



Solubility of pyrimidine derivatives in different organic solvents at different temperatures

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ABSTRACT

The objective of this study was to measure and correlate the solubility of pyrimidine derivatives in five different solvents namely chloroform, N,N-dimethylformamide, tetrahydrofuran, 1,4-dioxane and ethyl acetate from 298.15 to 328.15 K under atmospheric pressure of 0.1 MPa using gravimetric method. The characterization of all the synthesized compounds was done by IR, NMR and mass spectra. The modified Apelblat and Buchowski-Ksiazczak λh equations were used to correlate the experimental solubility data. Using Van't Hoff and Gibb's equations, some thermodynamic parameters such as Gibb's free energy, enthalpy and entropy of dissolution were evaluated from solubility data. It is found that solubility increases with temperature.

Keywords: pyrimidine derivatives; Apelblat equation; Buchowski-Ksiazczak λh equation; Gibb's energy

1. INTRODUCTION

Pyrimidine skeleton is known to be present in several biological molecules, deoxyribonucleic acid, ribonucleic acid, thymine, cytosine, in some vitamins such as thiamine, riboflavin and folic acid etc [1]. Pyrimidine derivatives exhibit variety of

pharmacological properties, such as anti-HIV [2], anti-histamine [3], anti-malarial [4], anti-arrhythmic [5], antiviral [6], antitumor [7], anti-diabetic [8] and anti-allergic [9], etc.

Literature survey shows that various researchers have studied the solubility of various organic [10,11], inorganic [12-14] and polymeric [15,16] materials, drugs [17-19], ionic liquids [20,21], protein [22], amino acid [23], etc in a wide variety of solvents.

Dependence of solubility on temperature allows thermodynamic analysis which explains the molecular mechanisms, involved in the solution processes [24].

In the present work the synthesis and solubility of pyrimidine derivatives in chloroform, N,N-dimethyl formamide, tetrahydrofuran, 1,4-dioxane and ethyl acetate at 298.15 K to 328.15 K temperature range are given. These data were correlated with a modified Apelblat and Buchowski-Ksiazczak λh equations and by these data some thermodynamic parameters were also evaluated.

2. EXPERIMENTAL

2. 1. Materials

Isobutyl propionate, different substituted aldehydes, urea and phenacyl bromide used for the synthesis, were supplied from Spectrochem Pvt. Ltd. (Mumbai, India) and were used without any treatment.

The solvents used in solubility determination were of AR grade supplied by Spectrochem Pvt. Ltd. (Mumbai, India) and were purified according to the standard procedure [25]. All the distilled solvents were stored over molecular sieves. The purity of solvents was confirmed by GC-MS (SHIMADZU-Model No.-QP-2010) and was found to be > 99%. The source and mole fraction purity of solvents are given in Table 1.

Table 1. The source and mole fraction purity of solvents and materials.

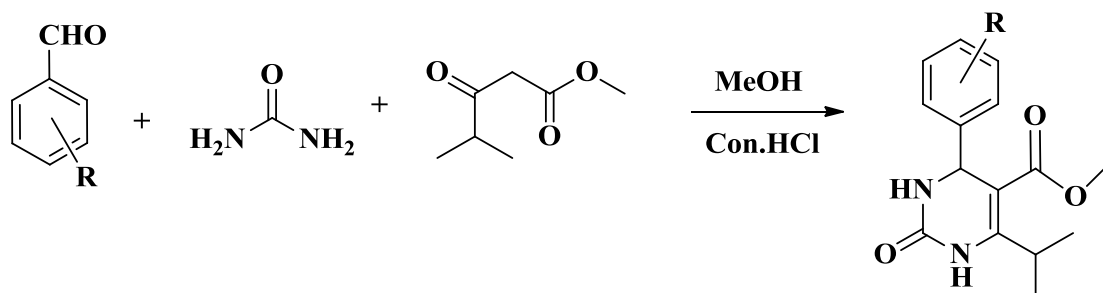
<i>Solvents/Chemicals</i>	<i>Source</i>	<i>Mole fraction purity</i>
Chloroform	Allied chemical corporation	0.995 ^s
DMF	Allied chemical corporation	0.993 ^s
THF	Allied chemical corporation	0.991 ^s
1,4-Dioxane	Allied chemical corporation	0.994 ^s
Ethyl acetate	Allied chemical corporation	0.996 ^s
Isobutyl propionate	Spectrochem	>0.950 ^s
aldehydes	Spectrochem	>0.950 ^s
urea	Spectrochem	>0.950 ^s
Phenacyl bromide	Spectrochem	>0.950 ^s
RP-1 to RP-5	Synthesis	0.994 ^t

^s: Analytical grade reagent dried over anhydrous sodium sulphate and kept over molecular sieves.

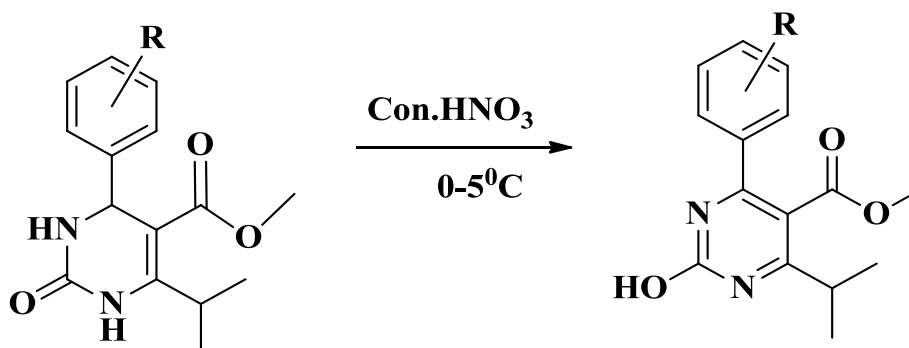
^t: HPLC method.

2. 2. Synthesis

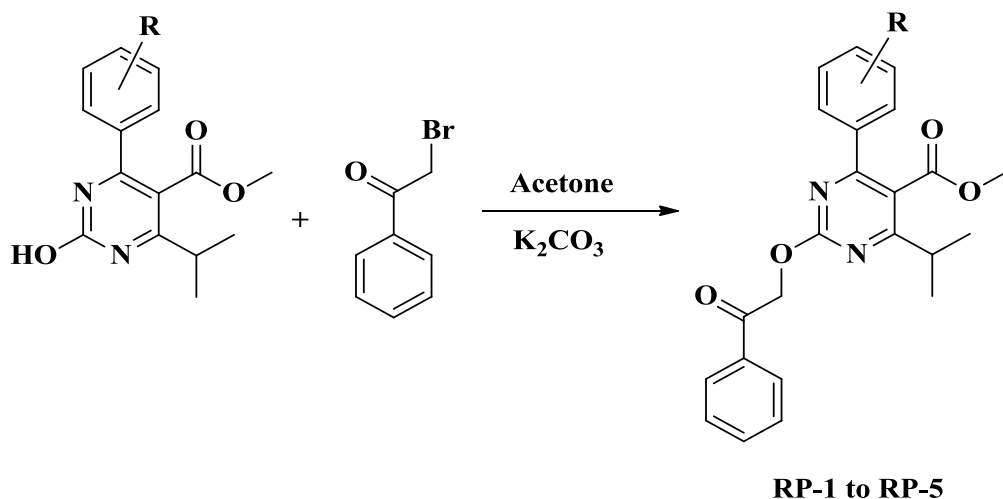
Synthesis of dihydropyrimidine derivatives: A methanolic solution of different substituted aldehyde (0.01 mol), isobutyl propionate (0.01 mol) and urea (0.012 mol) was refluxed for 16 hrs in presence of copper chloride and concentrated sulphuric acid. The completion of reaction was confirmed by analytical thin layer chromatography (TLC) (Performed on aluminum coated plates Gel 60F₂₅₄ (E. Merck)) using (3:2 - Hexane: Ethyl acetate) as mobile phase. After completion of reaction, the reaction mass was cooled and the resulting solid was filtered, washed with methanol to remove unreacted reagents and dried under vacuum to give crude product.



Oxidation of dihydropyrimidine derivatives: 10 ml nitric acid (60%) was stirred at 0°C for 10 min. and then above synthesized compound (0.01mol) was added fractionally to the chilled nitric acid. The mixture was then stirred at 0°C temperature for 30 min. The progress of reaction was monitored by thin layer chromatography. The reaction mixture was then poured into cold water and was neutralized with saturated sodium bicarbonate solution. The solid was filtered, washed with water and dried. The crude product was directly used for the next step.



Synthesis of methyl 4-isopropyl-2-(2-oxo-2-phenylethoxy)-6-phenylpyrimidine-5-carboxylate derivatives: Equimolar solution of above product and phenacyl bromide in dry acetone was refluxed in presence of dry K₂CO₃ for 1hr. The solvent from the reaction mixture was evaporated to get solid mass. This solid mass was poured into crushed ice to remove K₂CO₃. The solution was filtered. The resulting solid product was washed with cold water and dried under vacuum.



2. 3. Spectroscopy study

Spectroscopic study of pyrimidine derivatives has done by IR, ^1H NMR and mass spectroscopy. The IR spectra were recorded on IR affinity 1S (furrier transport infra-red spectroscopy) and ^1H -NMR spectra were taken on Bruker AVANCE II 400, in DMSO- d_6 using TMS as an internal standard. The NMR signals are reported in δ ppm. The mass spectra were determined using direct inlet probe on a Shimanzu GCMS-QP-2010 mass spectrometer. The melting point was measured by Differential Scanning Calorimeter (Shimadzu-DSC-60) which was calibrated using Indium and Zinc. The physical constants of all the five synthesized compounds (RP-1 to RP-5) are given in Table 2.

Table 2. Physical constants of synthesized compounds.

Compound Code	Substitution R	M.F.	M.W.	Yield (%)	M. P. ($^{\circ}\text{C}$)	R_f^* value
RP-1	-4- F	$\text{C}_{23}\text{H}_{21}\text{FN}_2\text{O}_4$	408	86	118	0.53
RP-2	-4- Br	$\text{C}_{23}\text{H}_{21}\text{BrN}_2\text{O}_4$	469	85	112	0.54
RP-3	-3,4-di- OCH_3	$\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_6$	450	87	115	0.59
RP-4	-3- OCH_3	$\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_5$	420	82	97	0.58
RP-5	-4- Cl	$\text{C}_{23}\text{H}_{21}\text{ClN}_2\text{O}_4$	424	84	101	0.54

*2:3 - Hexane: Ethyl acetate

2. 4. Solubility measurement

The solubility measurement was carried out by gravimetric method [26-28]. An excess mass of synthesized pyrimidine derivatives were added to a known mass of solvent. The solution was heated at constant temperature with continuous stirring until equilibrium

established. After few hours the stirring was stopped and the solution was kept at constant temperature for 2 hours. After 2 hours the change in concentration was less than 1%. So this solution was filtered and 2 ml of the solution was taken in pre weighted measuring vial. This vial was instantly weighted to determine the mass of the sample and then kept in vacuum oven at 318.15 K to evaporate solvent present in it. When in the vial mass of residue reached to the constant value then the final mass of residue was recorded. The weights were taken in electronic balance (Mettler Toledo AB204-S, Switzerland) with uncertainty of ± 0.0001 g. During the whole experiment, at each temperature the measurement was conducted three times and average value was used to determine the mole fraction solubility of solute (x_i) in solvents by using equation 1 and given in Table 3.

$$x_i = \frac{\frac{m_2}{M_2}}{\frac{m_1}{M_1} + \frac{m_2}{M_2}} \quad (1)$$

where, M_1 and M_2 is the molecular weight of solvent and compound respectively. m_1 and m_2 are weights of solvent and synthesized compound in the solution respectively.

3. RESULTS AND DISCUSSION

3. 1. Spectral data

RP-1:

IR (cm^{-1}): 1722.43 (carbonyl str. in COOCH_3), 1695.43 (Acyclic carbonyl str.), 1598.99 (Ar-C=C str.), 1390.68 (alkane C-H bending), 1334.78 (C-O str. of ester), 1066.64 (C-O str. of ether), 850.61 (p-di substituted aromatic ring). ^1H NMR (DMSO-d_6) δ (ppm): 1.250 (6H, doublet, $-\text{CH}_3$ of isopropyl), 3.12 (1H, multiplet, C-H of isopropyl), 3.715 (3H, singlet, $-\text{COOCH}_3$), 5.983 (2H, singlet, $-\text{OCH}_2$), 7.017 (2H, doublet, Ar-CH), 7.520 (2H, doublet, Ar-CH), 7.600 (2H, triplet, Ar-CH), 7.744 (1H, triplet, Ar-CH) and 8.043 (2H, doublet, Ar-CH). MS: (m/z) = 408

RP-2:

IR (cm^{-1}): 1722.43 (carbonyl str. in COOCH_3), 1695.43 (Acyclic carbonyl str.), 1546.91 (Ar-C=C str.), 1390.68 (alkane C-H bending), 1334.74 (C-O str. of ester), 1066.64 (C-O str. of ether), 850.61 (p-di substituted aromatic ring). ^1H NMR (DMSO-d_6) δ (ppm): 1.258 (6H, doublet, $-\text{CH}_3$ of isopropyl), 3.129 (1H, multiplet, C-H of isopropyl), 3.716 (3H, singlet, $-\text{COOCH}_3$), 5.985 (2H, singlet, $-\text{OCH}_2$), 7.019 (2H, doublet, Ar-CH), 7.528 (2H, doublet, Ar-CH), 7.609 (2H, triplet, Ar-CH), 7.746 (1H, triplet, Ar-CH) and 8.048 (2H, doublet, Ar-CH). MS: (m/z) = 469

RP-3:

IR (cm^{-1}): 1722.43 (carbonyl str. in COOCH_3), 1695.43 (Acyclic carbonyl str.), 1546.91 (Ar-C=C str.), 1390.68 (alkane C-H bending), 1334.74 (C-O str. of ester), 1008.77 (C-O str. of ether). ^1H NMR (DMSO-d_6) δ (ppm): 1.261 (6H, doublet, $-\text{CH}_3$ of isopropyl), 3.026 (1H, multiplet, C-H of isopropyl), 3.546 (3H, singlet, $-\text{COOCH}_3$), 3.827 (6H, singlet, $-\text{OCH}_3$),

5.885 (2H, singlet, -OCH₂), 7.014 (1H, doublet, Ar-CH), 7.115 (1H, doublet, Ar-CH), 7.214 (1H, singlet, Ar-CH), 7.598 (2H, triplet, Ar-CH), 7.740 (1H, triplet, Ar-CH), 8.040 (2H, doublet, Ar-CH).

MS: (m/z) = 450

RP-4:

IR (cm⁻¹): 1750.00 (carbonyl str. in -COOCH₃), 1541.12 (Acyclic carbonyl str.), 1446.61 (Ar-C=C str.), 1365.60 (alkane C-H bending), 1284.59 (C-O str. of ester), 1026.16 (C-O str. of ether), 840.99 (p-di substituted aromatic ring). 792.77 (m-di-substituted aromatic ring). ¹H NMR (DMSO-d₆) δ (ppm): 1.260 (6H, doublet, -CH₃ of isopropyl), 3.024 (1H, multiplet, C-H of isopropyl), 3.536 (3H, singlet, -COOCH₃), 3.820 (1H, singlet, -OCH₃), 5.861 (2H, singlet, -OCH₂), 7.570 (7H, multiplet, Ar-CH) and 8.062 (2H, doublet, Ar-CH).

MS: (m/z) = 420

RP-5:

IR (cm⁻¹): 1730.21 (carbonyl str. in COOCH₃), 1670.00 (Acyclic carbonyl str.), 1554.68 (Ar-C=C str.), 1383.01 (alkane C-H bending), 1334.78 (C-O str. of ester), 1082.10 (C-O str. of ether), 721.40 and 792.77 (m-di-substituted aromatic ring). ¹H NMR (DMSO-d₆) δ (ppm): 1.255 (6H, doublet, -CH₃ of isopropyl), 3.125 (1H, multiplet, C-H of isopropyl), 3.715 (3H, singlet, -COOCH₃), 5.984 (2H, singlet, -OCH₂), 7.018 (2H, doublet, Ar-CH), 7.524 (2H, doublet, Ar-CH), 7.608 (2H, triplet, Ar-CH), 7.745 (1H, triplet, Ar-CH) and 8.047 (2H, doublet, Ar-CH).

MS: (m/z) = 424

3. 2. Solubility data correlation and correlation models

The mole fraction solubilities x_i in some selected solvents at different temperatures is given in Table 3. The diagrammatic variation of solubility of all the synthesized compounds in studied solvents is given in Figure 1. As evident from Figure 1 that solubility is maximum for RP-1 in chloroform, DMF and 1,4-dioxane whereas for RP-2 in THF and for RP-3 in ethyl acetate. Different solvents have different dielectric constant, dipole moment and hydrogen bond capacity as shown in Table 4. Thus, there is no regular trend of solubility of compounds with respect to electronegativity of substituted group and dielectric constant, dipole moment and hydrogen donating capacity of solvents.

Table 3. Experimental mole fraction solubilities (x_i), calculated mole fraction solubilities (x_{ci}) and relative deviation (RD) of synthesized compounds in selected solvents at different temperature at 0.1 MPaⁿ

T/K	x_i	x_{ci}^a	$10^2 RD^a$	x_{ci}^b	$10^2 RD^b$
Chloroform					
RP-1					
298.15	0.0191	0.0191	-0.023	0.0195	-2.218
303.15	0.0230	0.0229	0.362	0.0229	0.302

308.15	0.0269	0.0272	-1.087	0.0269	0.053
313.15	0.0318	0.0318	0.119	0.0313	1.576
318.15	0.0368	0.0367	0.337	0.0363	1.327
323.15	0.0419	0.0418	0.213	0.0419	-0.016
328.15	0.0470	0.0471	-0.371	0.0482	-2.568
RP-2					
298.15	0.0288	0.0287	0.377	0.0287	0.302
303.15	0.0298	0.0298	0.001	0.0298	-0.094
308.15	0.0308	0.0309	-0.479	0.0309	-0.585
313.15	0.0319	0.0320	-0.402	0.0321	-0.511
318.15	0.0330	0.0332	-0.360	0.0332	-0.466
323.15	0.0343	0.0343	0.061	0.0343	-0.035
328.15	0.0355	0.0354	0.354	0.0354	0.275
RP-3					
298.15	0.0036	0.0036	-0.341	0.0036	0.792
303.15	0.0042	0.0042	0.389	0.0042	0.099
308.15	0.0048	0.0048	-0.147	0.0049	-1.252
313.15	0.0056	0.0056	-0.208	0.0057	-1.540
318.15	0.0065	0.0065	-0.687	0.0066	-1.698
323.15	0.0076	0.0075	0.658	0.0076	0.494
328.15	0.0087	0.0088	-0.325	0.0087	0.823
RP-4					
298.15	0.0167	0.0167	0.065	0.0166	0.989
303.15	0.0184	0.0184	0.041	0.0184	-0.024
308.15	0.0201	0.0203	-0.810	0.0204	-1.443
313.15	0.0224	0.0223	0.238	0.0225	-0.545
318.15	0.0247	0.0247	0.069	0.0248	-0.488
323.15	0.0273	0.0272	0.270	0.0272	0.299
328.15	0.0300	0.0301	-0.358	0.0298	0.588
RP-5					
298.15	0.0135	0.0135	-0.024	0.0134	1.228
303.15	0.0146	0.0146	-0.035	0.0146	-0.161
308.15	0.0157	0.0158	-0.423	0.0159	-1.338
313.15	0.0172	0.0171	0.328	0.0173	-0.795
318.15	0.0186	0.0187	-0.435	0.0188	-1.245
323.15	0.0204	0.0203	0.292	0.0203	0.304
328.15	0.0222	0.0222	-0.224	0.0219	1.066
DMF					
RP-1					
298.15	0.0078	0.0078	-0.788	0.0079	-1.737
303.15	0.0109	0.0107	2.166	0.0107	2.171
308.15	0.0140	0.0143	-2.584	0.0143	-2.034
313.15	0.0193	0.0191	1.268	0.0189	1.942
318.15	0.0246	0.0250	-1.538	0.0249	-1.059
323.15	0.0329	0.0324	1.546	0.0324	1.470
328.15	0.0412	0.0415	-0.656	0.0419	-1.611

RP-2					
298.15	0.0027	0.0027	0.362	0.0027	0.909
303.15	0.0030	0.0030	-0.958	0.0030	-1.372
308.15	0.0034	0.0034	-0.075	0.0035	-1.029
313.15	0.0039	0.0039	0.408	0.0039	-0.690
318.15	0.0044	0.0044	-0.503	0.0044	-1.387
323.15	0.0050	0.0050	0.487	0.0050	0.179
328.15	0.0056	0.0056	-0.433	0.0056	0.151
RP-3					
298.15	0.0082	0.0082	0.199	0.0082	0.014
303.15	0.0093	0.0093	-0.213	0.0093	-0.442
308.15	0.0105	0.0106	-0.347	0.0106	-0.600
313.15	0.0120	0.0120	0.248	0.0120	-0.008
318.15	0.0134	0.0135	-0.823	0.0135	-1.067
323.15	0.0152	0.0151	0.337	0.0152	0.126
328.15	0.0170	0.0170	0.035	0.0170	-0.130
RP-4					
298.15	0.0078	0.0078	0.017	0.0079	-0.097
303.15	0.0092	0.0092	-0.005	0.0092	-0.172
308.15	0.0107	0.0107	-0.535	0.0108	-0.732
313.15	0.0125	0.0125	0.181	0.0125	-0.020
318.15	0.0144	0.0144	-0.339	0.0145	-0.525
323.15	0.0167	0.0166	0.483	0.0166	0.335
328.15	0.0190	0.0191	-0.358	0.0191	-0.451
RP-5					
298.15	0.0173	0.0172	0.118	0.0173	0.007
303.15	0.0190	0.0189	0.344	0.0190	0.199
308.15	0.0207	0.0207	-0.403	0.0208	-0.568
313.15	0.0226	0.0226	-0.187	0.0227	-0.355
318.15	0.0244	0.0247	-1.024	0.0247	-1.183
323.15	0.0268	0.0268	0.027	0.0268	-0.105
328.15	0.0292	0.0290	0.595	0.0291	0.499
THF					
RP-1					
298.15	0.0063	0.0063	-0.437	0.0064	-1.341
303.15	0.0087	0.0085	1.856	0.0085	1.729
308.15	0.0110	0.0113	-3.097	0.0113	-2.783
313.15	0.0151	0.0149	1.298	0.0148	1.721
318.15	0.0192	0.0193	-1.005	0.0193	-0.741
323.15	0.0253	0.0249	1.778	0.0249	1.601
328.15	0.0313	0.0316	-1.018	0.0319	-1.910
RP-2					
298.15	0.0092	0.0094	-1.904	0.0094	-1.308
303.15	0.0130	0.0126	2.930	0.0126	2.838
308.15	0.0167	0.0168	-0.418	0.0169	-0.899
313.15	0.0224	0.0222	0.871	0.0223	0.291

318.15	0.0280	0.0292	-4.032	0.0293	-4.479
323.15	0.0388	0.0381	1.769	0.0381	1.740
328.15	0.0496	0.0495	0.131	0.0492	0.728
RP-3					
298.15	0.0085	0.0086	-1.261	0.0086	-1.386
303.15	0.0097	0.0096	0.766	0.0096	0.607
308.15	0.0108	0.0107	1.118	0.0107	0.941
313.15	0.0119	0.0119	0.380	0.0119	0.197
318.15	0.0129	0.0131	-1.763	0.0131	-1.941
323.15	0.0144	0.0144	-0.145	0.0144	-0.297
328.15	0.0159	0.0158	0.307	0.0159	0.191
RP-4					
298.15	0.0063	0.0062	0.648	0.0061	2.265
303.15	0.0079	0.0079	0.341	0.0079	0.110
308.15	0.0096	0.0100	-3.573	0.0101	-4.917
313.15	0.0128	0.0126	1.271	0.0128	-0.301
318.15	0.0161	0.0160	0.587	0.0162	-0.565
323.15	0.0206	0.0203	1.666	0.0203	1.615
328.15	0.0252	0.0256	-1.583	0.0252	0.110
RP-5					
298.15	0.0109	0.0109	-0.057	0.0110	-0.301
303.15	0.0117	0.0117	0.194	0.0117	-0.071
308.15	0.0124	0.0125	-0.145	0.0125	-0.423
313.15	0.0132	0.0132	-0.366	0.0133	-0.649
318.15	0.0140	0.0141	-0.265	0.0141	-0.542
323.15	0.0149	0.0149	-0.126	0.0150	-0.389
328.15	0.0158	0.0158	0.222	0.0158	-0.018
1,4-Dioxane					
RP-1					
298.15	0.0105	0.0105	-0.445	0.0104	0.565
303.15	0.0114	0.0114	0.364	0.0114	0.157
308.15	0.0123	0.0123	0.144	0.0124	-0.755
313.15	0.0133	0.0133	0.091	0.0134	-1.000
318.15	0.0143	0.0144	-0.946	0.0145	-1.766
323.15	0.0157	0.0157	0.147	0.0157	0.053
328.15	0.0171	0.0171	0.088	0.0169	1.114
RP-2					
298.15	0.0072	0.0072	0.555	0.0072	0.237
303.15	0.0077	0.0077	-0.169	0.0077	-0.507
308.15	0.0082	0.0083	-0.519	0.0083	-0.865
313.15	0.0088	0.0088	-0.154	0.0088	-0.498
318.15	0.0093	0.0094	-1.030	0.0094	-1.367
323.15	0.0100	0.0100	0.084	0.0100	-0.232
328.15	0.0107	0.0106	0.621	0.0106	0.331
RP-3					
298.15	0.0093	0.0093	-0.054	0.0093	0.100

303.15	0.0099	0.0099	-0.224	0.0099	-0.090
308.15	0.0105	0.0106	-0.081	0.0105	0.041
313.15	0.0112	0.0112	0.017	0.0112	0.136
318.15	0.0119	0.0119	0.175	0.0118	0.298
323.15	0.0125	0.0125	-0.381	0.0125	-0.245
328.15	0.0132	0.0132	-0.032	0.0132	0.122
RP-4					
298.15	0.0040	0.0040	0.727	0.0040	0.665
303.15	0.0049	0.0049	-0.597	0.0049	-0.728
308.15	0.0059	0.0060	-1.840	0.0060	-2.011
313.15	0.0074	0.0074	0.671	0.0074	0.497
318.15	0.0089	0.0089	0.513	0.0089	0.359
323.15	0.0108	0.0107	0.884	0.0107	0.777
328.15	0.0127	0.0128	-1.015	0.0128	-1.053
RP-5					
298.15	0.0096	0.0096	-0.110	0.0095	0.616
303.15	0.0101	0.0101	-0.244	0.0101	-0.360
308.15	0.0107	0.0107	0.095	0.0108	-0.500
313.15	0.0114	0.0114	-0.049	0.0115	-0.778
318.15	0.0121	0.0121	-0.314	0.0122	-0.853
323.15	0.0129	0.0129	-0.119	0.0129	-0.161
328.15	0.0138	0.0138	-0.051	0.0137	0.682
Ethyl acetate					
RP-1					
298.15	0.0152	0.0151	0.172	0.0154	-1.373
303.15	0.0176	0.0176	0.187	0.0176	0.051
308.15	0.0199	0.0202	-1.451	0.0200	-0.789
313.15	0.0230	0.0229	0.319	0.0227	1.190
318.15	0.0260	0.0258	0.563	0.0257	1.124
323.15	0.0289	0.0288	0.250	0.0289	0.003
328.15	0.0318	0.0319	-0.520	0.0324	-2.070
RP-2					
298.15	0.0033	0.0038	-1.4815	0.0033	1.195
303.15	0.0040	0.0045	-1.3261	0.0040	0.279
308.15	0.0048	0.0054	-1.2404	0.0048	-0.251
313.15	0.0057	0.0065	-1.4050	0.0058	-2.082
318.15	0.0067	0.0078	-1.6932	0.0070	-4.119
323.15	0.0084	0.0094	-1.2357	0.0083	1.287
328.15	0.0100	0.0114	-1.3882	0.0098	2.039
RP-3					
298.15	0.0041	0.0042	-1.524	0.0044	-7.090
303.15	0.0072	0.0069	4.558	0.0069	4.813
308.15	0.0102	0.0108	-5.508	0.0104	-1.945
313.15	0.0168	0.0164	2.385	0.0157	6.512
318.15	0.0235	0.0240	-2.189	0.0233	0.892
323.15	0.0350	0.0341	2.509	0.0342	2.307

328.15	0.0465	0.0470	-1.101	0.0496	-6.670
RP-4					
298.15	0.0117	0.0118	-0.656	0.0120	-2.566
303.15	0.0145	0.0144	0.937	0.0144	0.861
308.15	0.0172	0.0173	-0.286	0.0171	0.658
313.15	0.0205	0.0205	0.094	0.0202	1.318
318.15	0.0238	0.0240	-0.721	0.0238	0.114
323.15	0.0278	0.0278	-0.051	0.0279	-0.264
328.15	0.0319	0.0319	0.178	0.0325	-1.700
RP-5					
298.15	0.0059	0.0060	-0.245	0.0060	-0.208
303.15	0.0066	0.0066	0.045	0.0066	0.051
308.15	0.0072	0.0073	-0.431	0.0073	-0.442
313.15	0.0080	0.0080	0.007	0.0080	-0.007
318.15	0.0088	0.0088	0.584	0.0088	0.578
323.15	0.0096	0.0096	0.110	0.0096	0.125
328.15	0.0104	0.0105	-0.639	0.0105	-0.594

(x_i) = Experimental mole fraction solubility with an uncertainty of ± 0.00001

(x_{ci}^a) and (x_{ci}^b) = Calculated mole fraction solubility

^a = Values obtained by Apelblat equation (eq. 2)

^b = Values obtained by Buchowski-Ksiazczak equation (eq. 3)

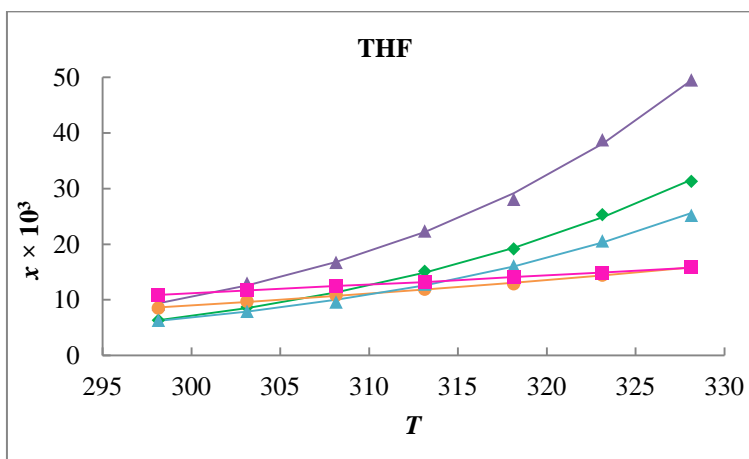
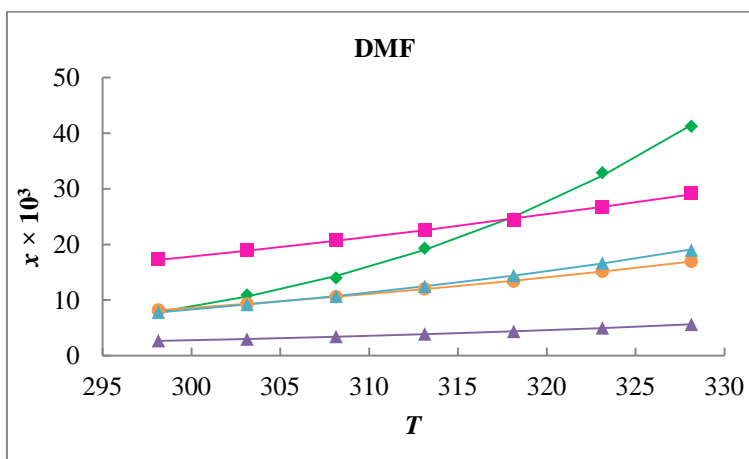
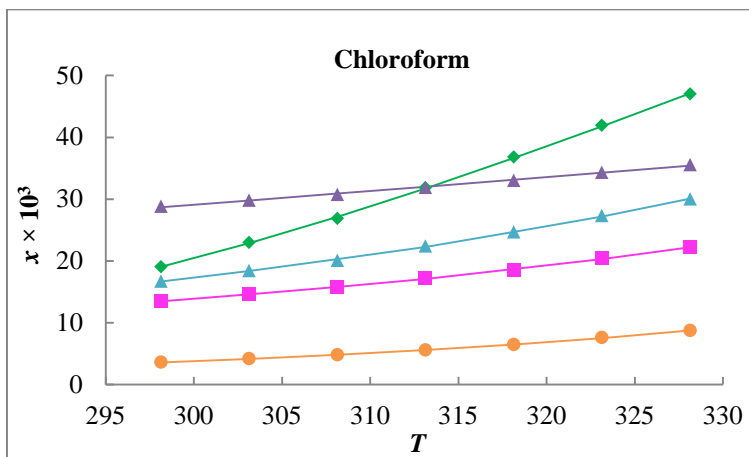
η = Standard uncertainty $u_r(T) = \pm 0.1\text{K}$, $u_r(P) = \pm 0.05\text{MPa}$ and $u_r(x) = \pm 0.0103$

Table 4. Dielectric constant, dipole moment and hydrogen bond capacity of studied solvents at 293.15 K.

Solvent	Dielectric constant	Dipole moment	δH Hydrogen bonding
Chloroform	4.81	1.15	5.7
DMF	36.71	3.86	11.3
THF	7.52	1.63	8.0
1,4-dioxane	2.22	0.45	9.0
Ethyl acetate	6.00	1.78	7.2

This suggests that although solubility is affected by nature of substitutions, the orientation of compounds in different solvents also affect solubility due to different types of interactions. This may be due to the fact that apart from substitutions, other groups or atoms in compounds also play important role in interacting with solvent molecules. These interactions may be hydrogen bonding, dipole-dipole, induced dipole-dipole, Vander Waals interactions etc.

Figure 1. The variation of experimental mole fraction solubilities (x_i) with temperature for the studied compounds in different solvents. RP-1, (\blacklozenge); RP-2, (\blacktriangle); RP-3, (\bullet); RP-4, (\blacktriangle); RP-5, (\blacksquare); Corresponding continues (—) are for calculated mole fraction solubilities x_{ci}^a by Apelblat equation.



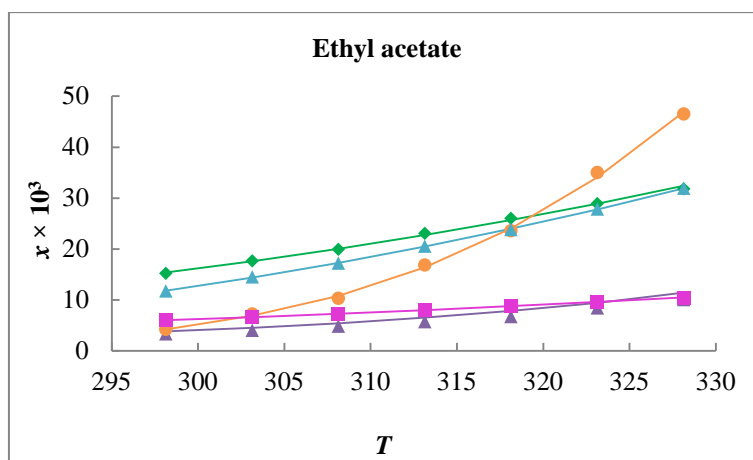
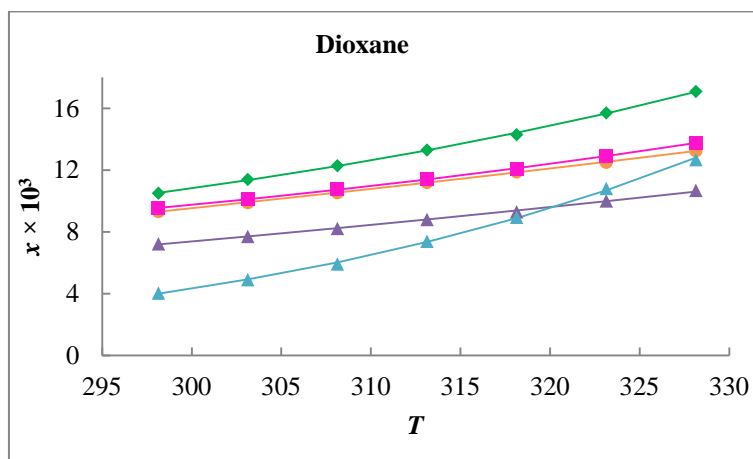


Table 5. Parameters of modified Apelblat equation for studied compounds in studied solvents.

Parameters	RP-1	RP-2	RP-3	RP-4	RP-5
Chloroform					
A	219.76	-3.08	-140.85	-98.78	-139.93
B	-12864.08	-601	3829.82	2769.06	4919.90
C	-31.69	0.27	21.48	14.99	20.90
10⁵ RMSD^a	0.14	0.11	2.89	8.17	5.37
100 RAD^a	-0.06	-0.06	-0.09	-0.07	-0.07
DMF					
A	109.04	-95.63	-1.58	-0.94	-2.13

B	-9878.50	2106.79	-2159.36	-2627.64	-1525.58
C	-14.17	14.50	0.70	0.86	0.56
10⁵ RMSD^a	0.32	2.02	5.02	4.96	0.13
100 RAD^a	-0.08	-0.10	-0.08	-0.08	-0.07
THF					
A	89.93	-55.69	-1.87	-180.15	-2.77
B	-8824.87	-2206.38	-1805.97	4210.14	-1094.46
C	-11.48	10.25	0.56	28.25	0.34
10⁵ RMSD^a	0.27	0.53	0.11	0.25	2.98
100 RAD^a	-0.09	-0.09	-0.08	-0.09	-0.08
1,4-Dioxane					
A	-123.19	-2.88	-2.88	-0.18	-86.36
B	4169.50	-1165	-1054.59	-3455.86	2782.59
C	18.37	0.33	0.31	1.09	12.70
10⁵ RMSD^a	5.78	4.98	2.18	7.92	2.07
100 RAD^a	-0.08	-0.09	-0.08	-0.09	-0.11
Ethyl acetate					
A	145.67	-226.13	589.45	188.99	-2.21
B	-8999.91	7187.25	-34222.1	-11705.1	-1682.58
C	-21	34.46	-84.27	-27.06	0.48
10⁵ RMSD^a	0.14	0.91	0.52	9.26	3.46
100 RAD^a	-0.07	-1.39	-0.12	-0.07	-0.08

a = value calculated by modified Apelblat equation

The temperature dependence solubility of compounds in solvents is described by modified Apelblat equation [29].

$$\ln x_i^a = A + B/T + C \ln(T) \quad (2)$$

where x_{ci}^a is the mole fraction solubility calculated by equation 2 and T is the absolute temperature. A, B and C are the empirical model parameters determined by least square

method and the values are given in Table 5. The values of A and B represent the variation in the solution activity and the solution behavior resulting from the non idealities on the solubility of solute and the value of C represents the association between the temperatures and the enthalpy of fusion.

The solubility is also correlated with temperature by Buchowski–Ksiazczak λh equation [30,31] which describes the solid-liquid equilibrium behavior by only two adjustable parameters λ and h . The Buchowski equation can be written as:

$$\ln \left(1 + \frac{\lambda(1-x_{ci}^b)}{x_{ci}^b} \right) = \lambda h \left[\frac{1}{T} - \frac{1}{T_m} \right] \quad (3)$$

where x_{ci}^b is calculated mole fraction solubility by equation 3. T and T_m are experimental temperature and melting temperature of compound in K. λ and h are the parameters of Buchowski-Ksiazczak λh model which are given in Table 6.

Table 6. Parameters of Buchowski equation for studied compounds in studied solvents.

Solvents	λ	h	100RAD ^b	10 ⁵ RMSD ^b
Chloroform				
RP-1	0.19	1496.29	-0.22	0.55
RP-2	0.05	13828.43	-0.16	0.12
RP-3	0.04	72406.12	-0.33	6.61
RP-4	0.06	30946.51	-0.09	0.16
RP-5	0.04	37128.66	-0.13	0.17
DMF				
RP-1	0.56	9640.39	-0.12	0.38
RP-2	0.02	132149.74	-0.46	3.39
RP-3	0.06	39812.16	-0.30	6.20
RP-4	0.06	50290.49	-0.24	5.38
RP-5	0.06	28477.67	-0.22	0.14
THF				
RP-1	0.39	13482.43	-0.25	0.32
RP-2	-0.35	7725.72	-0.16	0.58
RP-3	0.05	43839.65	-0.24	0.12

RP-4	0.15	31445.80	-0.24	0.23
RP-5	0.03	45680.24	-0.34	5.40
1,4-Dioxane				
RP-1	0.04	43920.65	-0.23	0.14
RP-2	0.02	64067.99	-0.41	6.18
RP-3	0.02	47232.98	0.05	2.03
RP-4	0.04	44893.17	-0.21	0.07
RP-5	0.02	52584.94	-0.19	7.11
Ethyl acetate				
RP-1	0.10	23507.16	-0.27	0.31
RP-2	0.06	62880.89	-0.24	0.14
RP-3	3.20	2459.05	-0.17	0.01
RP-4	0.11	28974.39	-0.23	0.27
RP-5	0.02	80618.36	-0.07	3.33

b = value calculated by Buchowski-Ksiazczak equation

The solubility of compounds calculated by Apelblat equation (x_{ci}^a) and Buchowski-Ksiazczak λh equation (x_{ci}^b) are also given in Table 3. It is observed from the Table 3 that solubility of compound increases nonlinearly with increasing temperature. Further, it is shown from the Table 3 that the values obtained by modified Apelblat equation and Buchowski-Ksiazczak λh equation shows good agreement with each other and also with experimental solubility data.

The relative deviations (RD), root-mean-square deviations (RMSD) and relative average deviations (RAD) between the experimental and calculated solubility are evaluated for both modified Apelblat and λh equations by equations 4, 5 and 6 respectively.

$$RD = \frac{(x_i - x_{ci}^{a/b})}{x_i} \quad (4)$$

$$RMSD = \left[\sum_{i=1}^N \frac{(x_{ci} - x_i)^2}{N-1} \right]^{\frac{1}{2}} \quad (5)$$

$$RAD = \frac{1}{N} \sum_i \frac{(x_i - x_{ci})}{x_i} \quad (6)$$

where, N is the number of experimental points. All these evaluated values are given in Tables 5 and 6 which again confirm that the results evaluated by modified Apelblat and λh equations are in good agreement with experimental solubility.

3. 3. Thermodynamic parameters of solution

The dissolution of compound in a solvent is associated with changes in thermodynamic functions such as enthalpy (ΔH_{sol}), Gibb's energy (ΔG_{sol}) and entropy of solution (ΔS_{sol}).

The enthalpies of solution (ΔH_{sol}) was calculated by modified Van't Hoff equation [32] i.e., from the slope of the plot of $\ln x$ versus $(1/T - 1/T_{hm})$. Figure 2 shows plot of $\ln x$ versus $(1/T - 1/T_{hm})$. From the slope of plot of $\ln x$ versus $(1/T - 1/T_{hm})$ the enthalpy of solution (ΔH_{sol}) determined.

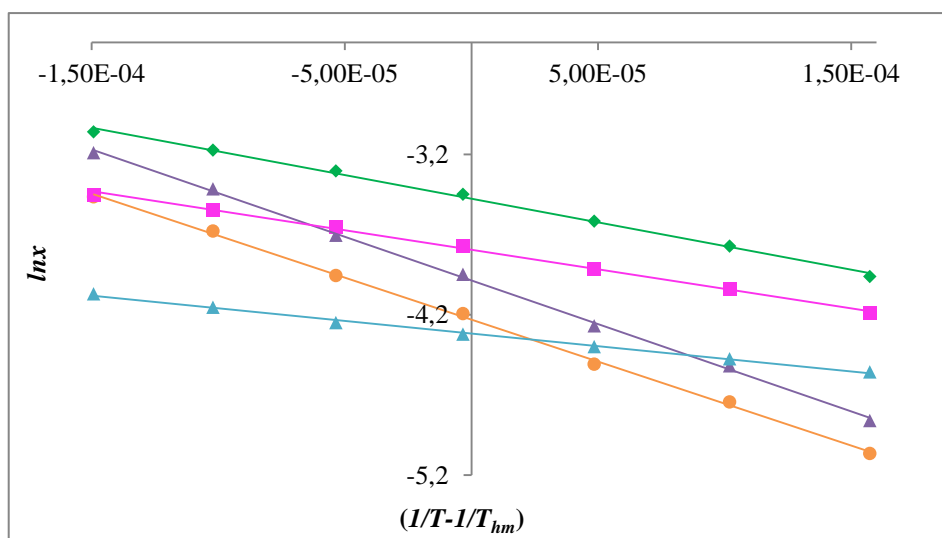
$$\left(\frac{\partial \ln x_i}{\partial \left(\frac{1}{T} - \frac{1}{T_{hm}} \right)} \right)_p = - \frac{\Delta H_{sol}}{R} \quad (7)$$

where T is the experimental temperature, T_m is mean harmonic temperature [33] which is calculated by equation (8) and R is universal gas constant (8.314 J/mol K).

$$T_{hm} = \frac{n}{\sum_{i=1}^n \left(\frac{1}{T} \right)} \quad (8)$$

where n is the number of experimental temperatures studied. The T_{hm} value calculated by this equation is found to be 312.83 K.

Figure 2. A van't Hoff plot of the experimental mole fraction solubility ($\ln x$) of RP-1 in chloroform, (\blacklozenge); DMF, (\blacktriangle); THF, (\bullet); 1,4-dioxane (\blacktriangle); ethyl acetate, (\blacksquare);



The change in Gibb's free energy during solubility process can be calculated by intercept of the plot of $\ln x_i$ versus $(1/T - 1/T_{hm})$ by following equation:

$$\Delta G_{sol} = -R \times T_{hm} \times \text{Intercept} \quad (9)$$

Finally, the entropy of solution (ΔS_{sol}) was obtained from these evaluated ΔH and ΔG values at T_{hm} [34].

$$\Delta S_{sol} = \frac{\Delta H_{sol} - \Delta G_{sol}}{T_{hm}} \quad (10)$$

All the thermodynamic parameters are given in Table 7.

Table 7 shows that for the studied compounds, values of ΔH_{sol} and ΔG_{sol} are positive. However, ΔS_{sol} values are both positive and negative in the studied solvents. The ΔS_{sol} values are negative for RP-2 in chloroform, for RP-5 in THF and for RP-2 and RP-3 and RP-5 in 1,4-dioxane. For other compounds, these values are positive in all the studied solvents.

Table 7. Thermodynamic parameters of dissolution of RP-1 to RP-5 in studied solvents.

Thermodynamic parameters	RP-1	RP-2	RP-3	RP-4	RP-5
Chloroform					
$\Delta G_{sol} / \text{kJ} \cdot \text{mol}^{-1}$	9.04	8.96	13.48	9.88	10.56
$\Delta H_{sol} / \text{kJ} \cdot \text{mol}^{-1}$	24.56	5.70	23.99	15.94	13.44
$\Delta S_{sol} / \text{J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$	49.62	-10.39	33.62	19.35	9.19
DMF					
$\Delta G_{sol} / \text{kJ} \cdot \text{mol}^{-1}$	10.37	14.44	11.53	11.42	9.86
$\Delta H_{sol} / \text{kJ} \cdot \text{mol}^{-1}$	45.29	20.18	19.78	24.08	14.13
$\Delta S_{sol} / \text{J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$	111.62	18.36	26.37	40.47	13.67
THF					
$\Delta G_{sol} / \text{kJ} \cdot \text{mol}^{-1}$	10.99	9.94	11.55	11.37	11.26
$\Delta H_{sol} / \text{kJ} \cdot \text{mol}^{-1}$	43.53	44.99	16.46	38.42	9.98
$\Delta S_{sol} / \text{J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$	103.99	112.07	15.69	86.46	-4.09
1,4-Dioxane					
$\Delta G_{sol} / \text{kJ} \cdot \text{mol}^{-1}$	11.23	12.32	11.69	12.81	11.63

$\Delta H_{sol} / \text{kJ}\cdot\text{mol}^{-1}$	13.08	10.53	9.56	31.58	9.89
$\Delta S_{sol} / \text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$	5.91	-5.70	-6.82	59.99	-5.58
Ethyl acetate					
$\Delta G_{sol} / \text{kJ}\cdot\text{mol}^{-1}$	9.87	13.42	10.87	10.18	12.57
$\Delta H_{sol} / \text{kJ}\cdot\text{mol}^{-1}$	20.22	29.81	65.46	26.97	15.23
$\Delta S_{sol} / \text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$	33.09	52.38	174.52	53.68	8.49

Comparison of solubility data with Gibb's energy values shows that these two are inversely related. As solubility increases, Gibb's energy decreases. The positive ΔG_{sol} indicates that the dissolution process is spontaneous whereas positive enthalpy of dissolution (ΔH_{sol}) indicates endothermic dissolution process. This may be due to the powerful interaction between compounds and solvent molecules than those between the solvent-solvent and compound-compound molecules. Thus, the newly formed bond energy between compound and solvent molecule is not powerful enough to compensate the energy needed for breaking the original association bond in various solvents. The positive entropy of dissolution suggests that the entropy of solubilization is more favorable [35], whereas negative entropy is due to more order in solutions [36].

4. CONCLUSION

The solubility of studied compounds in solvents is a function of temperature. Solubility of studied compounds increases non linearly with increase in temperature. The solubility of the synthesized compounds is different in studied solvents. The solubility data calculated by modified Apelblat and λh equations are in good agreement with experimental values. The positive ΔH_{sol} and ΔG_{sol} suggest endothermic and spontaneous dissolution of compounds in all the studied solvents.

Nomenclature

x_i	<i>Experimental mole fractions solubility.</i>
x_{ci}^a	<i>Calculated solubility by modified Apelblat equation.</i>
x_{ci}^b	<i>Calculated solubility by Buchowski equation.</i>
M_1	<i>Molecular weight of solvents</i>
M_2	<i>Molecular weight of synthesized compounds (RP-1 to RP-5)</i>
m_1	<i>weights of solvents</i>
m_2	<i>weights of synthesized compounds (RP-1 to RP-5)</i>
$A, B \text{ and } C$	<i>parameters of modified Apelblat equation</i>
$\lambda \text{ and } h$	<i>parameters of Buchowski equation</i>
N	<i>Number of experimental points</i>

n	Number of experimental temperatures studied.
T	Temperature in Kelvin
T_m	Melting temperature
T_{hm}	Mean harmonic temperature.
ΔH_{sol}	Enthalpy change ($\text{kJ}\cdot\text{mol}^{-1}$)
ΔG_{sol}	Gibb's energy change ($\text{kJ}\cdot\text{mol}^{-1}$)
ΔS_{sol}	Entropy change ($\text{J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$)
R	Universal gas constant ($8.314 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$)

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(Received 18 February 2016; accepted 01 March 2016)