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Measurement, correlation and dissolution thermodynamics of biological active chalcone in organic solvents at different temperatures

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ABSTRACT

The present study reports the synthesis, characterization and solubility of (E)-2-(4-chlorobenzylidene) -3,4-dihydronaphthalen-1(2H)-one. The compound was synthesized by standard process. The purity was monitored by TLC and confirmation of structure was done by using mass, IR and ^{1}H NMR spectral techniques. Further, solubility study of this synthesized compound was conducted in methanol, ethanol, 1-propanol, 1-butanol, tetrahydrofuran (THF), ethyl acetate (EA), acetone (AC) and chloroform (CF) at temperatures ranging from (293.15 to 323.15) K under atmospheric pressure. Further, the solubility data were correlated against temperature and were found to increase with temperature. The modified Apelblat and Buchowski–Ksiazczak λh equations were used to correlate the experimental solubility data. Further, some thermodynamic parameters such as dissolution enthalpy (ΔH), Gibbs free energy (ΔG) and entropy (ΔS) of mixing have also been calculated. The positive enthalpy and Gibbs free energy values suggest the dissolution process to be endothermic and spontaneous.

1. Introduction

Chalcones are α, β-unsaturated carbonyl compounds which are mostly present in flavonoids, isoflavonoids and other natural heterocyclic compounds [1–3]. Most of the chalcones are known to exhibit a wide spectrum of biological activities [4] such as anti-viral [5], anti-cancer [6], anti-inflammatory [7], anti-bacterial [8] and anti-oxidant activities [9] *etc.* For these reasons, synthesis of chalcones and their functionalized derivatives is a primary objective of the present work.

Further in the pharmaceutical field, solubility and dissolution rates play a prominent role for the discovery and development of drugs [10]. The crystallisation process is a critical method for the purification in pharmaceutical industries for both drug intermediates and final products. Therefore, solubility data are essential for the selection of proper solvents for the crystallisation process and in pre-formulation studies. Further, knowledge of solubility provides necessary information to select a wide range of solvents for the optimization of crystallisation processes [11–14].

The literature survey shows that the temperature dependent solubility measurement of various drugs and other compounds have been reported in different pure solvents [15–21].

In this context, the present paper describes the synthesis, characterization and solubility study of synthesized (E)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2H)-one. The solubility of synthesized chalcone was studied in methanol, ethanol, 1-propanol, 1-butanol, tetrahydrofuran (THF), ethyl acetate (EA), acetone and chloroform (CF) at temperatures ranging from (293.15 to 323.15) K. Also, the experimental solubility data were correlated with the modified Apelblat and Buchowski–Ksiazczak λh equations. Further, the thermodynamic parameters such as enthalpy, Gibbs free energy and entropy of solutions of chalcone have been evaluated.

2. Experimental

2.1. Materials

(E)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2H)-one (CD), used in this study was synthesized in our laboratory. The α-tetralone (CAS NO.: 529-34-0) and *p*-chloro benzaldehyde (CAS NO.: 104-88-1) used in the synthesis were supplied from Spectrochem Pvt. Ltd. (Mumbai, India) and were used without any further treatment. The solvents used in this studied were of AR grade and provided by the same supplier. All solvents were purified by drying over anhydrous sodium sulphate and fractionally distilled. After distillation, the solvents were kept over molecular sieves [22]. The purities of the solvents were confirmed by GC–MS

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Nomenclature

x_i	experimental mole fractions solubility.
x_{ci}^a	calculated solubility by modified Apelblat equation
x_{ci}^b	calculated solubility by Buchowsli equation
M_1	molecular weight of solvents
M_2	molecular weight of chalcone (*CD*)
m_1	weights of solvent
m_2	weights of chalcone
A, *B* and *C*	parameters
λ and *h*	parameters
RD	relative deviations
ARD	average relative deviations
RMSD	root-mean-square deviations
N	number of experimental points
n	number of experimental temperatures studied.
T	temperature in Kelvin
T_m	melting temperature
T_{hm}	mean harmonic temperature.
ΔH	enthalpy change ($kJ \cdot mol^{-1}$)
ΔG	Gibb's free energy change ($kJ \cdot mol^{-1}$))
ΔS	entropy change ($J \cdot K^{-1} \cdot mol^{-1}$)
R	universal gas constant ($8.314\ J \cdot mol^{-1} \cdot K^{-1}$)

Abbreviation

CD	(E)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2H)-one
h	hour
TLC	thin layer chromatography
THF	tetrahydrofuran
CF	chloroform
AC	acetone
EA	ethyl acetate
RD	relative deviations
ARD	relative average deviations
RMSD	Root-mean-square deviations

(SHIMADZU-Model No.-QP-2010) equipped with column (DB-5MS, 25 m in length, 0.20 mm internal diameter and 0.33 μm film). The source and mole fraction purity of all solvents and material are listed in table 1.

2.2. Synthesis

2.2.1. (E)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2H)-one (CD)

An equimolar mixture of α-tetralone (0.1 mmol) and *p*-chloro benzaldehyde (0.1 mmol) in ethanol was refluxed for 1.5 h in the presence of a catalytic amount of potassium hydroxide. The completion of reaction was confirmed by analytical thin layer chromatography (TLC) (performed on aluminium coated plates Gel $60F_{254}$ (E. Merck)) using (7:3-Hexane: Ethyl acetate) as the mobile phase. After completion of reaction, the reaction mass was cooled and the resulting solid was filtered, washed with water and dried under vacuum to give a crude product. The crude product obtained was purified by adding a suitable solvent (diethyl ether) to remove the coloured, non-polar impurity by scratching/stirring. The product was then allowed to stabilise and the above solution was decanted. The procedure was repeated 3–4 times to free product from impurities (tituration). The purity of CD was 0.995 in mole fraction as determined by gas chromatography. The reaction scheme is given in figure 1.

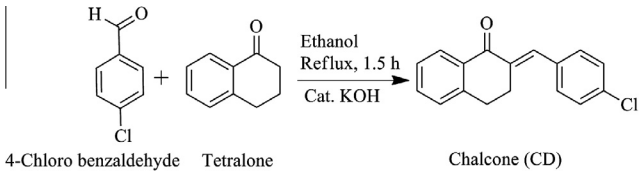

FIGURE 1. Synthesis scheme of chalcone.

2.2.2. Characterization study

The spectroscopic study of CD was done by IR, ^{1}H NMR and Mass spectroscopy. The IR spectrum was recorded on a KBr disc, using FT-IR Model No.-8400(Shimadzu) spectrophotometer. The ^{1}H-NMR spectra were taken on a Bruker Avance II 400 in DMSO using TMS as an internal standard and NMR signals are reported as $\delta \cdot$ ppm. The mass spectrum was determined using a direct inlet probe on a GCMS-QP-2010 mass spectrometer. The melting point was measured by Differential Scanning Calorimeter (Shimadzu-DSC-60). For calibration of the instrument, indium and zinc were used as a calibration substance. The calibrant and the sample to be investigated were in identical positions in the sample pan and the sample pan (crucible) itself was in the same position in the DSC measuring device. The type of crucible, purge gas of furnace,

TABLE 1
The source and mole fraction purity of solvents.

Chemicals	Source	Mole fraction purity
Methanol	Spectrochem	0.998[s]
Ethanol	Baroda Chemical Industries	0.999[s]
1-Propanol	Spectrochem	0.997[s]
1-Butanol	Sigma–Aldrich	0.996[s]
Acetone	Spectrochem	0.997[s]
Tetrahydrofuran	Spectrochem	0.998[s]
Ethyl acetate	Spectrochem	0.999[s]
Chloroform	Spectrochem	0.998[s]
α-Tetralone	Spectrochem	0.950[s]
p-chloro benzaldehyde	Spectrochem	0.980[s]
CD	Synthesis	0.995[t]

CD: (E)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2H)-one.
[s] Analytical grade reagent dried over anhydrous sodium sulphate and kept over molecular sieves.
[t] Gas Chromatography method.

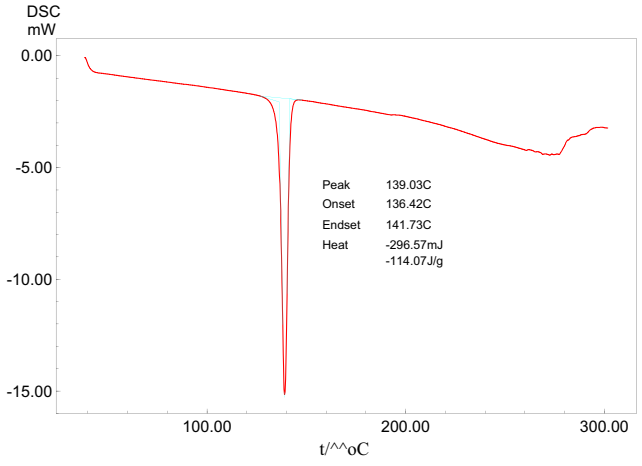

FIGURE 2. DSC thermogram of chalcone.