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Experimental determination of solubility of dihydropyridine derivatives in organic solvents at different temperatures: Interactions and thermodynamic parameters relating to the solvation process

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ABSTRACT

A novel series of dihydropyridine derivatives were synthesized and characterization of all these synthesized compounds was done by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For all these compounds, solubility was determined by gravimetric method in various polar and non-polar solvents such as methanol, ethanol, 1-propanol, 1-butanol, chloroform, ethyl acetate and 1,4-dioxane. It is found that solubility increases with temperature and is found to be greater in 1,4-dioxane for all the compounds. The modified Apelblat and Buchowski-Ksiazczak λ*h* models were used to correlate the experimental solubility with temperature. Using Van't Hoff and Gibb's equations, some thermodynamic parameters such as Gibb's free energy, enthalpy and entropy of dissolution were also evaluated from solubility data.

1. Introduction

The knowledge of solubility of compounds is required in different chemical, pharmaceutical and industrial applications, such as crystallization, separation, decontamination and liquid-liquid extraction [1–3]. For drugs, it is an important property because it affects drug's efficacy, formulation and pharmacokinetic properties such as release, transport and degree of absorption in the organism [4,5]. Dependence of solubility on temperature allows thermodynamic analysis which explains the molecular mechanisms, involved in the solution processes [6,7].

The solubility of heterocyclic compounds plays an important role in selection of solvent for syntheses, separation, crystallization etc. in many chemical industries [8,9]. To determine the proper purification method of compounds, it is necessary of know about the solubility of it in different solvents and their mixtures.

The dihydropyridine derivatives are an important class of heterocyclic compounds which have showed significant applications in different fields [10–13]. Literature survey shows that such class of compounds have wide spectrum of biological and pharmaceutical properties such as inhibition of HMG Co A-reductase [14], antihypertensive [15], used as K^{+} channel openers [16], antihistaminic [17], anticonvulsant [18], anticancer [19], antifungal [20], anti-tubercular [21,22], antiulcer [23], antimalarial [24,25] etc.

Due to multifold biological activities of dihydropyridine derivatives, it would be interesting to study their solubility in various solvents at different temperature. Hence in the present work, some new dihydropyridine derivatives were synthesized and their structure conformation was done by different spectroscopic techniques. The solubility of these synthesized compounds was also carried out in methanol, ethanol, 1-propanol, 1-butanol, chloroform, ethyl acetate and 1,4-dioxane at different temperatures ranging from T = (298.15 to 328.15 K) and at atmospheric pressure. Apelblat and Buchowski-Ksiazczak λ*h* models were applied to correlate the results. From the solubility data, some thermodynamic parameters such as Gibbs free energy, enthalpy and entropy have also been calculated.

2. Experiment

The chemicals used in the synthesis of dihydropyridine derivatives such as 4-hydroxy-3-methoxy benzaldehyde, different substituted acetophenones and ethyl cyano acetate etc., were purchased from Spectochem Pvt. Ltd. (Mumbai, India) as well as LOBA Chemie Pvt. Ltd. and the mole fraction purities of these chemicals were of 99.50–99.80%.

The solvents used in solubility determination were of Analytical Reagent (AR) grade and were further purified according to reported method [26]. All the distilled solvents were stored over dry molecular sieves. The purity of solvents was checked by GC–MS (SHIMADZU Model-QP-2010) and was found to be >99.90%. The source and mole fraction purity of solvents are given in Table 1.

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Nomenclature

x_i	experimental mole fraction solubility
δ_H	hydrogen bonding capacity
x_{ci}^a	mole fraction solubility calculated by modified Apelblat model
λh	Buchowski-Ksiazczak model
x_{ci}^b	mole fraction solubility calculated by Buchowski-Ksiazczak model
RD	relative deviation
RMSD	root mean square deviation
ARD	average relative deviation
A, *B* and *C*	various constants derived from modified Apelblat model
λ and h	various constants obtained from Buchowski-Ksiazczak model
ΔH_{sol}	enthalpy change of dissolution process
ΔS_{sol}	entropy change of dissolution process
ΔG_{sol}	Gibb's free energy change of dissolution process
%ξH	relative contribution of enthalpy in solvation process
%ξS	relative contribution of entropy in solvation process

2.1. Synthesis

An ethanolic solution of different acetophenones (0.01 mmol), 4-hydroxy-3-methoxy benzaldehyde (0.01 mmol), cyano ethylacetate (0.01 mmol) and ammonium acetate (0.04 mmol) was refluxed. The completion of reaction was confirmed by analytical thin layer chromatography (TLC) (Performed on aluminium coated plates Gel $60F_{254}$ (E. Merck)) using (0.6:0.4-hexane: ethyl acetate) as mobile phase. After completion of reaction, the reaction mass was allowed to cool at room temperature and obtained solid was stirred with toluene for half an hour. The resultant solid was filtered, washed with methanol to remove unreacted reagents and was dried under vacuum to give crude product.

The reaction scheme is given in Fig. 1. The IUPAC names of synthesized compounds are given as follow:

DPCE-1: 4-(4-hydroxy-3-methoxyphenyl)-6-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile

DPCE-2: 4-(4-hydroxy-3-methoxyphenyl)-6-(4-hydroxyphenyl)-2-oxo-1,2-dihydropyridine-3 -carbonitrile

DPCE-3:6-(4-fluorophenyl)-4-(4-hydroxy-3-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile

DPCE-4: 6-(4-chlorophenyl)-4-(4-hydroxy-3-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile

DPCE-5:6-(4-bromophenyl)-4-(4-hydroxy-3-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile.

All the synthesized compounds were recrystallized from methanol before use. The purity of synthesized compounds was checked by GC–MS (SHIMADZU Model-QP2010) and found to be >99.50%. The physical constants of all the synthesized compounds are given in Table 2.

The structures of synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For DPCE-5, IR, ^{1}H NMR, ^{13}C NMR and mass spectra are shown in Figs. 2 to 5 respectively.

3. Solubility measurement

The solubility measurement was carried out by gravimetric method [27]. For each measurement, an excess amount of compound was added to a known volume of solvent. The solution was heated at constant temperature with continuous stirring until equilibrium was established. The equilibrium time is optimized by checking concentration of solution at different interval of time. After few hours, the change in concentration was <1%, so saturated solution was assumed to be equilibrium. After the equilibrium was attained, the stirring was stopped and the solution was kept at constant temperature for some time. The clear solution was filtered and known volume of this solution was taken in pre weighted measuring vial (m_0). This vial was instantly weighted to determine the weight of the sample solution (m_1) and was then kept in vacuum oven at 318.15 K so the solvent is completely evaporated. After complete dryness of vial mass, the vial was reweighed (m_2). When the mass of the residue reached a constant value, the final mass was recorded ($m_2 - m_0$). All the weights were taken by electronic balance (Mettler Toledo AB204-S, Switzerland) with accuracy of ±0.0001 g. The concentration of compound in the solution i.e., mole fraction solubility of compound (x_i) was determined using the following equation:

$$x_i = \frac{\frac{(m_2-m_0)}{M_1}}{\left(\frac{m_2-m_0}{M_1}\right)+\left(\frac{m_1-m_2}{M_2}\right)} \quad (1)$$

where M_1 and M_2 is the molar masses of compound and solvent respectively. At each temperature, the measurement was repeated three times and an average value is given in Table 3.

4. Results and discussion

4.1. Spectral data

4.1.1. DPCE-1

IR (υ, cm^{-1}): 3479.58 (—CN), 2924.09 (—OH), 2222.00 (—CN), 1643.35, 1597.06 (—NH—), 1496.76 1427.3, 1381.03, 1350.17 (—CH—), 1280.73, 1211.30 (C—O), 1118.71, 1087.85, 1018.41 (O—C), 902.69 (—OH).

^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 3.8437–3.8628 (s, 6H, 2-OCH_3), 6.7742 (s, 1H, CH), 6.9256–6.9461 (d, 1H, *J* 8.2 Hz, CH), 7.0740–7.0956 (d, 2H, *J* 8.64 Hz, CH), 7.2294–7.2496 (d, 1H, *J* 8.08 Hz, CH), 7.3320 (s, 1H, CH), 7.8791–7.9000 (d, 2H, *J* 8.36 Hz, CH), 9.7386 (s, 1H, OH), 12.5543 (s, 1H, NH).

^{13}C NMR (400 MHz, DMSO-d_6) (δ ppm): 55.48, 55.73, 112.42, 114.31, 115.44, 117.28, 121.72, 126.76, 129.38, 147.47, 149.00, 161.59.

Mass (*m*/*z*): 348.

Table 1
The source, purification method and mole fraction purity of solvents.

Chemical name	Source	Initial mole fraction purity	Purification method	Final mole fraction purity	Analysis method
Methanol	Allied Chemical Corporation	>99.50%	Fractional distillation	>99.96%	GC–MS[a]
Ethanol	Baroda Chemical Industry	>99.40%	Fractional distillation	>99.94%	GC–MS[a]
1-Propanol	Spectrochem Pvt. Ltd.	>99.10%	Fractional distillation	>99.98%	GC–MS[a]
1-Butanol	Spectrochem Pvt. Ltd.	>98.30%	Fractional distillation	>99.93%	GC–MS[a]
Chloroform	Spectrochem Pvt. Ltd.	>98.10%	Fractional distillation	>99.96%	GC–MS[a]
Ethyl acetate	Allied Chemical Corporation	>98.50%	Fractional distillation	>99.95%	GC–MS[a]
1,4-Dioxane	Spectrochem Pvt. Ltd.	>99.70%	Fractional distillation	>99.94%	GC–MS[a]

[a] GC–MS = gas chromatography–mass spectrometry.