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Experiment-based physicochemical aspects for the coulombic hydration kinetics and thermodynamics of a pyrimidine and thiopyrimidine

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ABSTRACT

The hydration, solvation kinetics and thermodynamics of recently synthesized 5-benzoyl-1-(methylphenylmethyleneamino)-4-phenyl-1H-pyrimidine-2-one (**I**) and 5-benzoyl-1-(methylphenylmethyleneamino)-4-phenyl-1H-pyrimidine-2-thione (**II**) are studied in due to course of time at pH values from 1.0 to 13.0 using UV/vis spectroscopic analysis of their aged solutions for the first time, at a temperature of 25 ± 0.1 °C. In this sense, a time dependent intersection point was discovered in the UV/vis spectra obtained. The time dependent intersection point method is thus improved for the first time in this study. The improved method is found to be more useful in the determination of the existence of a time dependent equilibrium and the time to reach the equilibrium at a constant pH. Methanol solvation property of the compounds is also investigated only at pH values of ca. 1.13 and ca. 13.0. Pseudo-first-order hydration kinetics and thermodynamics data comprising rate constants, hydration equilibrium constants, and the corresponding Gibbs free energy changes are calculated for water molecules which are in direct contact with the molecules of **I** and **II**. A remarkable result is discovered with **II** for which the hydration Gibbs energy change was calculated to be −422.64 J/mol at a pH of ca. 12, indicating the hydration is exothermic, energetically downhill and weakly in forward direction. Plausible hydration mechanisms are suggested for the compounds based on the extensive experimental UV/vis data presented.

1. Introduction

Heterocyclic pyrimidine compounds containing heteroatoms are of considerable interest in various fields of industry [1–3]. Especially, sulfur derivatives are well known to be more important for biological systems to form metal complexes such as proteins to fight cancer [4]. For instance, several sulfur-containing pyrimidines exhibit high binding affinity to multiple receptors, thus providing applications in drug-delivery systems [5], biosensors [6], while others serve as corrosion inhibitors in acid medium [7] and dyes for solar cells [3]. Likewise, thin films of several pyrimidine derivatives have unique optical and electronic properties, thus they are often used in the field of electronics [8]. Heterocyclic pyrimidine compounds have many significant applications also in medicine, since these compounds demonstrate many biological [9, 10] and pharmacological properties such as antiviral [11], antibacterial [12] and anticancer activities [13]. Several sulfur-containing pyrimidines act as potent enzyme inhibitors [14]. Thus, the hydration kinetics and thermodynamics of pyrimidine derivatives are therefore important in drug discovery [15]. The interaction of water with organic and inorganic substances is termed hydration. Solvation is not interpreted in terms of permanent binding of solute by solvent. If the solvent is water then solvation is called hydration. In this sense, it has a considerable influence in many biologically important processes, as in DNA, where change in hydration affects the binding processes of DNA [16]. Therefore, measuring and calculating the Coulombic hydration and dehydration rates of pyrimidine compounds are important [17]. The hydration equilibrium constant for a compound is an important kinetic parameter by which hydration Gibbs energy change can be calculated. Unfortunately, there are very few experimental studies on the hydration constants given its significance [18]. One of the reasons for this scarcity is that hydration experiments must be carried out in accordance with the progress of time using aged solutions. Thus, it can take a long time to complete (e.g., 1 month) depending on the chemical character of the compounds. In recent studies, some experimental measurements using nuclear magnetic resonance (NMR) [19], time resolved fluorescence [20], and terahertz spectroscopy [21], and the computational approach of molecular dynamics (MD) simulations [22] have been performed to reveal the time dependent features of the hydration water.

Considering the above mentioned significance of the pyrimidine derivatives, the time dependent hydration properties of the recently synthesized pyrimidine derivatives 5-benzoyl-1-(methylphenylmethyleneamino)-4-phenyl-1H-pyrimidine-2-one

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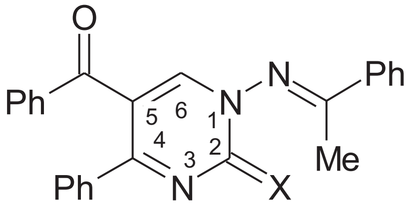

I : X = O

II : X = S

Fig. 1. Pyrimidine compounds investigated in this study.

(**I**) and 5-benzoyl-1-(methylphenylmethyleneamino)-4-phenyl-1H-pyrimidine-2-thione (**II**), are expected to display biological, pharmaceutical and industrial features. The structures of the compounds are given in Fig. 1.

As shown in Fig. 1, the pyrimidine compounds are analogs of each other containing semi- and thiosemicarbazone moiety at the same time. The acid-base properties of these compounds [23], and structurally close similar the two other compounds [24] have been previously investigated by Kılıç et al. Furthermore, the pH dependent hydration properties of the title compounds have been examined using fresh solutions of the compounds [25]. However, there is no experimental data regarding the time dependent hydration, and methanol solvation kinetics ("solvation" refers to methanol solvation henceforward) and thermodynamics of these compounds in their aged solutions.

In this study, hydration, solvation kinetics, and thermodynamics of the two pyrimidine compounds in due to course of time given in Fig. 1 have been investigated for the first time using UV/vis spectroscopic analysis of their aged solutions at all pH values conducted in order to i) get the first examples of the time dependent hydration absorption vs. wavelength plots at various time intervals and at a constant pH value using UV/vis absorption spectroscopy ii) determine whether if there is a time dependent hydration equilibrium or not and the time to reach the equilibrium, iii) calculate the related kinetic and thermodynamic parameters. This investigation provides extensive experimental data for computational chemists on the kinetics and thermodynamics of the hydration-dehydration and solvation-desolvation properties of **I** and **II**.

2. Experimental

2.1. Synthesis of pyrimidine compounds

Compounds **I** and **II** were synthesized in our laboratory according to procedures described elsewhere [26, 27]. Briefly, for the synthesis of **I**, 0.28 g furan-2,3-dione and 0.18 g methylphenyl semicarbazone (molar ratio 1:1) are refluxed in toluene for 45 min, yielding 0.14 g (38%) of **I**. For the synthesis of **II**, 5 g furan-2,3-dione and 3.5 g methylphenyl thiosemicarbazone are refluxed in 20 mL of toluene in a 100-mL round-bottom flask for 1 h, affording 2.4 g (33%) of **II**. The compounds are filtered from the reaction mixtures and purified by recrystallization from acetic acid. Their characteristic physical and chemical properties have been reported previously [26, 27]. Their purity is assessed by thin-layer chromatography (TLC) using methanol/chloroform (1:9 v/v) and methanol/benzene (1:9 v/v) [28]. All other chemicals are obtained from Fluka as reagent-grade materials. Triple-distilled water is used for all aqueous solutions. Preparation of triple-distilled water is described in previously [29]. Distilled methanol is used in the solvation studies. Stock solutions of the compounds are prepared in an appropriate volume of distilled acetonitrile.

2.2. Instrumentation

IR spectra are recorded from KBr disks using a Shimadzu 8300 FT-IR spectrometer in the range 4000–400 cm^{-1}. UV/vis spectroscopy studies are carried out using a Shimadzu 1601 PC UV/vis spectrophotometer with quartz cells (1.0-cm path length). The pH of the aqueous and methanol solutions is measured using a digital pH meter (Hanna Instruments 8314, Italy; ±0.01 pH unit) and a combined pH electrode that is calibrated using standard aqueous buffers (pH 4.00, 7.00, and 9.00) as described in previous reports [30]. The pH values measured are not corrected, and the symbol pH (defined as $-\log [H^+]$) is used in all cases. Glass electrodes in solvents containing up to 95% alcohol show responses very similar to the theoretical response in water. Of the organic solvents, methanol is the most similar to water in structure and properties. Therefore, acidic dissociation in methanol takes place in a fashion analogous to that of in water [31]. An Eppendorf micro-pipette is used for precise volumetric measurement of the solutions. The temperature of the solutions is kept constant at 25 ± 0.1 °C using a thermostat (WiseCircu, Daihan Scientific Co., Ltd. Korea). A Sartorius A120 S analytical balance (sensitivity of ±0.0001 g) is used for weighing the chemicals.

2.3. Kinetic measurements

Stock solutions of the compounds are prepared in acetonitrile and stored in the dark to avoid decomposition. Aqueous Britton-Robinson buffer (BRB) solutions [32] are prepared with the desired pH values for the experiments. Working solutions with concentrations of 1.641×10^{-5} M for **I** and 2.044×10^{-5} M for **II** are prepared daily by adding 1 mL of the stock solution of **I** or **II** to a flat-bottomed volumetric flask (20 mL) containing some BRB solution at 25 ± 0.1 °C and diluting it to 20 mL rapidly with the same solution. The final compositions for hydration and solvation experiments were 95% v/v water and 95% *v/v* methanol, respectively. The acetonitrile content is 5% v/v in both cases. The hydration and solvation experiments are conducted in BRB media over a pH range of 3.0 to 11.0 in increments of 1.0 pH unit. For more acidic or basic solutions, 0.1 M HCl, 0.01 M HCl, 0.01 M KOH and 0.1 M KOH are used. The ionic strength of the solution is constant with 0.10 M LiCl as the supporting electrolyte.

In typical experiments, hydration-dehydration and solvation are initiated as soon as 1.0 mL of the stock solution of **I** or **II** is mixed with the required buffer solution in a 20-mL volumetric flask at 25 ± 0.1 °C. The hydration and solvation kinetics are monitored by recording the UV/vis spectra at regular intervals until the maximum absorbance (A_∞) is reached. The absorbance (A) is determined after baseline correction. The reference beam contained a blank of the buffer containing the same amount of pure acetonitrile as the solvent. The UV/vis spectra are recorded from 600 to 200 nm for each compound at a medium scan rate (ca. 100 nm/min) between pH 1.0 and 13.0.

2.4. Evaluation of kinetic and thermodynamic data

Hydration of the pyrimidines in this study is assumed as shown below. S denotes the solute, i.e., **I** or **II**.

$$S + H_2O \leftrightarrow S \cdot H_2O \tag{1}$$

$$k_{hyd} \cdot [S] \cdot [H_2O] = k_{dehyd} \cdot [S \cdot H_2O] \tag{2}$$

$$K = \frac{\text{products}}{\text{reactants}} \tag{3}$$

Thus, the hydration equilibrium constant is [17],

$$K_{hyd} = \frac{K_{dehyd}}{K_{dehyd}} = \frac{S \cdot H_2O}{([S][H_2O])} \tag{4}$$