Int. J. Chem. Sci.: 7(3), 2009, 1595-1605

VISCOMETRIC INVESTIGATIONS OF SOME DERIVATIVES OF 5-SUBSTITUTED INDOLE DIHYDROPYRIMIDINES 2 - ONES 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 303 ± 0.1 K. 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, Solute-solvent interaction.

INTRODUCTION

In the family of heterocyclic compounds, nitrogen containing heterocycles are an important class of compounds in the medicinal chemistry and they also contribute to the society from biological and industrial point, which helps to understand life processes[1]. This is because pyrimidines represent 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] etc. Biginelli compounds show a diverse range of biological activities. The interest focused on Biginelli compounds leads to the development of nitractin[3], that has

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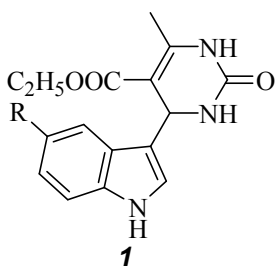
excellent activity against the virus of trachoma group. The same compounds also exhibit antibacterial activity. 4-Aryl dihydropyrimidines e. g. nifedipine are the important and most studied class as calcium channel modulars, in 1975, it leads to their introduction in clinical medicine for the treatment of cardiovascular diseases[4]. Some of the analogues were screened as antitumor agents. Pyrimidine–5-carboxamide was reported to possess anticarcinogenic, anti-inflammatory[5] and analgesic[6] activity.

The topsentins, as antiviral and antitumor agents from marine sponge, represent an emerging class of bis indole alkaloids. During the search of bioactive natural products, some cytotoxic and antifungal compounds belonging to class noprtopsentins[8] were obtained. 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[9]. Recently there is much interest in chemist towards the synthesis of small molecules, accelerating drug discovery[10].

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 this study. The mixed solvents have a tendency to interact with compounds, which affect the aggregation of molecules. The viscosity data based on various equations have 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



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Compound	R
A	H
B	Br
C	Cl
D	I

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[11, 12]. The further formylation with DMF/$POCl_3$ by Wismeyer – Hack method to obtain indole

3-carboxaldehyde resulted in good yields[13].

Cyclocondensation reaction of indole carboxaldehyde, urea and ethylacetoacetate in the presence of acid catalyst by refluxing in ethanol affords indole dihydropyrimidines ***(I)*** [14, 15].

Correlating ^{1}H NMR and IR data with data for corresponding compounds, the structural assignments of indole 3-carboxaldehydes and indole dihydropyrimidines were made. 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 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). 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[16-19]. 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.

Table 1 : Viscosity η of compound A-D in benzene-methanol at 303 ± 0.1 K

Comp.	% of methanol	Concentration						
		0.000	**0.000**	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**
A	40	0.583	0.594	0.603	0.607	0.613	0.619	0.628
	60	0.561	0.568	0.578	0.583	0.590	0.597	0.607
	80	0.541	0.549	0.558	0.562	0.567	0.570	0.576
	100	0.524	0.531	0.536	0.538	0.541	0.545	0.551

Cont…

Comp.	% of methanol	Concentration						
		0.000	**0.000**	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**
B	40	0.583	0.595	0.604	0.611	0.619	0.626	0.632
	60	0.561	0.572	0.580	0.586	0.593	0.600	0.609
	80	0.544	0.554	0.560	0.564	0.569	0.575	0.579
	100	0.524	0.531	0.538	0.542	0.546	0.549	0.553
C	40	0.586	0.601	0.613	0.616	0.623	0.629	0.636
	60	0.566	0.579	0.589	0.594	0.599	0.604	0.613
	80	0.546	0.555	0.564	0.567	0.571	0.578	0.582
	100	0.525	0.535	0.541	0.544	0.549	0.553	0.555
D	40	0.585	0.596	0.607	0.614	0.622	0.631	0.640
	60	0.566	0.579	0.589	0.593	0.601	0.608	0.617
	80	0.548	0.558	0.567	0.570	0.576	0.581	0.586
	100	0.528	0.538	0.544	0.547	0.552	0.556	0.560

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). 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.

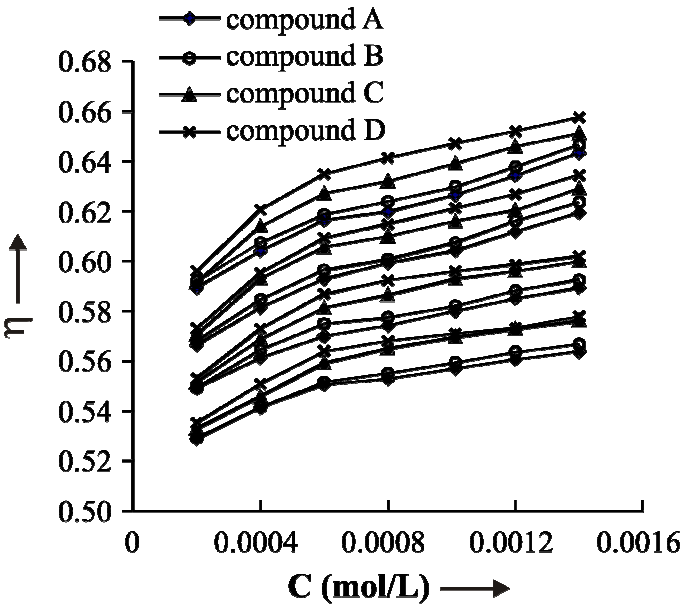

Fig. 1 : Plot of η v/s C for compound A-D in benzene-methanol

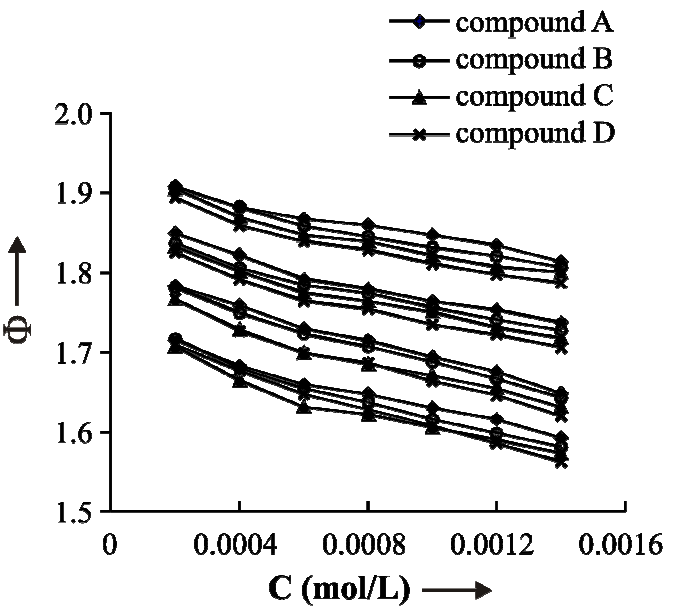

Fig. 2 : Plot of ϕ v/s C for compound A-D in benzene-methanol

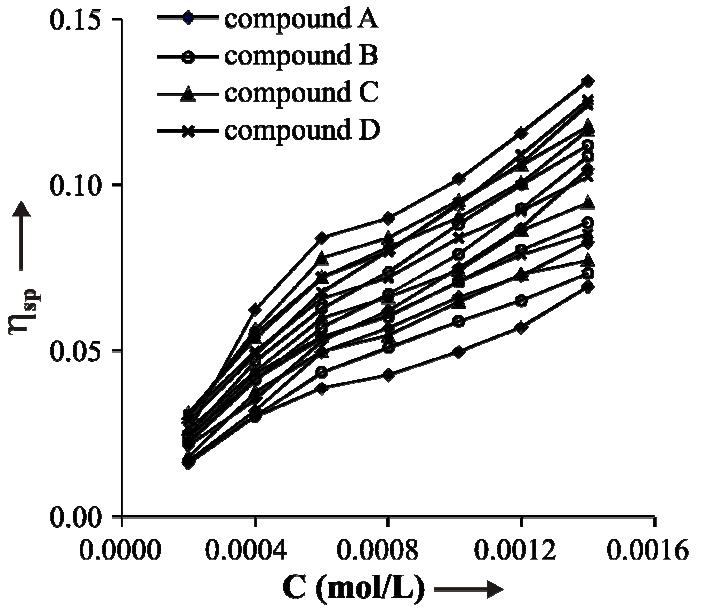

Fig. 3 : Plot of η_{sp} v/s C for compound A-D in benzene-methanol

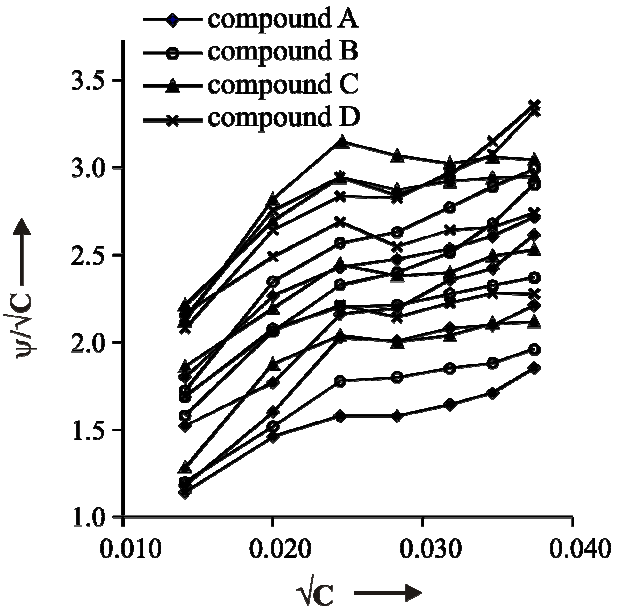

Fig. 4 : Plot of ψ v/s √C for compound A-D in benzene-methanol

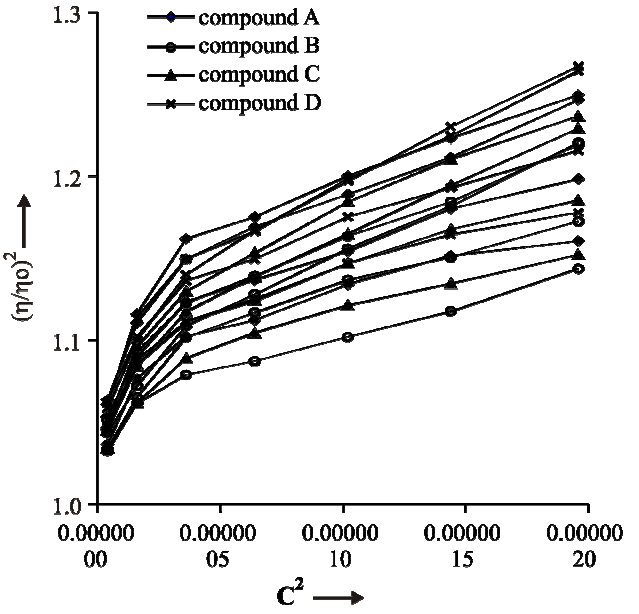

Fig. 5 : Plot $[\eta/\eta_o]^2$ versus C^2 for compound A-D in benzene-methanol

Table 2: Values of molar volume ($\overline{V}$) in benzene – methanol derived from Einstein and Thomas equations

Comp.	% of methanol	Einstein equation		Thomas equation	
		V_1	V_2	V_1	V_2
A	40	34.084	24.244	56.568	38.554
	60	31.438	28.130	46.272	32.396
	80	32.914	16.982	36.432	34.774
	100	22.541	17.553	36.020	23.044
B	40	38.514	25.470	52.724	43.528
	60	34.686	27.831	48.056	36.286
	80	30.120	19.136	53.556	36.364
	100	26.569	14.812	36.052	31.362

Comp.	% of methanol	Einstein equation		Thomas equation	
		V_1	V_2	V_1	V_2
C	40	47.836	22.495	64.236	52.632
	60	40.796	23.316	69.392	49.404
	80	33.600	19.576	58.216	40.136
	100	31.805	15.319	42.572	34.460
D	40	38.865	30.321	73.644	45.248
	60	41.712	29.188	67.380	45.828
	80	35.223	20.052	63.320	45.140
	100	30.254	16.527	54.196	38.267

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. 2). 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.

Table 3: Viscosity parameters in benzene – methanol derived from different equations

Comp.	% of methanol	Moulik equation				Jones-Dole equation			
		M_1	M_2	K_1	K_2	A_1	A_2	B_1	B_2
A	40	1.049	1.101	214715	59952	0.959	1.148	61.772	1.148
	60	1.037	1.084	201755	69364	0.629	0.339	60.825	0.339
	80	1.028	1.092	209556	41155	0.022	1.418	80.962	1.418
	100	1.032	1.059	138778	42377	0.558	0.734	42.821	0.734

Comp.	% of methanol	Moulik equation				Jones-Dole equation			
		M_1	M_2	K_1	K_2	A_1	A_2	B_1	B_2
B	40	1.046	1.117	242752	62736	0.597	1.424	82.703	42.142
	60	1.041	1.095	219326	68810	0.571	0.675	72.672	58.610
	80	1.046	1.097	188930	46284	1.001	1.363	50.634	27.245
	100	1.030	1.083	167577	35601	0.411	1.319	55.668	16.775
C	40	1.056	1.141	306297	56073	0.697	2.407	102.830	19.296
	60	1.059	1.130	260555	58553	1.228	2.165	71.083	24.106
	80	1.049	1.107	213929	47853	1.064	1.643	56.488	23.638
	100	1.035	1.093	197794	36406	0.278	1.352	74.434	21.098
D	40	1.053	1.121	248957	73047	1.042	1.190	70.130	57.074
	60	1.059	1.119	264473	75892	1.090	1.330	78.102	52.171
	80	1.058	1.121	224558	49170	1.460	1.994	50.625	19.798
	100	1.048	1.103	188256	39750	0.999	1.722	50.767	15.469

The viscosity results have been explained in terms of equations proposed by Einstein[20] and Vand[21].

Einstein : $\eta_{sp} = 2.5\ \overline{V}\ C$

Vand : $1/C = (0.921/\overline{V})\ x\ [1/\log(\eta/\eta_0)] + Q\overline{V}$

Where $\overline{V}$, 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[22]. The values of molar volume $\overline{V}$ (Table 2) were obtained from the plots of Einstein equation and Vand equation (Fig. 3). 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. The Moulik equation[23] 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 (Fig. 5) and are recorded in Table 3.

The viscosity data have also been interpreted in the light of Jones-Dole equation[24].

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

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. 4) 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_2, B_2, respectively (Table 3). 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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Accepted : 12.04.2009