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SOLUBILITY OF A SERIES OF PYRIMIDINE DERIVATIVES IN METHANOL AT 293.15 TO 313.15 K

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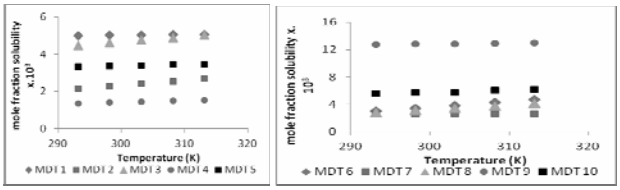
The solubility of some derivatives of pyrimidines in methanol was measured by gravimetrical method at different temperatures (293.15 to 313.15 K) under atmospheric pressure. The solubility data were correlated with temperature by Apelblat equation. Further, some thermodynamic parameters such as dissolution enthalpy, Gibbs' free energy of dissolution and entropy were evaluated from solubility data.



INTRODUCTION

Nitrogen containing heterocyclic ring such as pyrimidine is a promising structural moiety for drug design. Pyrimidine and its derivatives are potential bioactive molecules which exhibit wide spectrum of biological activities such as antibacterial,[1,2] antitumor,[3] antihistaminic,[4] analgesic,[5] anti-inflammatory,[6] anticancer,[7] anticonvulsant,[8] anti HIV,[9] antitubercular,[10] antiprotozoal,[11] antiparkinsonian,[12] antifungal[13] etc. Further, these heterocycles are integral part of DNA and RNA [14] and are present in many natural products.[15,16] Pyrimidine derivatives are also component in various drugs.[17-20]

Owing to their pharmacological properties, the study of solubility of some pyrimidine derivatives would be useful because solubility data play a prominent role for the discovery and development of drugs.[21] In our previous work, solubility behavior of some particular active pharmaceutical ingredients in different protic and aprotic solvents has been studied.[22-24] The study is further extended in the present paper to study the effect of functional groups on solubility of pyrimidine derivatives in methanol at different temperatures (293.15 to 313.15 K) at atmospheric pressure.

EXPERIMENTAL

Materials. Ten different derivatives of pyrimidines (MDT 1-MDT 10) have been synthesized in the laboratory and all the synthesized compounds are recrystallized from ethanol. The purity of these synthesized compounds was checked by elemental analysis, IR, NMR and mass spectral data. The melting temperature of synthesized compounds was determined by DSC method. Fig. 1 shows the general structure of these synthesized compounds. The IUPAC names of ten synthesized compounds are:

1. **MDT 1**: 4-amino-6-(4-hydroxy-3-methoxyphenyl)-2-sulfanyl-1,4,5,6-tetrahydro pyrimidine-5- carbonitrile.
2. **MDT 2**: 4-amino-6-(4-methoxyphenyl)-2-sulfanyl-1,4,5,6-tetrahydro pyrimidine-5-carbonitrile.
3. **MDT 3**: 4-amino-6-(4-hydroxyphenyl)-2-sulfanyl-1,4,5,6-tetrahydro pyrimidine-5-carbonitrile.
4. **MDT 4**: 4-amino-6-(4-chlorophenyl)-2-sulfanyl-1,4,5,6-tetrahydro pyrimidine-5-carbonitrile.
5. **MDT 5**: 4-amino-6-(3-chlorophenyl)-2-sulfanyl-1,4,5,6-tetrahydro pyrimidine-5-carbonitrile.
6. **MDT 6**: 4-amino-6-(4-fluorophenyl)-2-sulfanyl-1,4,5,6-tetrahydro pyrimidine-5-carbonitrile.
7. **MDT 7**: 4-amino-6-(3-nitrophenyl)-2-sulfanyl-1,4,5,6-tetrahydro pyrimidine-5-carbonitrile.

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8. **MDT 8**: 4-amino-6-phenyl-2-sulfanyl-1,4,5,6-tetrahydro pyrimidine-5-carbonitrile.
9. **MDT 9**: 4-amino-6-(furan-2-yl)-2-sulfanyl-1,4,5,6-tetrahydro pyrimidine-5-carbonitrile.
10. **MDT 10**: 4-amino-6-[(Z)-2-phenylethenyl]-2-sulfanyl-1,4,5,6-tetrahydro pyrimidine-5-carbonitrile.

Methanol was purified by fractional distillation and its purity was checked by SHIMADZU GC-MS (Model No QP-2010) and was found to be greater than 99.70 %.

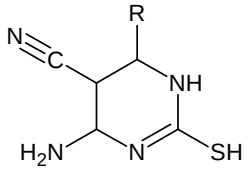

Figure 1 – General Structure of pyrimidine derivatives (MDT 1- MDT 10).

Where R = MDT 1: -4- OH, 3-OCH_3 C_6H_4, MDT 2: - 4- OCH_3 C_6H_4, MDT 3: - 4- OH C_6H_4, MDT 4: - 4- Cl C_6H_4, MDT 5: - 3- Cl C_6H_4, MDT 6: - 4- F C_6H_4, MDT 7: - 3- NO_2 C_6H_4, MDT 8: - C_6H_5, MDT 9: - C_4H_3O, MDT 10: - CH=CH, C_6H_5.

Solubility measurement: The solubility of these compounds is observed in methanol at different temperatures (293.15 to 313.15 K). 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, 5 ml of this clear solution was taken in another weighed measuring vial (m_0). The vial was quickly and tightly closed and weighed (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 methanol in the vial had completely evaporated at room temperature, the vial was dried and reweighed (m_2) to determine the mass of the constant solid residue (m_2- m_0). All the masses were measured 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 eq 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 methanol.

At each temperature, the measurement was repeated three times and an average value is given in Table 1.

Table 1

Observed Mass fraction Solubilities (*x) and* Calculated Mass fraction Solubilities (x_{ci}) of pyrimidine derivatives in methanol

-Temp. K	x. 10^3	$x_{ci}.10^3$	100 RD	x. 10^3	$x_{ci}.10^3$	100 RD
	MDT 1			MDT 6		
293.15	5.0027	5.0309	0.0001	2.9765	2.6330	-0.0159
298.15	5.0167	5.0460	0.0002	3.3969	2.9391	-0.0168
303.15	5.0337	5.0612	0.0001	3.8218	3.2808	-0.0177
308.15	5.0474	5.0764	0.0002	4.2439	3.6622	-0.0185
313.15	5.0611	5.0916	0.0001	4.6704	4.0880	-0.0193
	MDT 2			MDT 7		
293.15	2.1561	1.6945	-0.0075	2.5740	2.5814	-0.0059
298.15	2.2855	1.7814	-0.0083	2.5826	2.5918	-0.0081
303.15	2.4118	1.8727	-0.0089	2.5945	2.6022	-0.0097
308.15	2.5478	1.9687	-0.0097	2.6032	2.6126	-0.0106
313.15	2.6774	2.0696	-0.0103	2.6152	2.6231	-0.0109
	MDT 3			MDT 8		
293.15	4.4797	3.6202	0.0005	2.7468	2.8062	0.0010
298.15	4.6153	3.7118	0.0006	3.0801	3.1012	0.0004
303.15	4.7537	3.8057	0.0005	3.4193	3.4273	0.0001
308.15	4.8889	3.9021	0.0005	3.7579	3.7877	0.0005
313.15	5.0237	4.0008	0.0006	4.0991	4.1860	0.0016

Table 1 (continued)

	MDT 4			MDT 9		
293.15	1.3729	1.0733	-0.0045	12.722	12.567	-0.0111
298.15	1.4164	1.1005	-0.0048	12.777	12.617	-0.0113
303.15	1.4449	1.1283	-0.0048	12.829	12.668	-0.0115
308.15	1.5000	1.1569	-0.0053	12.884	12.719	-0.0124
313.15	1.5439	1.1862	-0.0055	12.941	12.770	-0.0120
	MDT 5			MDT 10		
293.15	3.3490	2.7182	-0.0036	5.5568	4.6902	-0.0167
298.15	3.3750	2.7318	-0.0037	5.7198	4.8089	-0.0176
303.15	3.4008	2.7455	-0.0037	5.7340	4.9306	-0.0156
308.15	3.4614	2.7593	-0.0038	6.0485	5.0554	-0.0194
313.15	3.4520	2.7731	-0.0039	6.2107	5.1834	-0.0202

RESULTS AND DISCUSSION

The mass fraction solubilities x of pyrimidines derivatives (MDT 1-MDT 10) in methanol at different temperatures (293.15 to 313.15 K) are summarized in Table 1. The variation of these mole fraction solubilities for all the compounds with temperature are also shown in Fig. 2. It is observed that solubility increases linearly with increase in temperature.

By the modified Apelblat equation,[25,26] mole fraction solubilities are related to temperature.

$$ln\, x_{ci} = A + B/T \qquad (2)$$

where x_{ci} is the mass fraction solubility of pyrimidines and T is the absolute temperature. A and B are the parameters. The values of these parameters are given in Table 2. Using these parameters, solubilities x_{ci} are calculated and are given in Table 1.

Further, relative average deviations (*ARD*) and root-mean-square deviations (*RMSD*), calculated by equations (3) and (4) are listed in Table 2.

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

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

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

The relative deviations (*RD*) between the experimental and calculated values of solubilities are also calculated by equation 5 and are given in Table 1.

$$Relative\ Deviation = \left(\frac{x - x_{ci}}{x}\right) \qquad (5)$$

It is observed from Table 1 that solubility is minimum for MDT 4 and maximum for MDT 9. The order of solubility is MDT 9 > MDT 10 > MDT 1 > MDT 3 > MDT 5 > MDT 6 > MDT 8 > MDT 2 > MDT 7 > MDT 4. All the compounds have the same central moiety but different side chains. Thus, solubility is affected by the side chain. MDT 9 contains furan as side chain. Thus, higher solubility in MDT 9 among the studied compound is due to furan whereas MDT 4 containing p-chloro alkyl group exhibited minimum solubility. The position of functional group in side chain also affects the solubility. MDT 5 also contains chloro alkyl group but in this compound, chloro group is at *meta* position which causes an increase in solubility. There may be hydrogen bond formation between methanol molecules and oxygen of furan ring. MDT 1 and MDT 3 also exhibit comparatively good solubility which may also be due to hydrogen bonding of -OH group with methanol molecules. Solubility of MDT 1 is higher than MDT-3. From this observation, it can be assumed that the solubility of compound with vanillin is higher than compound with –OH group which may be due to positive effect of $–OCH_3$ group. However, MDT 2 which possesses only $–OCH_3$ group, exhibited less solubility.

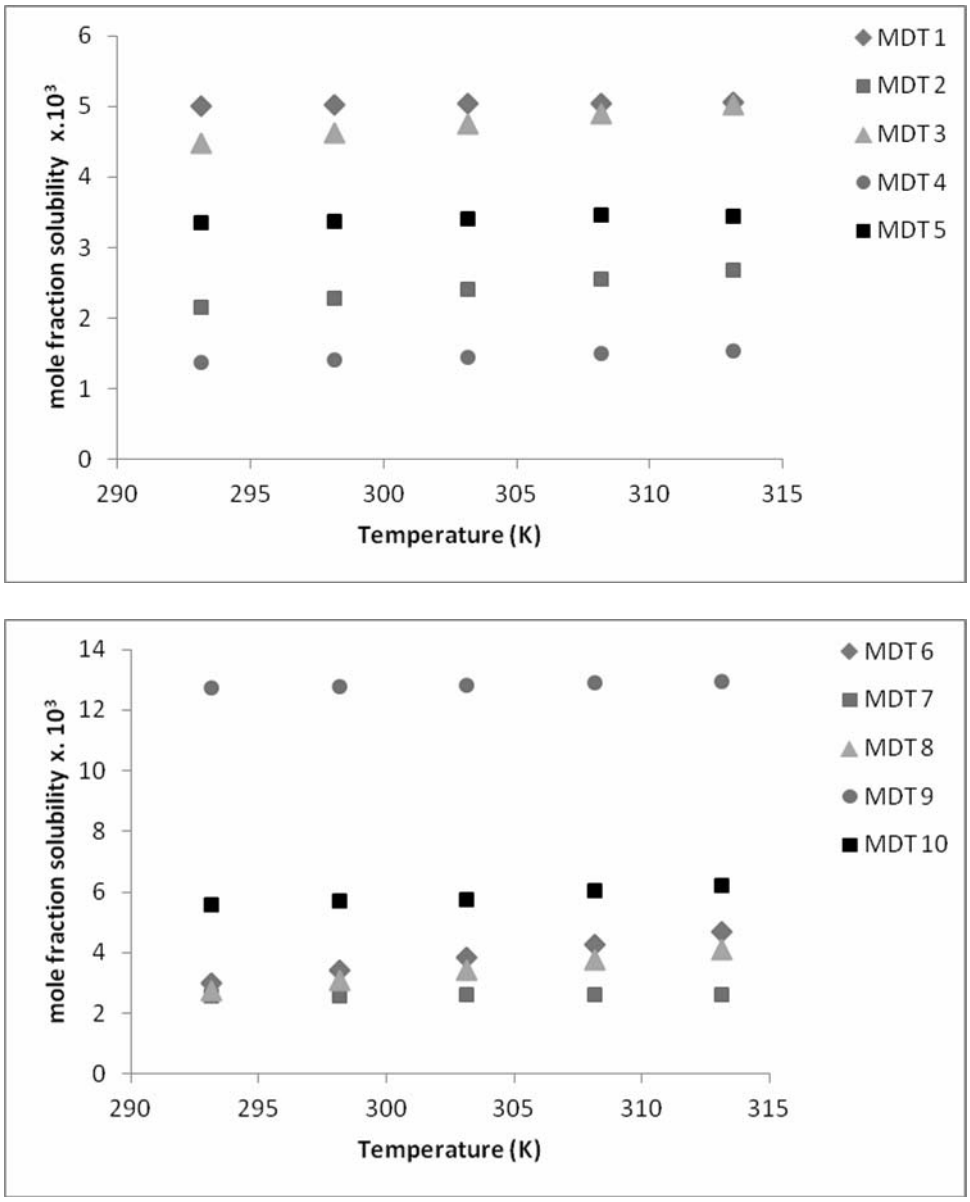

Fig. 2 – Variation of mole fraction solubility of pyrimidine compounds in methanol with temperature.

Table 2

Constants *A* and *B* of eq (2), Relative Average Deviations (*ARD*),
and Root Mean Square Deviation (*RMSD*) of pyrimidine derivatives in methanol

Compounds Code	A	B(K)	10^8 RMSD	100 ARD
MDT 1	-5.469	0.0006	0.0209	0.0006
MDT 2	-9.313	0.01	7.3130	-0.0089
MDT 3	-7.088	0.005	22.369	-0.0177
MDT 4	-8.304	0.005	2.6778	-0.0050
MDT 5	-6.202	0.001	10.975	-0.0117
MDT 6	-12.39	0.022	6.4896	-0.0090
MDT 7	-6.195	0.0008	0.0017	0.0001
MDT 8	-11.74	0.02	0.0623	0.0007
MDT 9	-4.612	0.0008	0.6629	-0.0037
MDT 10	-6.829	0.005	21.339	-0.0179

Table 3

Thermodynamic parameters of dissolution of pyrimidine derivatives in methanol

Compounds code	ΔH_{sol} kcal.mol^{-1}	ΔG_{sol} kcal.mol^{-1}	ΔS_{sol} cal.mol^{-1}.K^{-1}
MDT 1	0.4470	14.8302	-47.4715
MDT 2	8.2716	11.2998	-9.9946
MDT 3	4.3782	14.9547	-34.9077
MDT 4	4.4605	15.1652	-35.3311
MDT 5	1.1565	11.7306	-34.8997
MDT 6	17.1684	11.6039	18.3658
MDT 7	0.6058	12.4475	-39.0835
MDT 8	15.2645	12.5825	8.8520
MDT 9	0.6463	12.8354	-40.2299
MDT 10	4.2493	12.4669	-27.1221

Further, from the solubility data, some thermodynamic parameters such as solution enthalpy (ΔH_{sol}), Gibbs' free energy change (ΔG_{sol}) and entropy of solution (ΔS_{sol}) have also been evaluated.

The solution enthalpy (ΔH_{sol}) was calculated by modified Van't Hoff equation[27]

$$\frac{\partial \ln x}{\partial\left(1/T - 1/T_{hm}\right)_P} = -\frac{\Delta H_{Sol}}{R} \qquad (6)$$

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

$$T_{hm} = \frac{n}{\sum_{i}^{n}\left(1/T\right)} \qquad (7)$$

where n is the number of experimental temperatures. In the present case, the T_{hm} value obtained is only 302.99 K. The slope of the plot of $ln\ x$ versus ($1/T$-$1/T_{hm}$) gives the value of ΔH_{sol}.

The Gibbs' energy change (ΔG_{sol}) for the solution process was then evaluated from intercept of the above plot using following relation:[28]

$$\Delta G_{sol} = -RT.\ intercept \qquad (8)$$

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

$$\Delta S_{sol} = \frac{\Delta H_{sol} - \Delta G_{sol}}{T_{hm}} \qquad (9)$$

All these thermodynamic parameters are given in Table 3.

It is evident from Table 3 that for all the compounds ΔH_{sol} and ΔG_{sol} are positive. However, ΔS_{sol} values are negative for most of the compounds except MDT 6 and MDT 8 where it is positive. When stronger bonds are broken and weaker bonds are formed, energy is consumed. So, ΔH_{sol} becomes positive[29] indicating thereby endothermic dissolution of compounds. The positive value of ΔG_{sol} indicates spontaneous dissolution of studied compounds in methanol.[30] The positive entropy ΔS_{sol} indicates more randomness in solution as observed for most of the compounds whereas negative ΔS_{sol} suggests more order in solutions.

CONCLUSIONS

The solubility of synthesized pyrimidine derivatives in methanol increases with the rise of temperature. The modified Apelblat equation is used to correlate the solubility data with temperature. The solubility calculated by Apelblat equation is in good agreement with experimental solubility. Further, solubility in the studied compounds is affected by the function groups

present in the compounds and compound containing furan exhibited maximum solubility in methanol. The positive enthalpy and Gibbs free energy values indicate the dissolution process to be endothermic and spontaneous. For most of the studied compounds, dissolution results in more ordered structure as indicated by negative entropy values whereas positive entropy suggests less ordered structure for some compounds. The more ordered structure may be due to hydrogen bonding between compound and methanol molecules.

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