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Research Article

SOLUBILITY OF SOME SYNTHETIC BENZODIAZEPINES IN N, N DIMETHYLFORMAMIDE AND TETRAHYDROFURAN FROM (308.15 TO 328.15) K

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ABSTRACT
Some new benzodiazepines of chloro quinoline (2-(2-chloro-6-flouroquinoline-3yl)-1H-1, 5-Benzodiazepine) have been synthesized and their characterization was done by elemental analysis, IR, NMR and mass spectral data. The solubility data of benzodiazepines derivatives are useful in pharmaceutical industry. Thus, the solubility of synthesized benzodiazepines have been studied in N, N dimethyl formamide and tetra hydro furan by gravimetrical method from (308.15 to 328.15) K under atmospheric pressure and the solubility data were correlated against temperature. The solubility is found to be greater in DMF than in THF. Further, with increase in temperature, solubility increases in both the solvents.

Keywords: *Benzodiazepines, Solubility, N, N Dimethyl Formamide, Tetra Hydro Furan, Apelblat Equation*

INTRODUCTION
The benzodiazepine nucleus is a pharmacophoric scaffold and represents a class of heterocycles with a wide range of biological applications (Randall, 1974). Many of them are widely used as anticonvulsant, ant anxiety and sedative, ant depressive, hypnotic and narcoleptic agents (Fryer, 1991; Hussenether *et al.*, 2004). Some heterocyclic containing benzodiazepines moiety were reported to possess anti inflammatory (Roma *et al.,* 1991). Antiviral (Kavali and Badami, 2000), anti-HIV (Braccio *et al.,* 2001), antimicrobial (Kumar and Joshi, 2007) and antitumor (Kamal *et al.,* 2001) activities. Research in this area is still very active and is directed towards the synthesis of compounds with enhanced pharmacological activity. The physicochemical properties of benzodiazepines such as lipid solubility and protein binding have also been studied (Rey *et al.,* 1999). The study of solubility of benzodiazepine derivatives in different solvents may helps to understand various metabolic processes.
Thus, in the present study, the solubility's of benzodiazepines in DMF and THF have been measured from (308.15 to 328.15) K at atmospheric pressure.

MATERIALS AND METHODS
Material: The Benzodiazepine derivatives have been synthesized in our laboratory. The general structure of benzodiazepine derivative and reaction scheme for the synthesis is given in Figure 1 and 2 respectively. These synthesized Benzodiazepine derivatives were recrystallized in ethanol and their purity was checked by elemental analysis, IR, NMR and mass spectral data. The elemental analysis data and % purity of compounds are given in Table 1. The melting temperature of all the synthesized compounds was determined by an open capillary method as well as by DSC method. The values obtained by these two methods are in good agreement and these melting points are reported in Table 2.
The choice of solvent depends upon solubility and relative permeability. Both the solvents, DMF and THF were analytical grade reagents. These solvents were purified by fractional distillation. Their purities were checked by SHIMADZU GC-MS (Model No QP-2010) and were found to be greater than 99.75 %.
***Method for Solubility Measurement*:** The solubility of all the compounds was measured by a gravimetric method (Zhu and Chem, 2001). For each measurement, an excess mass of compound was added to a known mass of solvent. Then, the equilibrium cell was heated to a constant temperature with continuous stirring. After, at least 3 h (the temperature of the water bath approached constant value, then the actual

value of the temperature was recorded), the stirring was stopped and the solution was kept still for 2 h. A portion of this solution was filtered and by a preheated injector, 2 ml of this clear solution was taken in another weighted measuring vial (m_0). The vial was quickly and tightly closed and weighted (m_1) to determine the mass of the sample (m_1- m_0).

Then, the vial was covered with a piece of filter paper to prevent dust contamination. After the solvent in the vial had completely evaporated at room temperature, the vial was dried and reweighed (m_2) to determine the mass of the constant residue solid (m_2- m_0). All the masses were taken using an electronic balance (Mettler Toledo AB204-S, Switzerland) with an uncertainty of ± 0.0001 g. Thus, the concentration of the solid sample in the solution, mole fraction, x, could be determined from equation 1.

$$x = \frac{(m_2 - m_0)/M_1}{(m_2 - m_0)/M_1 + (m_1 - m_2)/M_2} \quad (1)$$

Where M_1 is the molar mass of compound and M_2 is the molar mass of the solvent.

At each temperature, the measurement was repeated three times and an average value is given in Tables 3 and 4 along with uncertainty.

RESULTS AND DISCUSSION

The mole fraction solubility x of benzodiazepine derivatives in DMF and THF at different temperatures (308.15 to 328.15 K) are summarized in Tables 3 and 4. It is observed that for all the compounds, solubility is found to increase with temperature and is higher in DMF than in THF. The dielectric constant and dipole moment of DMF (36.71, 3.86) are higher than those for THF (7.58, 1.75). So, solubility is found to be greater in DMF than in THF. Thus, these properties affect the solubility. Further, solubility is maximum for NBN-7 and minimum in NBN-2 in both the solvents.

The variation of solubility with temperature is also shown in Figure 3. It is observed that solubility increases linearly with increase in temperature. The temperature dependence of benzodiazepines solubility in solvents is described by the modified Apelblat equation (Apelblat *et al.*, 1999; Gao *et al.*, 2007)

$$\ln x = A + \frac{B}{T} \quad (2)$$

Where x is the mole fraction solubility of benzodiazepines; T is the absolute temperature and A and B are the parameters.

The values of these parameters are given in Tables 5 and 6. Using these values of parameters, solubility values (x_{ci}) were evaluated and are also reported in Tables 3 and 4.

Further, relative average deviations (RAD) and root-mean-square deviations (RMSD), calculated by equations (3) and (4) are listed in Tables 5 and 6.

$$\mathrm{RAD} = \frac{1}{N}\sum_i^N \frac{(x - x_i)}{x} \quad (3)$$

$$RMSD = \left[\sum_{i=1}^{N} \frac{(x_{ci} - x_i)^2}{N-1}\right]^{1/2} \quad (4)$$

Where N is the number of experimental points and x_{ci} is the solubility calculated by equation 2.

The enthalpy of solution (ΔH_{sol}) was calculated by modified van't Hoff equation.

$$\frac{\partial \ln x}{\partial\left(1/T - 1/T_{hm}\right)_P} = -\frac{\Delta H_{sol}}{R} \quad (5)$$

Where T is the experimental temperature and R is gas constant. T_{hm} is the mean harmonic temperature which is given as

$$T_{hm} = \frac{n}{\sum_i^n \left(1/T\right)} \quad (6)$$

Where *n* is the number of experimental temperatures (Aragon *et al.*, 2007). In the present case, the T_{hm} value obtained is only 318 K. The slope of the plot of ln *x* versus (*1/T*-1/318) gives the value of ΔH_{sol}.
From the intercepts of these plots, Gibbs energy change (ΔG_{sol}) for the solubility process were evaluated from the following relation[15]

$$\Delta G_{sol} = -RT.\ intercept \quad (7)$$

Using these evaluated ΔH_{sol} and ΔG_{sol} values, the entropies of solutions ΔS_{sol} were obtained from equation [15, 16]

$$\Delta S_{sol} = \frac{\Delta H_{sol} - \Delta G_{sol}}{T_{hm}} \quad (8)$$

All these thermodynamic parameters are given in Tables 7 and 8.
It is evident from Tables 7 and 8 that for all the compounds ΔH_{sol} and ΔG_{sol} values are positive whereas ΔS_{sol} values are negative. When stronger bonds are broken and weaker bonds are formed, energy is consumed. So, ΔH_{sol} becomes positive[16]. This indicates endothermic dissolution of compounds where the enthalpy term contributes to an unfavorable positive value of ΔG_{sol}. Thus, positive value of ΔG_{sol} indicates that the dissolution process is not spontaneous (Kalsi, 2004). It is evident from Tables 7 and 8 that ΔG_{sol} is minimum for NBN-7 and maximum for NBN-2. This is in agreement with the solubility data of compounds where maximum solubility is observed for NBN-7 in both the solvents and minimum is found for NBN-2. Similar results have been reported by various workers in other systems (Szterner, 2008; Buryukin *et al.*, 2008). Further, the entropy term of the solubility process is found to be lower than the enthalpy term. This confirms that the solubility process is enthalpy controlled. The endothermic effect in the dissolving process may be due to powerful interaction between solute and solvent molecules.

Table 1: Elemental analysis Data (calculated (Cal) and found)

Compounds	C % Cal	Found	H % Cal	Found	N % Cal	Found	% Purity
NBN-1	69.85	69.83	3.99	4.00	9.77	9.76	99.57
NBN-2	69.48	69.47	3.89	3.91	13.50	13.48	98.77
NBN-3	60.21	60.23	2.95	2.93	8.78	8.78	99.46
NBN-4	64.80	64.81	3.17	3.16	12.59	12.57	99.14
NBN-5	64.80	64.82	3.17	3.15	12.59	12.56	99.69
NBN-6	69.32	69.30	3.64	3.66	10.10	10.11	98.94
NBN-7	72.55	72.52	4.14	4.17	10.15	10.14	99.31
NBN-8	68.18	68.17	3.54	3.53	10.66	10.67	98.82
NBN-9	69.32	69.30	3.64	3.65	10.10	10.12	98.87
NBN-10	72.09	72.10	3.78	3.76	10.51	10.49	99.42

Table 2: Melting points of synthesized benzodiazepine compounds

Compounds	Molecular weight $g.mol^{-1}$	Melting point K
NBN-1	429.91	399
NBN-2	414.94	432
NBN-3	478.72	511
NBN-4	444.88	547
NBN-5	444.88	439
NBN-6	415.83	501
NBN-7	413.94	496
NBN-8	434.45	513
NBN-9	415.83	538
NBN-10	399.80	536

Table 3: Observed Mole fraction Solubilities (x) and Calculated Mole fraction Solubilities (x_{ci}) of Benzodiazepines in DMF and THF

T/K	$10^2 x$	$10^2 x_{ci}$	$10^2 x$	$10^2 x_{ci}$
NBN-1				
DMF			**THF**	
308.15	0.8205 ± 0.003	0.8149 ± 0.006	0.7179 ± 0.002	0.7212 ± 0.003
313.15	0.8319 ± 0.004	0.8219 ± 0.001	0.7337 ± 0.003	0.7325 ± 0.001
318.15	0.8348 ± 0.001	0.8289 ± 0.002	0.7448 ± 0.005	0.7439 ± 0.001
323.15	0.8407 ± 0.003	0.8360 ± 0.001	0.7523 ± 0.006	0.7555 ± 0.001
328.15	0.8478 ± 0.005	0.8431 ± 0.004	0.7651 ± 0.001	0.7673 ± 0.001
		NBN-2		
308.15	0.5742 ± 0.001	0.5721 ± 0.002	0.5179 ± 0.004	0.5242 ± 0.006
313.15	0.5805 ± 0.002	0.5807 ± 0.003	0.5312 ± 0.008	0.5321 ± 0.008
318.15	0.5939 ± 0.002	0.5895 ± 0.001	0.5329 ± 0.006	0.5401 ± 0.007
323.15	0.6008 ± 0.002	0.5984 ± 0.005	0.5461 ± 0.007	0.5483 ± 0.008
328.15	0.6087 ± 0.003	0.6074 ± 0.002	0.5532 ± 0.003	0.5566 ± 0.001
		NBN-3		
308.15	1.0298 ± 0.004	1.0151 ± 0.008	0.9069 ± 0.005	0.9091 ± 0.006
313.15	1.0312 ± 0.005	1.0177 ± 0.001	0.9126 ± 0.006	0.9182 ± 0.004
318.15	1.0320 ± 0.007	1.0202 ± 0.003	0.9227 ± 0.004	0.9274 ± 0.005
323.15	1.0453 ± 0.001	1.0228 ± 0.004	0.9359 ± 0.004	0.9367 ± 0.001
328.15	1.0389 ± 0.005	1.0253 ± 0.001	0.9428 ± 0.007	0.9462 ± 0.002
		NBN-4		
308.15	0.6306 ± 0.002	0.6275 ± 0.005	0.5666 ± 0.001	0.5664 ± 0.008
313.15	0.6419 ± 0.003	0.6347 ± 0.006	0.5741 ± 0.001	0.5755 ± 0.004
318.15	0.6433 ± 0.006	0.6421 ± 0.001	0.5830 ± 0.003	0.5848 ± 0.006
323.15	0.6526 ± 0.001	0.6495 ± 0.003	0.5927 ± 0.006	0.5942 ± 0.004
328.15	0.6631 ± 0.005	0.6570 ± 0.007	0.6031 ± 0.005	0.6038 ± 0.003
		NBN-5		
308.15	0.9434 ± 0.001	0.9535 ± 0.004	0.8443 ± 0.001	0.8374 ± 0.001
313.15	0.9511 ± 0.003	0.9622 ± 0.002	0.8521 ± 0.008	0.8467 ± 0.006
318.15	0.9556 ± 0.003	0.9709 ± 0.001	0.8630 ± 0.004	0.8561 ± 0.004
323.15	0.9724 ± 0.007	0.9796 ± 0.002	0.8739 ± 0.003	0.8655 ± 0.004
328.15	0.9757 ± 0.005	0.9885 ± 0.001	0.8823 ± 0.001	0.8751 ± 0.001
		NBN-6		
308.15	0.8654 ± 0.005	0.8633 ± 0.003	0.8307 ± 0.004	0.8243 ± 0.003
313.15	0.8762 ± 0.002	0.8716 ± 0.002	0.8415 ± 0.006	0.8338 ± 0.003
318.15	0.8809 ± 0.003	0.8799 ± 0.003	0.8468 ± 0.005	0.8434 ± 0.008
323.15	0.8925 ± 0.004	0.8883 ± 0.001	0.8619 ± 0.004	0.8532 ± 0.005
328.15	0.8974 ± 0.006	0.8968 ± 0.005	0.8702 ± 0.002	0.8631 ± 0.001
		NBN-7		
308.15	1.4061 ± 0.002	1.3856 ± 0.004	1.2589 ± 0.002	1.2771 ± 0.002
313.15	1.4146 ± 0.001	1.3926 ± 0.005	1.2704 ± 0.005	1.2841 ± 0.001
318.15	1.4196 ± 0.001	1.3996 ± 0.001	1.2721 ± 0.006	1.2912 ± 0.005
323.15	1.4311 ± 0.006	1.4066 ± 0.001	1.2826 ± 0.001	1.2983 ± 0.003
328.15	1.4333 ± 0.002	1.4136 ± 0.001	1.2882 ± 0.003	1.3055 ± 0.001
		NBN-8		
308.15	0.8950 ± 0.006	0.8929 ± 0.006	0.8012 ± 0.001	0.8142 ± 0.008
313.15	0.9016 ± 0.008	0.9005 ± 0.005	0.8156 ± 0.002	0.8207 ± 0.004
318.15	0.9112 ± 0.002	0.9082 ± 0.004	0.8151 ± 0.008	0.8273 ± 0.006

323.15	0.9218 ± 0.006	0.9160 ± 0.001	0.8204 ± 0.008	0.8339 ± 0.007
328.15	0.9239 ± 0.005	0.9238 ± 0.001	0.8298 ± 0.007	0.8406 ± 0.001
		NBN-9		
308.15	1.1323 ± 0.004	1.1298 ± 0.008	0.9806 ± 0.006	0.9964 ± 0.002
313.15	1.1407 ± 0.003	1.1343 ± 0.006	0.9906 ± 0.005	1.0034 ± 0.006
318.15	1.1414 ± 0.003	1.1389 ± 0.005	0.9934 ± 0.001	1.0104 ± 0.005
323.15	1.1502 ± 0.008	1.1435 ± 0.002	1.0023 ± 0.001	1.0175 ± 0.004
328.15	1.1535 ± 0.001	1.1480 ± 0.004	1.0292 ± 0.001	1.0247 ± 0.003
		NBN-10		
308.15	0.7107 ± 0.006	0.7167 ± 0.006	0.6179 ± 0.003	0.6155 ± 0.001
313.15	0.7224 ± 0.004	0.7224 ± 0.007	0.6226 ± 0.001	0.6223 ± 0.005
318.15	0.7223 ± 0.005	0.7282 ± 0.004	0.6312 ± 0.005	0.6292 ± 0.008
323.15	0.7365 ± 0.002	0.7341 ± 0.001	0.6405 ± 0.009	0.6362 ± 0.008
328.15	0.7343 ± 0.004	0.7400 ± 0.002	0.6427 ± 0.004	0.6432 ± 0.006

Table 4: Constants A and B of eq (2), relative average deviations (RAD), and root Mean square deviation (RMSD) of Benzodiazepines in DMF

Compounds	***A***	***B***	**10^7 RMSD**	**100 ARD**
NBN-1	-5.3345	0.0017	0.1349	-0.1599
NBN-2	-6.0891	0.0030	0.0115	-0.0754
NBN-3	-4.7450	0.0005	0.7867	-0.3139
NBN-4	-5.7808	0.0023	0.0596	-0.1161
NBN-5	-5.2082	0.0018	0.0595	0.2504
NBN-6	-5.3384	0.0019	0.0009	-0.0362
NBN-7	-4.5879	0.0010	0.1646	-0.3548
NBN-8	-5.2431	0.0017	0.0023	-0.0583
NBN-9	-4.7304	0.0008	0.0073	-0.0941
NBN-10	-5.4322	0.0016	0.0100	0.1169

Table 5: Constants A and B of eq (2), relative average deviations (ARD), and root Mean square deviation (RMSD) of Benzodiazepines in THF

Compounds	***A***	***B***	**10^7 RMSD**	**100 RAD**
NBN-1	-5.8881	0.0031	0.0043	0.0519
NBN-2	-6.1764	0.0030	0.0139	0.1700
NBN-3	-5.3176	0.0020	0.0121	0.0987
NBN-4	-6.1606	0.0032	0.0042	0.0628
NBN-5	-5.4613	0.0022	0.0141	-0.1582
NBN-6	-5.5080	0.0023	0.0147	-0.1635
NBN-7	-4.7003	0.0011	0.1205	0.2900
NBN-8	-5.3046	0.0016	0.0634	0.2998
NBN-9	-5.0410	0.0014	0.1011	0.3245
NBN-10	-5.7692	0.0022	0.0012	-0.0503

Table 6: Thermodynamic parameters of dissolution of benzodiazepines in DMF and THF

Compound	DMF			THF		
	ΔG /KJ·mol^{-1}	ΔH /KJ·mol^{-1}	-ΔS /J·mol^{-1}	ΔG /KJ·mol^{-1}	ΔH /KJ·mol^{-1}	-ΔS /J·mol^{-1}
NBN-1	12.6518	1.3765	35.4637	13.0491	2.6817	32.6082
NBN-2	13.6393	2.4532	35.1828	13.9120	2.7623	35.0685
NBN-3	12.0953	0.3674	36.8871	12.4312	1.6256	33.9866
NBN-4	13.3918	2.1033	35.5052	13.6747	2.6213	34.7657
NBN-5	12.3270	1.4099	34.3370	12.6202	1.8453	33.8898
NBN-6	12.5549	1.5221	34.7010	12.6631	1.9417	33.7214
NBN-7	11.2720	0.8034	32.9261	11.5644	0.9636	33.3420
NBN-8	12.4661	1.3334	35.0149	12.7589	1.3749	35.8056
NBN-9	11.8446	0.6699	35.1472	12.2248	1.2077	34.6516
NBN-10	13.0756	1.3703	36.8159	13.4454	1.6532	37.0894

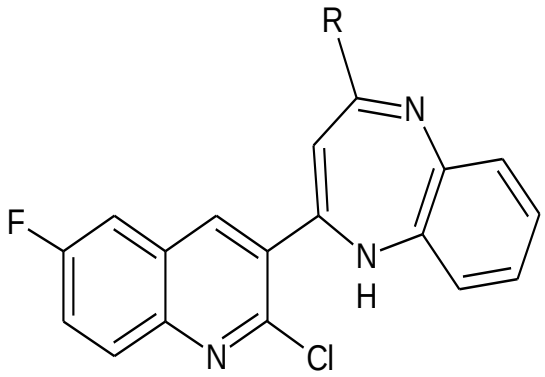

Figure 1: General Structure of Benzodiazepine derivative

Where, R =
NBN-1: p- $OCH_3C_6H_4$ NBN-6: p- OHC_6H_4
NBN-2: p- $NH_2C_6H_4$ NBN-7: p- $CH_3C_6H_4$
NBN-3: p- BrC_6H_4 NBN-8: p- ClC_6H_4
NBN-4: p- $NO_2C_6H_4$ NBN-9: o- OHC_6H_4
NBN-5: m- $NO_2C_6H_4$ NBN-10: H

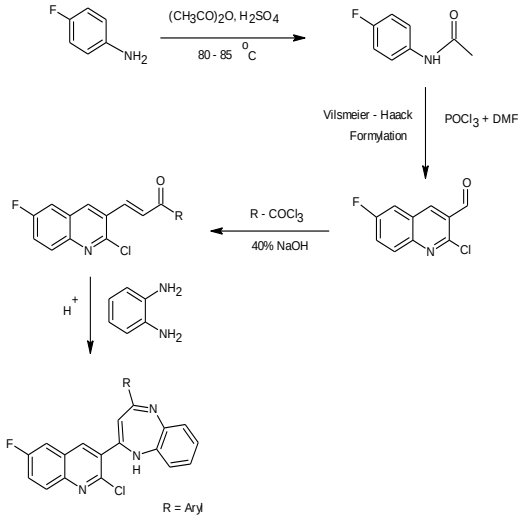

Figure 2: Reaction Scheme

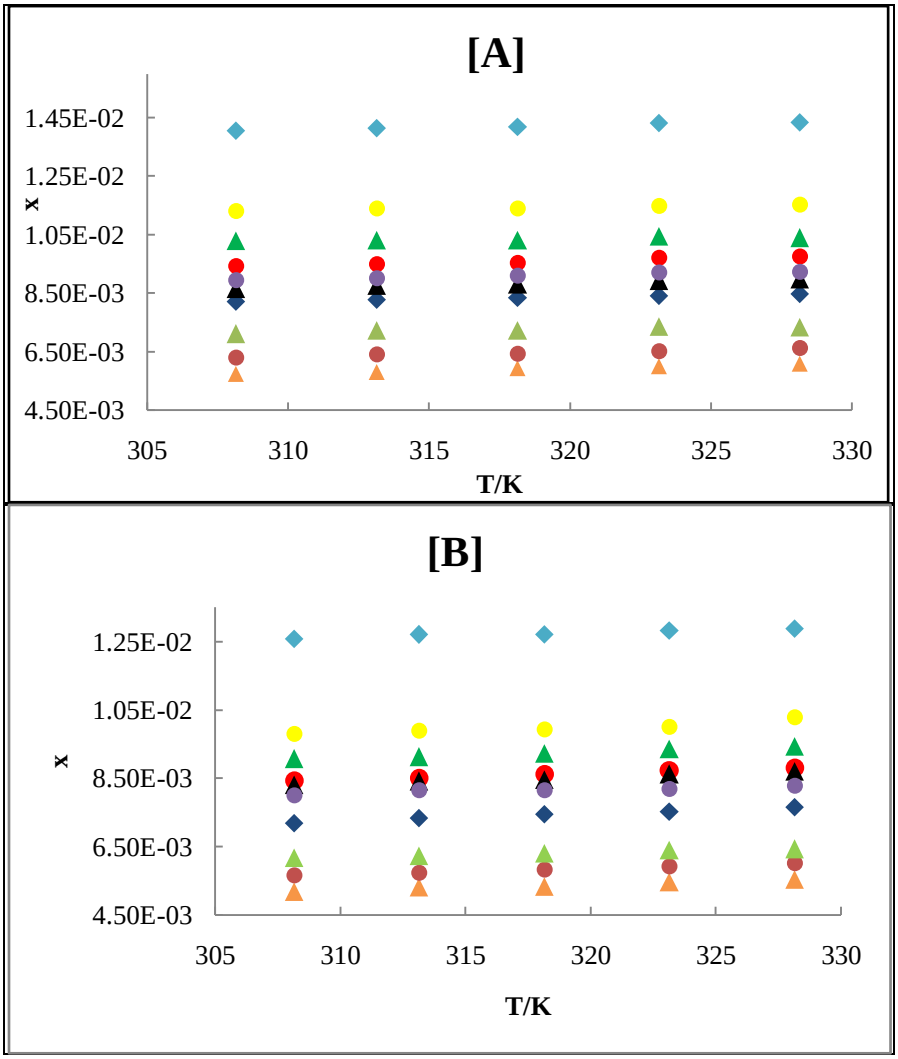

Figure 3: Variation of mole fraction solubilities (*x*) with temperature (T) for benzodiazepines in DMF [A] and THF [B]. ♦, NBN-1; ▲, NBN-2; ▲ , NBN-3; ●, NBN-4; ●, NBN-5; ▲, NBN-6; ♦, NBN-7; ●, NBN-8; ●, NBN-9; ▲, NBN-10

Conclusion

The solubility of benzodiazepine derivatives in the DMF and THF increased with an increase in temperature and the solubility is maximum in DMF for all the compounds. In both the solvents i.e., DMF and THF, solubility is maximum for NBN-7. The solubility data calculated by the modified Apelblat equation are in good agreement with the experimental values. The positive ΔH_{sol} values suggest endothermic dissolution of compounds in both the studied solvents whereas positive ΔG_{sol} values indicate that dissolution process is not spontaneous.

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REFERENCES

Apelblat A and Manzurola E (1999). Solubilities of o-acetylsalicylic, 4-aminosalic, 3,5-di nitro salicylic, and p-toluic acid, and magnesium-DL-aspartate in water from *T*= (278 to 348) K. J. *Journal of Chemical Thermodynamics* **31** 85-91.

Aragon DM, Ruidiaz MA, Vargas EF, Bregni C, Chiappetta DA, Sosnik A and Martinez F (2008). Solubility at several temperatures of the antimicrobial agent triclosan in organic solvents of different hydrogen bonding capability. *Journal of Chemical & Engineering Data* **53** 2576-2580.

Buryukin FA, Tverdokhlebov VP, Fedorov VA, Tetenkova EV, Fedorova AV and Azanova OO (2008). The Solubility of Acetylferrocene and Diacetylferrocene in Dimethyl sulfoxide and Its Mixtures with Water. *Russian Journal of Physical Chemistry* **82** 1545-1548.

Bustamante SP, Romero AP, Escalera B and Reillo A (1998). Nonlinear enthalpy-Entropy Compensation for the Solubility of Drugs in Solvent Mixtures: Paracetamol, Acetanilide and Nalidixic acid in dioxane-water. *Journal of Pharmaceutical Sciences* **87** 1590-1596.

Devi TK, Achaiah G and Reddy VM (1988). Synthesis of 6-alkyl/aryl-5, 11-dihydro-9-nitro [1] benzo pyrano [2,3-b] [1,5] benzodiazepine-1,3-ones as possible antipsychotic agents. *Journal of Indian Chemical Society* **65** 567-570.

Di Braccio M, Grossi GC, Roma G, Vargiu L, Mura M and Marongiu ME (2001). 1,5-Benzo diazepines, Part XII, synthesis and biological evaluation of tricyclic and tetracyclic 1,5-benzodiazepines derivatives as nevirapine analogues. *European Journal of Medicinal Chemistry* **36** 935-949.

Fryer RI (1991). Bicyclic Diazepines, In: *Comprehensive Heterocyclic Chemistry*, Chapter II, edited by Taylor EC (Wiley) New York **50**.

Gao J, Wang ZW, Xu DM and Zhang RK (2007). Solubilities of Triphenylphosphine in Ethanol, 2-Propanol, Acetone, Benzene and Toluene. *Journal of Chemical & Engineering Data* **52** 189-191.

Hussenether T, Hübner H, Gmeiner P and Troschutz R (2004). Clozapine derived 2,3-dihydro-1H-1,4 and 1,5-benzodiazepines with D4 receptor selectivity: synthesis and biological testing Bioorg. *Medicinal Chemistry* **12** 2625-2637.

Kalsi PS (2004). *Organic Reactions and their Mechanisms*, 2nd edition (New age international (P) limited) New Delhi 119.

Kamal A, Shankaraiah N, Prabhakar S, Reddy CR, Markandeya N, Laxma K and Devaiah X (2008). Solid-phase synthesis of new pyrrolobenzodiazepine-chalcone conjugates: DNA-binding affinity and anticancer activity. *Bioorganic & Medicinal Chemistry Letters* **18** 2434-2439.

Kavali JR and Badami BV (2000). 1,5-Benzodiazepine derivatives of 3-arylsydnones: Synthesis and antimicrobial activity of 3- aryl-4-[2'-aryl-2',4',6',7'-tetrahydro-(1'H)-1',5'- benzo diazepine-4'-yl]sydnonesIl. *Farmaco* **55** 406-409.

Krug RR, Hunter WG and Grieger RA (1976). Enthalpy-entropy compensation, 2. Separation of the Chemical from the Statistical Effects. *Journal of Physical Chemistry* **80** 2341-2351.

Kumar R and Joshi YC (2007). Synthesis spectral studies and biological activity of 3H-1, 5-benzodiazepine derivatives. *Arkivoc* **13** 142-149.

Narayana B, VijayaRaj KK, Ashalatha BV and Suchetha Kumari N (2006). Synthesis of some new substituted triazolo [4,3-a] [1,4] benzodiazepine derivatives as potent anti convulsants. *European Journal of Medicinal Chemistry* **41** 417-422.

Randall LO (1974). *Psychopharmacological Agents*, edited by Gordon M (Academic Press) New York **3** 175-281.

Rey E and Treluyer JM (1999). Pharmacokinetic Optimisation of benzodiazepine Therapy for Acute Seizures: Focus on Delivery Routes. *Clinical Pharmacology & Therapeutics* **36** 409-424.

Roma G, Grossi GC, Di Braccio M, Ghia M and Mattioli F (1991). New route to substituted 4H-[1,2,4] triazolo [4,3-a] [1,5] benzodiazepin-5-amines with analgesic and/or anti-inflammatory activity. *European Journal of Medicinal Chemistry* **26** 489-496.

Szterner P (2008). Solubilities in Water of Uracil and Its Halogenated Derivatives. *Journal of Chemical & Engineering Data* **53** 1738-1744.

Zhu M (2001). Solubility and Density of the Disodium Salt Hemiheptahydrate of Ceftriaxone in Water + Ethanol Mixtures. *Journal of Chemical & Engineering Data* **46** 175-176.