Synthesis and Evaluation of Thermodynamic Solubility of Triazolo Quinolone Class Derivatives in Various Solvents at 298.15-328.15 K

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Abstract. The solubility of triazolo quinolone class derivatives in methanol, ethanol, n-propanol, n-butanol and ethyl acetate was measured using a gravimetric method at temperature ranging from 298.15 K to 328.15 K. The results of these measurements were correlated with semi empirical equations. Some thermodynamic parameters such as. dissolution enthalpy, Gibb's free energy and entropy of mixing have also been calculated.

1. Introduction

Heterocyclic compounds have wide range of applications in the chemistry [1], biology [2], pharmaceuticals [3] and industries [4] etc. Triazole derivatives readily bind with a variety of enzymes and receptors in biological system via weak interactions such as coordination bonds, hydrogen bonds, ion-dipole, cation- stacking, hydrophobic effect, van der Waals force etc. and show broad spectrum of biological activities [5]. Further, it is also useful in agrochemicals [6], artificial acceptors [7] etc.

The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. It is one of the parameters which plays an important role in various processes [8, 9]. For solid compounds, it plays a crucial role in the determination of proper solvents for crystallization process [10, 11]. In organic synthesis, the knowledge of solubility of starting materials or products is useful to select appropriate solvent for reaction and to improve the purity and yield of product [12, 13].

In the present work, two new triazolo quinolone class derivatives were synthesized and their structures were confirmed by fundamental spectroscopic techniques. solubility of synthesized compounds has been determined in different solvents over a range of temperatures. Solubility data was correlated with temperature by using Apelblat [14, 15] and Buchowski-Ksiazczak λh [16, 17] models. For the better understanding of dissolution process of these compounds with different solvents, some thermodynamic parameters have also been evaluated from the solubility data.

2. Experimental

2.1. Materials:

All the chemicals used in synthesis were laboratory grade and solvents were of analytical grade.

2.2. Synthesis:

2.2.1. Step-1: Synthesis of arylidene

2.2.2. Step-2: Synthesis of oxime

2.2.3. Step-3: Synthesis of MPT-1

Another compound was synthesized using furfural as starting material in step-1. Table 1 shows the physical parameters of synthesized compounds.

The IUPAC name of both the synthesized compounds are:

MPT-1: 8,8-dimethyl-6-oxo-2-(pyridine-4-yl)-5-(thiophene-2-yl)-1,2,6,7,8,9-hexahydro-[1,2,4]-triazolo-[1,5-a]quinolone-4-carboxamide

MPT-2: 5-(furan-2-yl)-8,8-dimethyl-6-oxo-2-(pyridine-4-yl)-1,2,6,7,8,9-hexahydro-[1,2,4]-triazolo-[1,5-a] quinolone-4-carboxamide.

Table 1: Physical parameters of synthesized compounds

Compound Code	Molecular Weight	Molecular Formula	% yield	Melting Point °C	R _f value
MPT-1	419.49	C ₂₂ H ₂₁ N ₅ O ₂ S	70%	214-216 °C	0.78
MPT-2	403.49	C ₂₂ H ₂₁ N ₅ O ₃	64%	208-210 °C	0.69

2.3.Characterization study:

The structure of both the synthesized compounds were confirmed by spectroscopic techniques such as FTIR (SHIMADZU FT-IR 8400), ¹H NMR and ¹³C NMR (BRUKER ADVANCE II 400 NMR) and Mass spectroscopy (Shimadzu-QP 2010 Mass spectrometer). ¹H NMR was taken in deuterated DMSO with TMS as a standard and it is reported in δppm. The IR spectrum was recorded on KBr disc.

2.4.Solubility measurements:

Both the synthesized compounds were recrystallized from methanol. All the solvents used for solubility study were of HPLC grade (except ethanol) and their purity was checked by SHIMADZU GC-MS (Model No QP-2010) and was found to be greater than 99.85 %.

By gravimetric method, solubility of both the synthesized compounds is determined. In a solvent (methanol, ethanol, n-propanol, n-butanol and ethyl acetate), saturated solution of compound was prepared at a given temperature. The temperature of the solution was controlled by a thermostat (NOVA NV-8550 E, India) with an accuracy of ±0.05 K. At constant temperature, solution was continuously stirred for 15 -30 minutes. The stirring was then stopped and solution was allowed to reach the solid-liquid equilibrium. In a pre-weighed vial, 2 ml of upper clear solution was taken very

carefully by a syringe and weight of vial was taken to determine the weight of solution. The solvent was then allowed to evaporate completely in a vacuum oven. When the solvent is evaporated completely, again weight of vial was taken to determine the weight of residue. The weight of the vial was recorded periodically until the weight did not change. All the masses were measured by an analytical balance (Mettler Toledo AB204-S, Switzerland) with accuracy of ± 0.0001 gm. Every experimental point was repeated three times and the mean values were used to calculate the mole fraction solubility.

$$x_i = \frac{(m_2 - m_0)/M_1}{(m_2 - m_0)/M_1 + (m_1 - m_2)/M_2}$$

where M_1 and M_2 are the molecular weight of compound and solvent. m_0 , m_1 and m_2 are the weights of empty vial, weight of solution and weight of residue.

3. Results and Discussion

The mole fraction solubility of both the synthesized compounds are given in Table 2 at different temperatures. It is evident from the Table 2 that the mole fraction solubility increases with increasing temperature in all the solvents. Further, among alcohols, both the compounds exhibited maximum solubility in n-butanol whereas minimum solubility is observed in methanol.

Thus, solubility increases with increase the $-\text{CH}_2$ group in alcohol. In ethyl acetate, solubility of compounds is lower and almost similar to that in methanol.

The pattern of solubility of both the synthesized compounds in different solvents is compared with the dipole moment and dielectric constant of solvents which are given in Table 3. As evident from Table 3, there is slight change in dipole moment for alcohols. Further, both dipole moment and dielectric constant decreases with increase the number of $-\text{CH}_2$ group. Thus, solubility of both the compounds in alcohols is reverse of dielectric constant and dipole moment. For ethyl acetate, dipole moment is maximum whereas dielectric constant is minimum. Thus, for ethyl acetate, solubility is according to dielectric constant and is almost similar to methanol.

3.1. Apelblat model: The modified Apelblat equation [14, 15] is widely used to correlate the solubility with the temperature due to its simplicity, and it can be expressed as follows:

$$\ln x_i^a = A + \frac{B}{T} + C \ln T$$

where x_{ci}^a is the calculated mole fraction solubility of compound, T is the absolute temperature and A , B and C are empirical model parameters. The values of A and B represent the variation in the solution activity coefficient and C represents the effect of temperature on the fusion enthalpy. These parameters were evaluated using least square method and are given in Table 4. Using these parameters, solubility mole fractions of both the compounds were calculated in studied solvents and are given in Table 2. Figure 1 shows the comparison of experimental solubility values with those evaluated by Apelblat model.

Table 2: Experimental and calculated mole fraction solubility and relative deviation (RD) of both the synthesized compounds in different solvents at different temperatures

Temp. (K)	$x_i \cdot 10^4$	$x_{ci}^a \cdot 10^4$	100RD ^a	$x_{ci}^b \cdot 10^4$	100RD ^b
MPT-1					
Methanol					
298.15	0.6471	0.6790	-4.9226	0.8270	-27.7969
303.15	1.0790	1.0316	4.3921	1.0220	5.1953
308.15	1.5103	1.4233	5.7609	1.2560	16.8060
313.15	1.7470	1.7941	-2.6942	1.5333	12.2318
318.15	1.9842	2.0774	-4.6951	1.8594	6.2890
323.15	2.1410	2.2210	-3.7385	2.2415	-4.6919
328.15	2.2972	2.2032	4.0942	2.6866	-16.9504
Ethanol					
298.15	0.8811	0.8809	-0.0049	0.9909	-12.4881
303.15	1.2950	1.2836	0.8816	1.2780	1.3141
308.15	1.7102	1.7591	-2.9339	1.6347	4.3441
313.15	2.2790	2.2758	0.1500	2.0746	8.9700
318.15	2.8487	2.7892	2.0918	2.6132	8.2702
323.15	3.2200	3.2488	-0.8946	3.2682	-1.4974
328.15	3.5909	3.6072	-0.4518	4.0597	-13.0516
n-Propanol					
298.15	1.4100	1.4166	-0.4729	1.3386	5.0623
303.15	1.6800	1.6659	1.1277	1.6708	0.8409
308.15	1.9600	1.9962	-1.8480	2.0705	-5.6395
313.15	2.4600	2.4339	1.0580	2.5483	-3.5912
318.15	2.9563	3.0163	-2.0323	3.1116	-5.4041
323.15	3.8750	3.7951	2.0622	3.7865	2.2839
328.15	4.7941	4.8453	-1.0155	4.5740	4.5914
n-Butanol					
298.15	3.9986	4.0097	-0.2785	4.2382	-5.9932
303.15	4.6720	4.6827	-0.2279	4.6749	-0.0625
308.15	5.3461	5.3175	0.5363	5.1402	3.8523
313.15	5.8500	5.8817	-0.5420	5.6347	3.6802
318.15	6.3539	6.3471	0.1089	6.1590	3.0689
323.15	6.6380	6.6920	-0.8133	6.7135	-1.1375
328.15	6.9218	6.9032	0.2680	7.2988	-5.4465
Ethyl acetate					
298.15	0.6822	0.7048	-3.3106	0.7715	-13.0828
303.15	0.9832	0.9554	2.8267	0.9526	3.1139
308.15	1.2841	1.2351	3.8217	1.1682	9.0334
313.15	1.5090	1.5271	-1.1972	1.4232	5.6837
318.15	1.7342	1.8106	-4.4019	1.7232	0.6345
323.15	2.0300	2.0638	-1.6656	2.0742	-2.1762
328.15	2.3248	2.2668	2.4948	2.4825	-6.7827

MPT-2					
Methanol					
298.15	7.3099	7.3927	-1.1320	7.1618	2.0271
303.15	8.3960	8.3044	1.0900	8.3300	0.7860
308.15	9.4830	9.4248	0.6142	9.6414	-1.6701
313.15	10.8230	10.7987	0.2249	11.1073	-2.6265
318.15	12.1634	12.4831	-2.6280	12.7392	-4.7337
323.15	14.6480	14.5498	0.6704	14.5491	0.6755
328.15	17.1324	17.0895	0.2505	16.5489	3.4061
Ethanol					
298.15	13.2348	13.2282	0.0502	13.2301	0.0361
303.15	15.5000	15.5046	-0.0300	15.5138	-0.0888
308.15	17.7643	18.0828	-1.7929	18.0979	-1.8781
313.15	21.1360	20.9900	0.6907	21.0089	0.6015
318.15	24.5069	24.2549	1.0280	24.2740	0.9503
323.15	28.0450	27.9073	0.4911	27.9215	0.4405
328.15	31.5835	31.9778	-1.2484	31.9803	-1.2563
n-Propanol					
298.15	10.3246	10.3509	-0.2548	10.9397	-5.9578
303.15	12.5540	12.5569	-0.0228	12.5328	0.1692
308.15	14.7842	14.7931	-0.0606	14.2946	3.3112
313.15	16.9290	16.9544	-0.1499	16.2359	4.0943
318.15	19.0739	18.9349	0.7284	18.3671	3.7056
323.15	20.3050	20.6381	-1.6407	20.6988	-1.9396
328.15	22.1112	21.9849	0.5710	23.2419	-5.1134
n-Butanol					
298.15	14.0465	14.0364	0.0716	14.4289	-2.7227
303.15	16.9220	16.9099	0.0711	16.9037	0.1082
308.15	19.7979	20.0228	-1.1358	19.7014	0.4874
313.15	23.3500	23.3259	0.1033	22.8502	2.1406
318.15	26.9013	26.7604	0.5239	26.3789	1.9418
323.15	30.2590	30.2598	-0.0027	30.3176	-0.1937
328.15	33.6163	33.7532	-0.4073	34.6969	-3.2147
Ethyl acetate					
298.15	7.9390	8.0387	-1.2563	7.5577	4.8030
303.15	8.4450	8.3440	1.1959	8.3738	0.8430
308.15	8.9510	8.8807	0.7853	9.2472	-3.3096
313.15	9.7040	9.6762	0.2867	10.1795	-4.8997
318.15	10.4580	10.7768	-3.0484	11.1719	-6.8263
323.15	12.3500	12.2517	0.7957	12.2258	1.0054
328.15	14.2420	14.1991	0.3014	13.3425	6.3158

x_{ci}^a and x_{ci}^b are calculated values from Apelblat and λh models.

3.2. Buchowski-Ksiazczak λh model: The Buchowski-Ksiazczak λh equation [16, 17] describes the solid-liquid equilibrium by using only two parameter λ and h . The Buchowski-Ksiazczak equation is:

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

where T and T_m are the experimental temperature and melting temperature respectively. λ and h are the adjustable parameters. x_{ci}^b is the calculated mole fraction solubility. The evaluated values of λ and h are given in Table 5. Using these parameters, solubility mole fractions of both the compounds were calculated in studied solvents and are given in Table 2. Figure 2 shows the comparison of experimental solubility values with those evaluated by Buchowski-Ksiazczak λh model.

The relative deviation (RD), root mean square deviation (RMSD) and average relative deviation (ARD) were used to assess the fitting degree and applicability of these two models to the experiment values and were calculated by following equations:

$$RD = \frac{(x_i - x_{ci})}{x_i}$$

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

$$ARD = \frac{1}{N} \sum_i \frac{(x_i - x_{ci})}{x_i}$$

where x_i and x_{ci} are experimental and calculated value of the solubility mole fraction of the compound, N is the number of experimental points. The RD values for both models are given in Table 2 whereas RMSD and ARD values are listed in Table 6. It is evident from Table 6 that the solubility evaluated by Apelblat model is better than that evaluated by Buchowski-Ksiazczak model.

Table 3: Dipole moment and Dielectric constant of solvents

Solvents	Dipole moment	Dielectric constant
Methanol	1.70	32.70
Ethanol	1.69	24.55
n-Propanol	1.68	20.33
n-Butanol	1.66	17.50
Ethyl acetate	1.78	6.02

Table 4: The Apelblat coefficients A, B, C and correlation coefficient (γ) for both the compounds in different solvents

MPT-1				
Solvents	A	B	C	γ
Methanol	2089.777	-100542.22	-309.281	0.994
Ethanol	1243.577	-61952.35	-183.433	0.9995
n-Propanol	-599.911	24007.13	89.604	0.9994
n-Butanol	577.115	-28606.72	-85.8241	0.9997
Ethyl acetate	950.172	-47698.83	-140.366	0.9971
MPT-2				
Methanol	-351.561	13651.144	52.4017	0.9991
Ethanol	-1.61361	-2664.0956	0.68798	0.9995
n-Propanol	582.076	-29371.299	-86.0783	0.9996
n-Butanol	286.311	-15991.27	-41.9907	0.9999
Ethyl acetate	-663.404	28849.243	98.2021	0.9975

Table 5: λ and h parameters of Buchowski-Ksiazczak and correlation coefficient (γ) for both the compounds in different solvents

	MPT-1			MPT-2		
Solvents	λ	$h \cdot 10^{-5}$	Γ	λ	$h \cdot 10^{-5}$	γ
Methanol	0.0125	3.0811	0.994	0.0236	1.1563	0.9991
Ethanol	0.0401	1.1460	0.9995	0.0527	0.5465	0.9995
n-Propanol	0.0250	1.601	0.9994	0.0254	0.9671	0.9996
n-Butanol	0.0043	4.1351	0.9997	0.0562	0.5091	0.9999
Ethyl acetate	0.0112	3.4116	0.9971	0.0081	2.2872	0.9975

3.3. Thermodynamic parameters:

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 [18] i.e., from the slope of the plot of $\ln x$ versus $(1/T - 1/T_{hm})$.

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

where T is the experimental temperature, T_m is mean harmonic temperature [19] and R is universal gas constant (8.314 J/mol K).

The harmonic temperature is calculated by the relation:

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

where n is the number of temperatures analyzed. In the present study, harmonic temperature is 312.83K.

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

$$\Delta G_{sol.} = -R \times T_{hm} \times \text{Intercept}$$

Finally, the entropy of solution (ΔS_{sol}) was obtained from these evaluated ΔH_{sol} and ΔG_{sol} values at T_{hm} [20].

$$\Delta S_{sol.} = \frac{\Delta H_{sol.} - \Delta G_{sol.}}{T_{hm}}$$

The calculated thermodynamic parameters are listed in Table 7 for both the compounds in studied solvents. It is observed that both enthalpy and Gibb's free energy of dissolution are positive in all the solvents for both the compounds. However, entropy values are both positive and negative.

Comparison of solubility data with Gibb's energy values shows that these two are inversely related. As solubility increases, Gibb's energy decreases. The lower Gibb's free energy corresponds to stronger interaction between solute and solvent which results to higher solubility. 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, whereas negative entropy is due to more order in solutions [21]. The thermodynamic studies will help to optimize the dissolution of studied compounds in different solvents.

Table 6: Root mean square deviation (RMSD) and relative average deviation (ARD) values of both the synthesized compounds for both models in different solvents

Solvents	Apelblat		Buchowski	
	RMSD.10 ⁵	ARD.10 ²	RMSD.10 ⁵	ARD.10 ²
	MPT-1			
Methanol	0.79	-0.258	2.32	-1.274
Ethanol	0.35	-0.167	2.37	-0.591
n-Propanol	0.50	-0.16	1.34	-0.265
n-Butanol	0.30	-0.135	2.35	-0.291
Ethyl acetate	0.49	-0.205	0.97	-0.511
	MPT-2			
Methanol	1.49	-0.130	3.68	-0.305
Ethanol	2.45	-0.116	2.43	-0.171
n-Propanol	1.57	-0.118	7.11	-0.247
n-Butanol	1.22	-0.111	5.55	-0.208
Ethyl acetate	1.52	-0.134	5.47	-0.295

Table 7: Thermodynamic parameters for both the synthesized compounds in different solvents

Solvents	MPT-1			MPT-2		
	ΔH (KJ/mole)	ΔG (KJ/mole)	ΔS (J/mole)	ΔH (KJ/mole)	ΔG (KJ/mole)	ΔS (J/mole)
Methanol	31.95	22.88	28.99	22.72	17.72	15.96
Ethanol	38.25	22.10	51.61	23.93	16.06	25.16
n-Propanol	33.32	21.56	37.60	20.43	16.73	11.85
n-Butanol	14.74	19.47	-15.14	23.79	15.84	25.42
Ethyl acetate	31.69	23.07	27.55	15.41	17.94	-8.06

Figure 1: The variation of experimental mole fraction solubility (x_i) with temperature for MPT-1 in different solvents $\blacklozenge$: Methanol; $\blacklozenge$: Ethanol; $\blacklozenge$: n-Propanol; $\blacklozenge$: n-Butanol; $\blacklozenge$: Ethyl acetate. Corresponding dotted lines (...) are for calculated mole fraction solubility x_{ci}^a by Apelblat model.

Figure 2: The variation of experimental mole fraction solubility (x_i) with temperature for MPT-2 in different solvents $\blacklozenge$: Methanol; $\blacklozenge$: Ethanol; $\blacklozenge$: n-Propanol; $\blacklozenge$: n-Butanol; $\blacklozenge$: Ethyl acetate. Corresponding dotted lines (....) are for calculated mole fraction solubility x_{ci}^b by Buchowski-Ksiazczak model.

Conclusions

The mole fraction solubility of both the synthesized compounds increase with increasing temperature in all the solvents. Among alcohols, solubility increases with increase the $-\text{CH}_2$ group in alcohol. In ethyl acetate, solubility of compounds is lower and almost similar to that in methanol. The solubility evaluated by Apelblat model is better than that evaluated by Buchowski-Ksiazczak model. The thermodynamic parameters indicate spontaneous endothermic dissolution process.

Conflict of Interest

There is no conflict of interest.

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