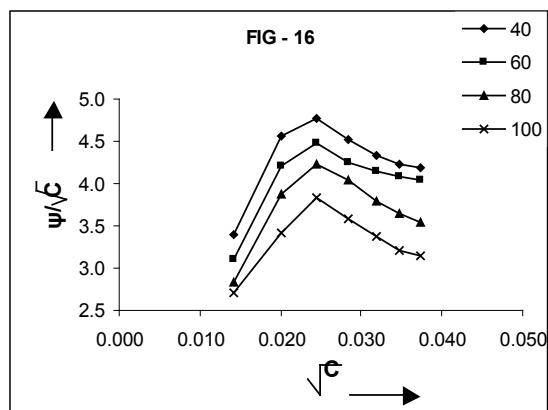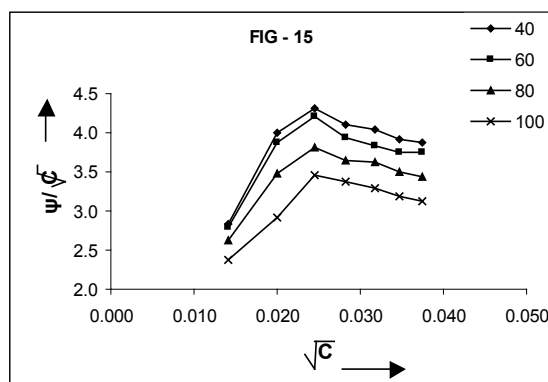
FIG - 13

FIG - 14

FIG - 15

FIG - 16
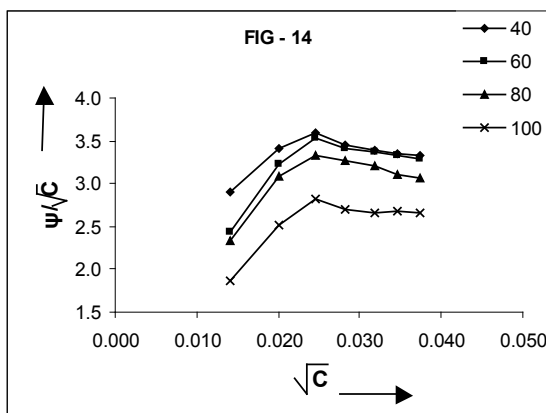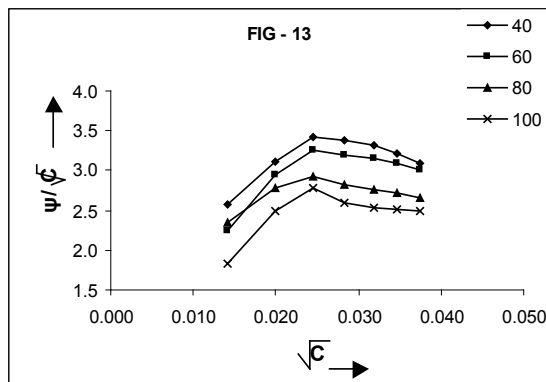
Fig. 13-16 Plot of $\psi /\sqrt{C}$ versus $\sqrt{C}$ for compound A-D in benzene-methanol.

for the molecules studied here were found to be linear, with least scatter. These plots are characterized by two straight lines intersecting at a point corresponding to the TCP of compounds. The values of TCP are in good agreement with the values derived from the plots of η, η_{sp} and ϕ vs. C. In view of the two intersecting straight lines for $\psi / \sqrt{C}$ vs. $\sqrt{C}$ plots, it is logical to evaluate two values of both the coefficients below and above TCP designated as A_1, B_1 and A_1, B_1 respectively.

30

Table – 6. Viscosity parameters in benzene – methanol derived from different equations

compound % of methanol		Moulik equation				Jones-Dole equation			
		M_1	M_2	K_1	K_2	A_1	A_2	B_1	B_2
compound A	40%	1.069	1.143	307187	70036	1.407	2.102	83.566	36.505
	60%	1.060	1.150	308995	62869	0.861	2.430	99.986	25.952
	80%	1.064	1.139	246195	47155	1.552	2.587	58.107	8.589
	100%	1.049	1.130	266636	34176	0.568	2.742	92.133	-6.651
compound B	40%	1.080	1.159	301055	68177	1.995	2.666	66.859	25.271
	60%	1.066	1.152	331527	71956	1.003	2.268	105.700	36.054
	80%	1.064	1.150	308373	48528	1.029	2.884	96.627	4.645
	100%	1.049	1.137	272615	37966	0.581	2.804	93.413	-3.860
compound C	40%	1.078	1.202	409288	57418	0.877	4.100	144.87	-5.829
	60%	1.078	1.197	409288	58197	0.898	4.496	139.79	-20.573
	80%	1.071	1.195	363636	41453	1.018	4.349	117.09	-24.338
	100%	1.059	1.180	333095	35690	0.866	4.350	104.72	-27.271
compound D	40%	1.096	1.243	445140	49099	1.610	5.564	134.880	-37.644
	60%	1.086	1.217	427059	60826	1.271	4.865	136.160	-22.329
	80%	1.077	1.224	411421	30275	0.966	5.589	137.170	-55.580
	100%	1.071	1.193	359936	31496	1.193	4.977	108.730	-49.811

It is observed that the values of these constants depend on the composition of the solvent mixtures.

CONCLUSION

It has been observed that the viscosity of the system increases with the increase in concentration. The increasing trend of viscosity may be due to combined effect of the variation of dielectric constant of solvent, degree of aggregation and nature of the compound agglomerate. The TCP values obtained from different viscosity data are in good agreement and show maximum concentration of molecular dispersion at which aggregation of molecule initiates.

It is noteworthy to point out on the basis of results obtained that the above treatment gives a phenomenological description of clustering profile and confirms the existence of aggregation in the non-aqueous mixed solvent.

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