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RESEARCH ARTICLE

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

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.

INTRODUCTION

The benzodiazepine nucleus is a pharmacophoric scaffold and represents a class of heterocycles with a wide range of biological applications. Many of them are widely used as anticonvulsant, antianxiety, sedative, antidepressive, hypnotic and neuroleptic agents. Some heterocycles containing benzodiazepines moiety were reported to possess anti inflammatory, antiviral, anti-HIV, antimicrobial and antitumor 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. The study of solubility of benzodiazepine derivatives in different solvents may helps to understand various metabolic processes.

Thus, in the present study, the solubilities of benzodiazepines in DMF and THF have been measered from (308.15 to 328.15) K at atmospheric pressure.

EXPERIMENTAL SECTION

Materials

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 %.

Solubility measurement

The solubilities were measured by a gravimetric method. 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

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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.

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

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 solubilities *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.

$$\ln x = A + B/(T/\mathrm{K}) \qquad (2)$$

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. The calculated solubilities x_{ci} are also reported in Tables 3 and 4. The experimental solubility of drug in the studied solvents was compared with calculated solubility (x_{ci}).

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

$$ARD = \frac{1}{N}\sum_{i}^{N}\frac{x_i - x_{ci}}{x_i} \qquad (3)$$

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

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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.

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

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

$$T_{hm} = \frac{n}{\sum_{i}^{n}\left(1/T\right)} \qquad (6)$$

Where n is the number of experimental temperatures. 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

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

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

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

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.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. 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.

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.

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CONCLUSION

(1) The solubility of benzodiazepine derivatives in the DMF and THF increased with an increase in temperature.

(2) The solubility is maximum in DMF for all the compounds.

(3) In both the solvents i.e., DMF and THF, solubility is maximum for NBN-7.

(4) The solubility data calculated by the modified Apelblat equation are in good agreement with the experimental values.

(5) 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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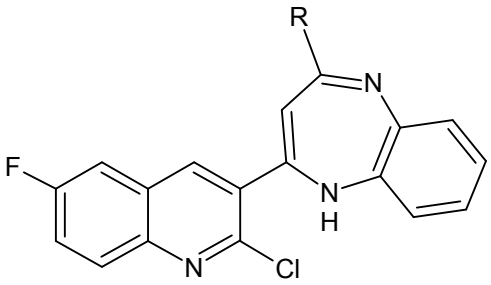

Figure 1. General Structure of Benzodiazepine derivative

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Where, R =

NBN-1: p- $OCH_3C_6H_4$

NBN-2: p- $NH_2C_6H_4$

NBN-3: p- BrC_6H_4

NBN-4: p- $NO_2C_6H_4$

NBN-5: m- $NO_2C_6H_4$

NBN-6: p- OHC_6H_4

NBN-7: p- $CH_3C_6H_4$

NBN-8: p- ClC_6H_4

NBN-9: o- OHC_6H_4

NBN-10: C_6H_5

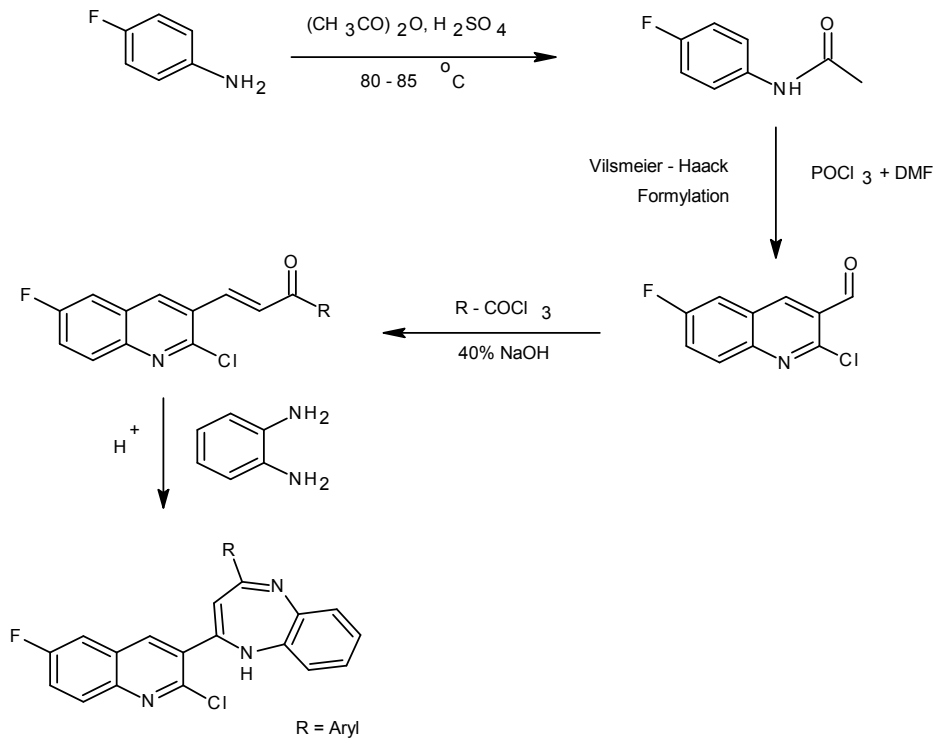

Figure 2. Reaction Scheme

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Compounds	C %		H %		N %		% Purity
	Cal	Found	Cal	Found	Cal	Found	
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 1. Elemental analysis Data (calculated (Cal) and found).

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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 2. Melting points of synthesized benzodiazepine compounds.

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T/K	$10^2 x$	$10^2 x_{ci}$
	NBN-1	
308.15	0.8205 ± 0.003	0.8149 ± 0.006
313.15	0.8319 ± 0.004	0.8219 ± 0.001
318.15	0.8348 ± 0.001	0.8289 ± 0.002
323.15	0.8407 ± 0.003	0.8360 ± 0.001
328.15	0.8478 ± 0.005	0.8431 ± 0.004
	NBN-2	
308.15	0.5742 ± 0.001	0.5721 ± 0.002
313.15	0.5805 ± 0.002	0.5807 ± 0.003
318.15	0.5939 ± 0.002	0.5895 ± 0.001
323.15	0.6008 ± 0.002	0.5984 ± 0.005
328.15	0.6087 ± 0.003	0.6074 ± 0.002
	NBN-3	
308.15	1.0298 ± 0.004	1.0151 ± 0.008
313.15	1.0312 ± 0.005	1.0177 ± 0.001
318.15	1.0320 ± 0.007	1.0202 ± 0.003
323.15	1.0453 ± 0.001	1.0228 ± 0.004
328.15	1.0389 ± 0.005	1.0253 ± 0.001
	NBN-4	
308.15	0.6306 ± 0.002	0.6275 ± 0.005
313.15	0.6419 ± 0.003	0.6347 ± 0.006
318.15	0.6433 ± 0.006	0.6421 ± 0.001
323.15	0.6526 ± 0.001	0.6495 ± 0.003
328.15	0.6631 ± 0.005	0.6570 ± 0.007
	NBN-5	
308.15	0.9434 ± 0.001	0.9535 ± 0.004
313.15	0.9511 ± 0.003	0.9622 ± 0.002
318.15	0.9556 ± 0.003	0.9709 ± 0.001
323.15	0.9724 ± 0.007	0.9796 ± 0.002
328.15	0.9757 ± 0.005	0.9885 ± 0.001

T/K	$10^2 x$	$10^2 x_{ci}$
	NBN-6	
308.15	0.8654 ± 0.005	0.8633 ± 0.003
313.15	0.8762 ± 0.002	0.8716 ± 0.002
318.15	0.8809 ± 0.003	0.8799 ± 0.003
323.15	0.8925 ± 0.004	0.8883 ± 0.001
328.15	0.8974 ± 0.006	0.8968 ± 0.005
	NBN-7	
308.15	1.4061 ± 0.002	1.3856 ± 0.004
313.15	1.4146 ± 0.001	1.3926 ± 0.005
318.15	1.4196 ± 0.001	1.3996 ± 0.001
323.15	1.4311 ± 0.006	1.4066 ± 0.001
328.15	1.4333 ± 0.002	1.4136 ± 0.001
	NBN-8	
308.15	0.8950 ± 0.006	0.8929 ± 0.006
313.15	0.9016 ± 0.008	0.9005 ± 0.005
318.15	0.9112 ± 0.002	0.9082 ± 0.004
323.15	0.9218 ± 0.006	0.9160 ± 0.001
328.15	0.9239 ± 0.005	0.9238 ± 0.001
	NBN-9	
308.15	1.1323 ± 0.004	1.1298 ± 0.008
313.15	1.1407 ± 0.003	1.1343 ± 0.006
318.15	1.1414 ± 0.003	1.1389 ± 0.005
323.15	1.1502 ± 0.008	1.1435 ± 0.002
328.15	1.1535 ± 0.001	1.1480 ± 0.004
	NBN-10	
308.15	0.7107 ± 0.006	0.7167 ± 0.006
313.15	0.7224 ± 0.004	0.7224 ± 0.007
318.15	0.7223 ± 0.005	0.7282 ± 0.004
323.15	0.7365 ± 0.002	0.7341 ± 0.001
328.15	0.7343 ± 0.004	0.7400 ± 0.002

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

T/K	$10^2 x$	$10^2 x_{ci}$
	NBN-1	
308.15	0.7179 ± 0.002	0.7212 ± 0.003
313.15	0.7337 ± 0.003	0.7325 ± 0.001
318.15	0.7448 ± 0.005	0.7439 ± 0.001
323.15	0.7523 ± 0.006	0.7555 ± 0.001
328.15	0.7651 ± 0.001	0.7673 ± 0.001
	NBN-2	
308.15	0.5179 ± 0.004	0.5242 ± 0.006
313.15	0.5312 ± 0.008	0.5321 ± 0.008
318.15	0.5329 ± 0.006	0.5401 ± 0.007
323.15	0.5461 ± 0.007	0.5483 ± 0.008
328.15	0.5532 ± 0.003	0.5566 ± 0.001
	NBN-3	
308.15	0.9069 ± 0.005	0.9091 ± 0.006
313.15	0.9126 ± 0.006	0.9182 ± 0.004
318.15	0.9227 ± 0.004	0.9274 ± 0.005
323.15	0.9359 ± 0.004	0.9367 ± 0.001
328.15	0.9428 ± 0.007	0.9462 ± 0.002
	NBN-4	
308.15	0.5666 ± 0.001	0.5664 ± 0.008
313.15	0.5741 ± 0.001	0.5755 ± 0.004
318.15	0.5830 ± 0.003	0.5848 ± 0.006
323.15	0.5927 ± 0.006	0.5942 ± 0.004
328.15	0.6031 ± 0.005	0.6038 ± 0.003
	NBN-5	
308.15	0.8443 ± 0.001	0.8374 ± 0.001
313.15	0.8521 ± 0.008	0.8467 ± 0.006
318.15	0.8630 ± 0.004	0.8561 ± 0.004
323.15	0.8739 ± 0.003	0.8655 ± 0.004
328.15	0.8823 ± 0.001	0.8751 ± 0.001

T/K	$10^2 x$	$10^2 x_{ci}$
	NBN-6	
308.15	0.8307 ± 0.004	0.8243 ± 0.003
313.15	0.8415 ± 0.006	0.8338 ± 0.003
318.15	0.8468 ± 0.005	0.8434 ± 0.008
323.15	0.8619 ± 0.004	0.8532 ± 0.005
328.15	0.8702 ± 0.002	0.8631 ± 0.001
	NBN-7	
308.15	1.2589 ± 0.002	1.2771 ± 0.002
313.15	1.2704 ± 0.005	1.2841 ± 0.001
318.15	1.2721 ± 0.006	1.2912 ± 0.005
323.15	1.2826 ± 0.001	1.2983 ± 0.003
328.15	1.2882 ± 0.003	1.3055 ± 0.001
	NBN-8	
308.15	0.8012 ± 0.001	0.8142 ± 0.008
313.15	0.8156 ± 0.002	0.8207 ± 0.004
318.15	0.8151 ± 0.008	0.8273 ± 0.006
323.15	0.8204 ± 0.008	0.8339 ± 0.007
328.15	0.8298 ± 0.007	0.8406 ± 0.001
	NBN-9	
308.15	0.9806 ± 0.006	0.9964 ± 0.002
313.15	0.9906 ± 0.005	1.0034 ± 0.006
318.15	0.9934 ± 0.001	1.0104 ± 0.005
323.15	1.0023 ± 0.001	1.0175 ± 0.004
328.15	1.0292 ± 0.001	1.0247 ± 0.003
	NBN-10	
308.15	0.6179 ± 0.003	0.6155 ± 0.001
313.15	0.6226 ± 0.001	0.6223 ± 0.005
318.15	0.6312 ± 0.005	0.6292 ± 0.008
323.15	0.6405 ± 0.009	0.6362 ± 0.008
328.15	0.6427 ± 0.004	0.6432 ± 0.006

. Table 4. Observed Mole fraction Solubilities (x) and Calculated Mole fraction Solubilities (x_{ci}) of Benzodiazepines in THF

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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 DMF.

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Compounds	*A*	*B*	10^7 RMSD	100 ARD
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. Constants A and B of eq (2), relative average deviations (ARD), and root mean square deviation (RMSD) of Benzodiazepines in THF.

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Compounds	ΔG/KJ·mol^{-1}	ΔH/KJ·mol^{-1}	-ΔS/J·mol^{-1}
NBN-1	12.6518	1.3765	35.4637
NBN-2	13.6393	2.4532	35.1828
NBN-3	12.0953	0.3674	36.8871
NBN-4	13.3918	2.1033	35.5052
NBN-5	12.3270	1.4099	34.3370
NBN-6	12.5549	1.5221	34.7010
NBN-7	11.2720	0.8034	32.9261
NBN-8	12.4661	1.3334	35.0149
NBN-9	11.8446	0.6699	35.1472
NBN-10	13.0756	1.3703	36.8159

Table 7. Thermodynamic parameters of dissolution of benzodiazepines in DMF.

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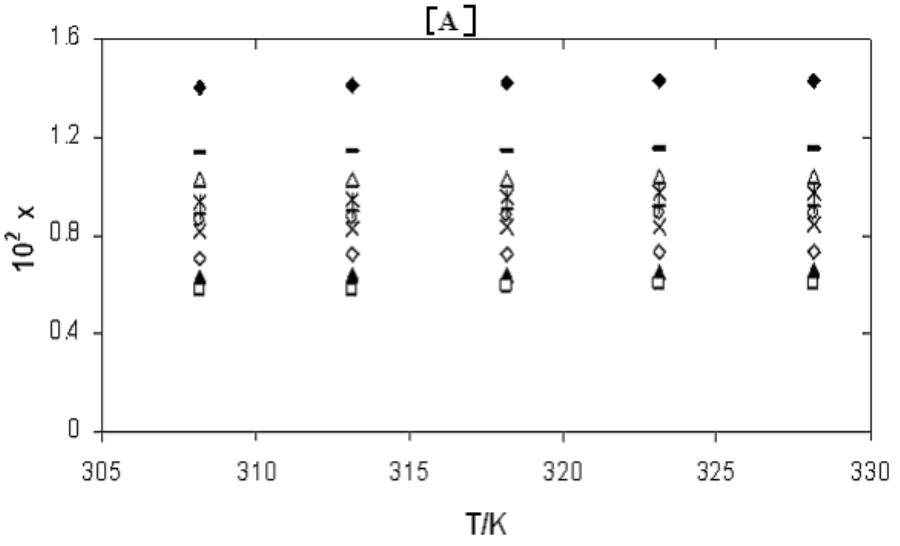
Compounds	ΔG/KJ·mol^{-1}	ΔH/KJ·mol^{-1}	-ΔS/J·mol^{-1}
NBN-1	13.0491	2.6817	32.6082
NBN-2	13.9120	2.7623	35.0685
NBN-3	12.4312	1.6256	33.9866
NBN-4	13.6747	2.6213	34.7657
NBN-5	12.6202	1.8453	33.8898
NBN-6	12.6631	1.9417	33.7214
NBN-7	11.5644	0.9636	33.3420
NBN-8	12.7589	1.3749	35.8056
NBN-9	12.2248	1.2077	34.6516
NBN-10	13.4454	1.6532	37.0894

Table 8. Thermodynamic parameters of dissolution of benzodiazepines in THF.



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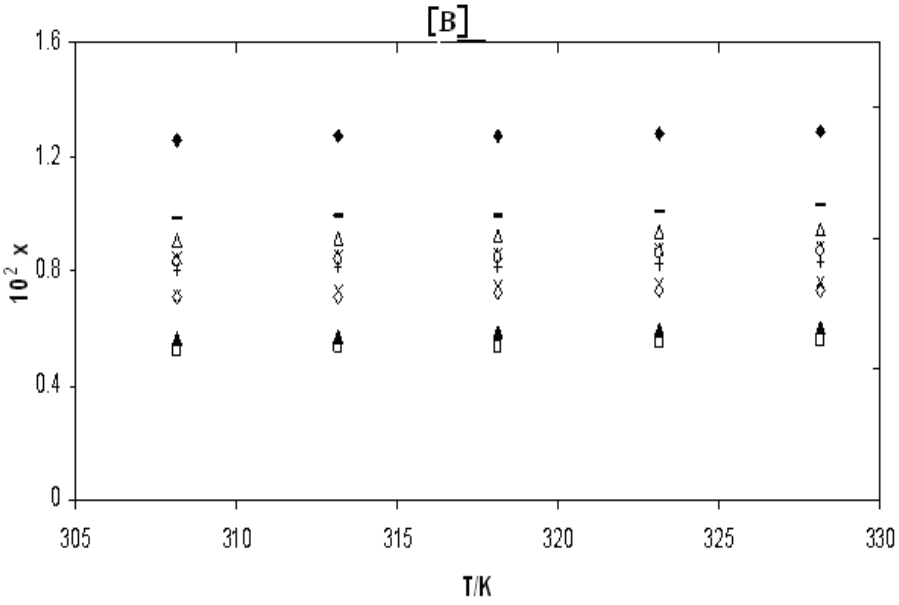

FIGURE 3.Variation of mole fraction solubilities (*x*) with temperature for benzodiazepines in DMF [A] and THF [B]. ×, NBN-1; □, NBN-2; Δ, NBN-3; ▲, NBN-4; ✱, NBN-5; o, NBN-6; ♦, NBN-7; +, NBN-8; –, NBN-9; ◊, NBN-10.

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