

Solubility of a pharmacological intermediate drug Isatin in different solvents at various temperatures

Shipra Baluja*, Rahul Bhalodia, Mehul Bhatt, Nayan Vekariya, Ravi Gajera

Physical Chemical Laboratory, Department of Chemistry, Saurashtra University,
Rajkot 360 005, India

*E-mail address: shipra_baluja@rediffmail.com

ABSTRACT

The solubility of isatin in different solvents was studied by a gravimetric method from (298.15 to 318.15) K under atmospheric pressure and the solubility data were correlated against temperature. The solvents selected for the present study are: water, methanol, ethanol, 1-butanol, dichloromethane, dichloroethane, chloroform and carbon tetra chloride. Among chlorinated solvents, solubility is observed to be maximum in 1, 2-dichloroethane and minimum in dichloromethane whereas in alcohols, maximum solubility is observed in methanol. In water, solubility is found to be minimum. Further, some thermodynamic parameters such as Gibb's energy (ΔG_{sol}), heat of solution (ΔH_{sol}) and entropy of solution (ΔS_{sol}) have also been evaluated.

Keywords: Isatin, solubility, Thermodynamic parameters.

1. INTRODUCTION

Isatin or 1H-indole-2,3-dione is an indole derivative which is found in many plants. It is a yellow to red needle crystalline solid which has aroused great attention in recent years due to their wide variety of biological activities and pharmacological studies as fungicides,¹ insecticides², anticancer³, anticonvulsant⁴, anti HIV⁵, anti protozoal⁶, enzymatic⁷, antimicrobial⁸, antifungal⁹, anti-inflammatory¹⁰, anticonvulsant¹¹ and cytotoxic¹² and antioxidant¹³ etc. Moreover, isatins are the synthetic precursors of some biologically important compounds^{14,15}.

Because of the continuing interest about isatin and its derivatives¹⁶⁻¹⁹, the present work was undertaken to test the solubility of isatin in different solvents at different temperatures and as a result, to evaluate different thermodynamic parameters. Further, various thermodynamic parameters have been evaluated from these solubility data. The solubility data of isatin may be used in the various fields of chemistry and pharmaceutical industry.

This work is the continuation of our systematic study of solubilities of drug in different solvents. In this paper the solubility of isatin in different solvents such as water, methanol,

ethanol, 1-butanol, dichloromethane, dichloroethane, chloroform and carbon tetrachloride have been determined²⁶.

2. EXPERIMENTAL

Isatin, with a mass purity of 99.7 %, was purchased from (Loba Chemicals, Mumbai). All the solvents selected for the present study were analytical grade reagents, which were purified by fractional distillation. Their purities were checked by SHIMADZU GC-MS (Model No QP-2010) and were found to be greater than 99.70 %.

The drug was recrystallized and its melting point was determined by DSC. The observed value was found to be 472 K which is in good agreement with the reported value²⁰ (473 K).

2. 1. Description of experiment

The solubilities were measured by a gravimetric method²¹. For each measurement, an excess mass of isatin was added to a known mass of solvent. Then, the equilibrium cell was heated to a constant temperature (± 0.1 °C) with continuous stirring. After, 3 hours, temperature of water was constant and was recorded. The stirring was stopped and the solution was kept still for 2 hrs. 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. Then, the vial was placed in at room temperature to evaporate the solvent.

After the solvent in the vial had completely evaporated, the vial was dried and reweighed (m_2) to determine the mass of the constant residue solid ($m_2 - m_0$). All the weights were taken using an electronic balance (Mettler Toledo AB204-S, Switzerland) with an accuracy of ± 0.0001 g. Thus, the solid concentration of the sample solution of 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 isatin 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 Table 1.

Table 1. Observed mole fraction solubilities (x), calculated mole fraction solubilities (x_{ci}) and relative deviation (RD) of Isatin in different solvents.

T/K	x	x_{ci}	100 RD
Dichloromethane			
298.15	0.0030 \pm 0.001	0.0031	0.21
300.15	0.0033 \pm 0.006	0.0032	-0.34

303.15	0.0037 ±0.005	0.0035	-1.00
305.15	0.0039 ±0.010	0.0037	-1.34
308.15	0.0043 ±0.009	0.0039	-1.71
310.15	0.0045 ±0.008	0.0041	-1.36
313.15	0.0047 ±0.006	0.0045	-0.80
315.15	0.0048 ±0.012	0.0047	-0.41
318.15	0.0050 ±0.015	0.0051	0.23
1,2-dichloroethane			
298.15	0.0540 ±0.003	0.0547	0.39
300.15	0.0562 ±0.004	0.0561	-0.05
303.15	0.0606 ±0.007	0.0585	-1.30
305.15	0.0636 ±0.005	0.0601	-2.09
308.15	0.0661 ±0.003	0.0626	-2.05
310.15	0.0674 ±0.013	0.0643	-1.79
313.15	0.0690 ±0.011	0.0669	-1.16
315.15	0.0698 ±0.002	0.0687	-0.59
318.15	0.0711 ±0.008	0.0716	0.24
Chloroform			
298.15	0.0306 ±0.015	0.0306	0.01
300.15	0.0312 ±0.001	0.0311	-0.12
303.15	0.0317 ±0.006	0.0319	0.10
305.15	0.0321 ±0.002	0.0324	0.26
308.15	0.0326 ±0.003	0.0332	0.50
310.15	0.0334 ±0.002	0.0337	0.24
313.15	0.0347 ±0.013	0.0345	-0.13
315.15	0.0355 ±0.005	0.0351	-0.36
318.15	0.0357 ±0.003	0.0359	0.16
Carbon tetrachloride			

298.15	0.0235 ±0.016	0.0230	-0.61
300.15	0.0258 ±0.012	0.0257	-0.20
303.15	0.0293 ±0.015	0.0302	0.86
305.15	0.0316 ±0.013	0.0337	1.84
308.15	0.0351±0.015	0.0397	3.68
310.15	0.0419 ±0.018	0.0443	1.76
313.15	0.0521 ±0.011	0.0522	0.07
315.15	0.0589 ±0.011	0.0583	-0.39
318.15	0.0691±0.010	0.0687	-0.25
Methanol			
298.15	0.0057 ±0.0005	0.0057	-0.3425
300.15	0.0058 ±0.0002	0.0058	0.1459
303.15	0.0058 ±0.0004	0.0059	0.2903
305.15	0.0059 ±0.0003	0.0060	0.0067
308.15	0.0060 ±0.0002	0.0061	-0.9809
310.15	0.0061 ±0.0002	0.0062	-0.2050
313.15	0.0064 ±0.0001	0.0064	0.3667
315.15	0.0065 ±0.0002	0.0065	0.2746
318.15	0.0067 ±0.0001	0.0068	-0.3899
Ethanol			
298.15	0.0040 ±0.0002	0.0041	0.4431
300.15	0.0043 ±0.0001	0.0043	1.5018
303.15	0.0045 ±0.0005	0.0046	-1.5929
305.15	0.0048 ±0.0004	0.0048	0.1470
308.15	0.0050 ±0.0007	0.0051	-1.8806
310.15	0.0053 ±0.0006	0.0054	-0.9412
313.15	0.0057 ±0.0004	0.0057	0.1131
315.15	0.0059 ±0.0002	0.0060	0.5238

318.15	0.0064 ±0.0004	0.0064	0.7780
1-Butanol			
298.15	0.0049 ±0.0001	0.0049	-0.1593
300.15	0.0053 ±0.0002	0.0054	-0.2327
303.15	0.0060 ±0.0001	0.0061	-0.2313
305.15	0.0065 ±0.0004	0.0065	0.0975
308.15	0.0072 ±0.0005	0.0071	1.0539
310.15	0.0074 ±0.0003	0.0075	-0.2152
313.15	0.0079 ±0.0004	0.0080	-1.0073
315.15	0.0081 ±0.0001	0.0083	-0.7963
318.15	0.008 ±0.0001	0.0085	0.7016
Water			
298.15	5.1384E-05 ±0.0021E-05	5.2410E-05	-1.9955
300.15	5.8717E-05 ±0.0011E-05	5.8017E-05	1.1932
303.15	6.8491E-05 ±0.0057E-05	6.7124E-05	1.9955
305.15	7.3372E-05 ±0.0060E-05	7.3658E-05	-0.3895
308.15	8.3138E-05 ±0.0043E-05	8.4142E-05	-1.2077
310.15	9.0458E-05 ±0.0044E-05	9.1575E-05	-1.2340
313.15	10.2657E-05 ±0.0020E-05	10.336E-05	-0.6857
315.15	11.2417E-05 ±0.0031E-05	11.162E-05	0.7082
318.15	12.4604E-05 ±0.0034E-05	12.457E-05	0.0286

Table 2. Dielectric constant and Dipole moment of solvents.

Solvent	Dielectric Constant	Dipole Moment
1,2-Dichloroethane	10.36	1.20
Dichloromethane	9.08	1.60
Chloroform	4.81	1.01
Carbon tetrachloride	2.24	0.00

Methanol	33.00	1.70
Ethanol	24.3	1.69
1-Butanol	17.8	1.66
Water	78.8	1.85

Table 3. Constants A, B and C of eq (2) and root mean square deviation (RMSD) of isatin in different solvents.

Solvents	A	B	C	10^{-5} RMSD
dichloromethane	869.25	-42785.87	-130.47	0.0036
1,2-dichloroethane	470.55	-22012.18	-66.87	4.0500
chloroform	-93.65	-13312.23	-39.91	0.0069
carbon tetrachloride	-693.62	13915.78	-63.99	2.9265
Methanol	-440.85	19273.15	65.12	0.7891
Ethanol	-2.27	-1930.97	0.5691	5.9600
1-Butanol	1103.4604	-52942.48	-163.44	4.9312
Water	342.41	-19593.67	-50.292	0.4741

Table 4. Thermodynamic parameters Gibb's energy (ΔG_{sol}), heat of solution (ΔH_{sol}) and entropy of solution (ΔS_{sol}) of dissolution of Isatin in various solvents.

Solvents	$\Delta G/\text{kJ}\cdot\text{mol}^{-1}$	$\Delta H/\text{kJ}\cdot\text{mol}^{-1}$	$\Delta S/\text{J}\cdot\text{mol}^{-1}\text{K}^{-1}$
dichloromethane	14.09	19.57	17.83
1,2-dichloroethane	7.04	10.90	12.54
chloroform	8.73	6.52	-7.17
carbon tetrachloride	8.35	43.08	112.82
Methanol	13.0359	6.4184	-21.4868
Ethanol	13.5137	17.5101	12.9759
1-Butanol	12.7609	21.9190	29.7358
Water	24.0763	34.2013	32.8755

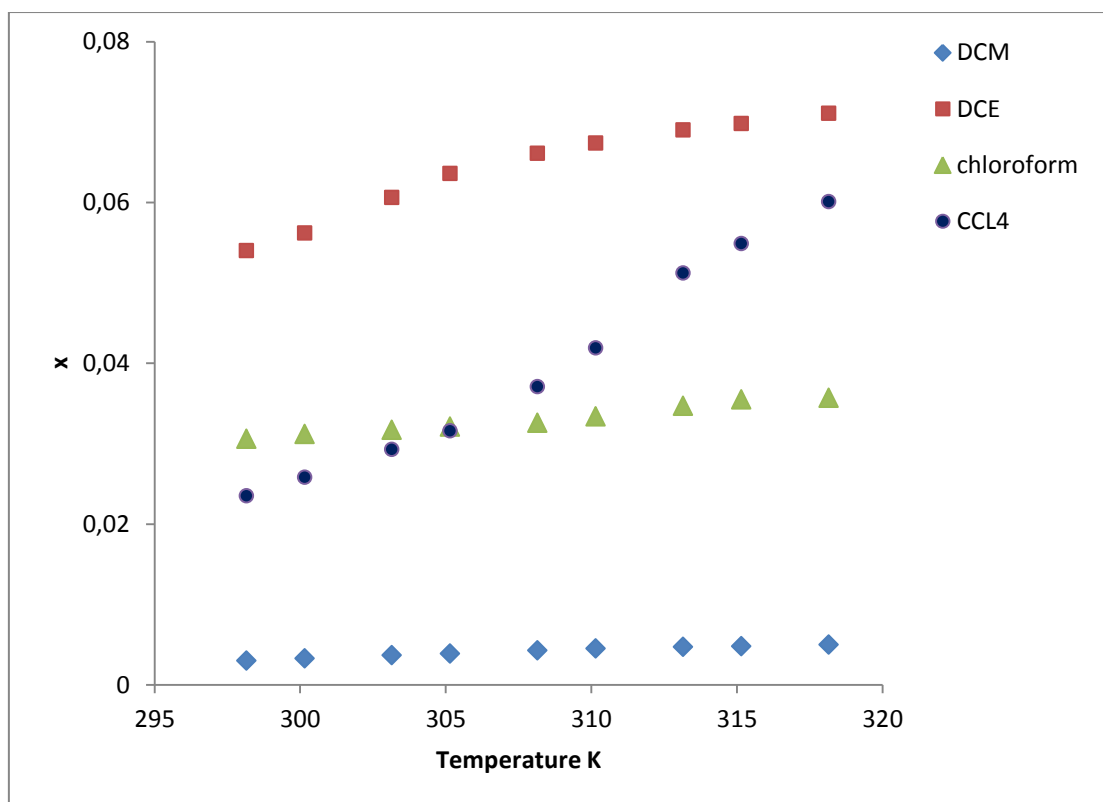


Figure 2(a). Variation of mole fraction solubilities (x) with temperature in different solvents.

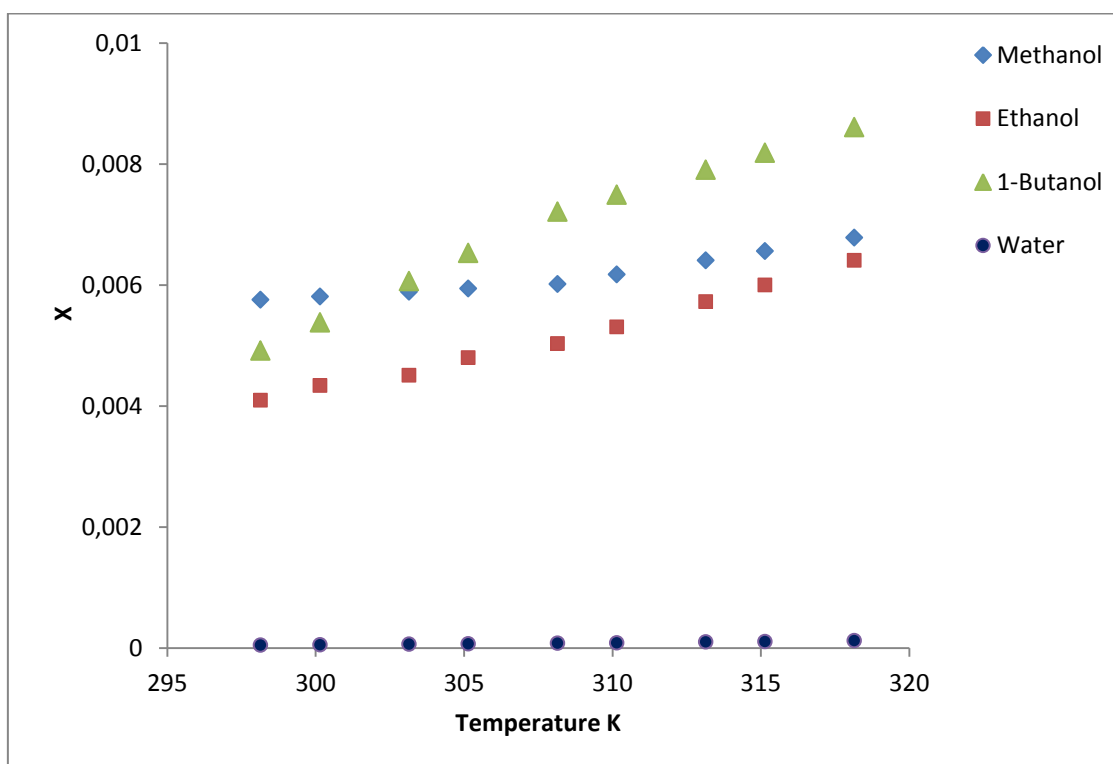
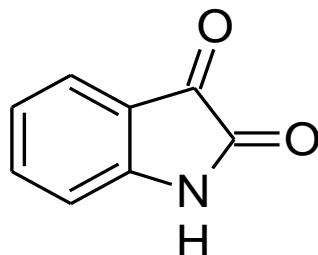


Figure 2(b). Variation of mole fraction solubilities (x) with temperature in different solvents.



1*H*-indole-2,3-dione

Figure 1. Structure of Isatin.

3. RESULTS AND DISCUSSION

The mole fraction solubilities x of isatin in studied solvents at different temperatures (298.15 to 318.15) are summarized in Table 1. It is evident from Table 1 that among chlorinated solvents, solubility is minimum in dichloromethane and maximum in 1,2-dichloroethane whereas in alcohols, maximum solubility is observed in methanol. In water, solubility is found to be minimum.

Table 2 shows dielectric constants and dipole moments of the studied solvents. It is well known fact that solubility is affected by dielectric constant and dipole moment of the solvents. Among alcohols and water, dielectric constant and dipole moments is maximum for water and minimum for 1-butanol. But, it is observed that solubility is minimum in water and maximum for 1-butanol. If water is excluded from alcohols then maximum dielectric constant and dipole moments are for methanol where solubility is higher at lower temperature but at higher temperatures, solubility is found to be greater for 1-butanol. This may be due to disruption of structure due to bulky 1-butanol as compared to other two alcohols.

Among chlorinated solvents, dielectric constant and dipole moments is maximum for 1,2-dichloroethane and minimum for carbon tetrachloride. The maximum solubility in 1,2-dichloroethane can be explained due to its high dielectric constant. However, minimum solubility is observed in dichloromethane which is having dielectric constant greater than chloroform and carbon tetra chloride. When dipole moments of the four solvents are compared, it is observed that dipole moment is maximum for dichloromethane which may be the reason for less solubility in this solvent. Again, in this case also, bulky 1,2-dichloroethane may cause greater solubility as compared to other chlorinated solvents.

The variation of solubility with temperature is also shown in Figure 2. It is observed that solubility increases with increase of temperature. As shown in Figure 2, the mole fraction solubility x of isatin was correlated as a function of temperature. The temperature dependence of the drug solubility in solvents is described by the modified Apelblat equation²²

$$\ln(x) = A + B/(T/K) + C \ln(T/K) \quad (2)$$

where x is the mole fraction solubility of isatin, T is the absolute temperature and A , B and C are the parameters.

The values of these parameters are given in Table 3. The calculated solubilities x_{ci} are also reported in Table 1. The experimental solubility of isatin in the studied solvents was compared with calculated solubility (x_{ci}).

Further, root-mean-square deviations (RMSD), calculated by equations 3 is listed in Table 2.

$$RMSD = \left[\sum_{i=1}^N \frac{(x_{ci} - x_i)^2}{N-1} \right]^{1/2} \quad (3)$$

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 4 and are given in Table 1.

$$\text{Relative Deviation} = \left(\frac{x - x_{ci}}{x} \right) \quad (4)$$

The heat of solution (ΔH_{sol}) was calculated by modified van't Hoff equation^{23,24}:

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

where T is the experimental temperature and R is perfect gas constant ($8.314 \text{ J. mole}^{-1} \cdot \text{K}^{-1}$). T_{hm} is the mean harmonic temperature which is given as

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

where n is the number of experimental temperatures¹⁷. In the present case, the T_{hm} value obtained is only 307.79 K. The slope of the plot of $\ln x$ versus $(1/T - 1/307.79)$ gives the value of ΔH_{sol} .

The Gibbs energy change for the solubility process was then evaluated from the following relation²³:

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

Using these evaluated ΔH_{sol} and ΔG_{sol} values, the entropy of solution ΔS_{sol} were obtained from equation^{23,24}:

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

All these thermodynamic parameters are given in Table 4.

It is evident from Table 4 that for all the solvents ΔG_{sol} and ΔS_{sol} values are positive. When stronger bonds are broken and weaker bonds are formed, energy is consumed. So, ΔH_{sol} becomes positive²⁴. 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 spontaneous¹⁶. The positive ΔS_{sol} for dichloromethane, 1,2-dichloroethane and carbon tetrachloride confirms the complex formation. However negative ΔS_{sol} values in chloroform may due to absence of complex formation²⁵.

4. CONCLUSION

In alcohols, maximum solubility is observed in 1-Butanol whereas in chloriated solvents, it is maximum in 1,2-dichloroethane. Further, solubility increases with temperature. The dissolution process is not spontaneous and is endothermic.

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