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Physico-chemical effects of caffeine on aqueous solutions of pyrimidine based model compounds of nucleic acids

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ABSTRACT

Caffeine, a widely used stimulant is a purine based xanthine alkaloid which can lead to mutagenic effects in DNA helix via pairing errors. In order to study the interactions between caffeine and the pyrimidine based model compounds of nucleic acids, densities ρ, viscosities η, and enthalpies of dilution, q of aqueous solutions of some nucleic acid bases and nucleosides have been determined at different concentrations of caffeine over a temperatures range (288.15–318.15) K. Apparent molar volumes at infinite dilution ($V^{o}_{2,\phi}$), viscosity B-coefficient (B), and standard molar enthalpy of dilution ($\Delta_{dil}H^{o}$), and the corresponding transfer parameters at infinite dilution have also been calculated. The nature of solute–co-solute interactions is exothermic. UV–visible and NMR spectroscopic studies have been carried out and the shifts in absorption spectra and NMR spectra signify the role of hydrophobic interactions. An effort has been made to compare the present work with the similar properties in other co-solutes.

1. Introduction

Caffeine (1,3,7-trimethylxanthine) is a bitter, white crystalline (Scheme 1), widely consumed stimulant present in beverages such as coffee, tea, cold drinks etc. [1]. Caffeine (CAF) belongs to a class of naturally occurring purine based xanthine alkaloids, and is one of the most biologically active substances [2]. Apart from its main role in mood alteration [3], it exerts numerous other physiological effects on human body, such as stimulation of central nervous system, respiratory system and cardiac muscles [4]. It also influences blood pressure, increases the blood sugar level and leads to increased urine production [3]. CAF is a base analogue of adenine and guanine, which can damage DNA helix through pairing errors [5], such errors in DNA sequencing, may cause genetic mutations. Moreover, there are evidences of inhibition of binding between DNA and anticancer drugs or other intercalating mutagenic organic compounds in the presence of CAF, which might be due to greater interactions of CAF with the nucleic acids [6,7]. Modern sedentary life style may be one of the reasons for extensive consumption of CAF molecules in the form of human diet and drugs. Energy drinks are a class of sweetened caffeinated beverages which along with alcohol may have potential impact on health and well being of consumers [8–10]. It is therefore of immense interest to study the nature of interactions between the CAF molecules and the nucleic acid components. Poltev et al. [11] carried out the molecular mechanics calculations of CAF interactions with nucleic acid bases and base pairs, and obtained three interaction energy minima in terms of stacking interactions [12] and in-plane and nearly perpendicular (hydrogen-bonding) molecular arrangements. However, most of the physiological processes occur in aqueous media and various types of interactions and changes in thermodynamic and structural parameters are involved, so it is important to study such systems and throw light on the nature of various interactions in the ternary systems. Therefore, the present work aims at studying the effect of CAF (co-solute) on the aqueous solutions of nucleic acid bases and nucleosides (solutes) using volumetric, viscometric, calorimetric, UV–visible and nuclear magnetic resonance spectroscopy methods. Derived properties such as apparent molar volume, viscosity B-coefficient, enthalpy of dilution, absorption spectra and changes in chemical shift etc. have been obtained and discussed in terms of solute–co-solute interactions. To the best of our knowledge, this is the first report on the physico-chemical properties of aqueous solutions of nucleic acid bases and nucleosides in the presence of CAF at various temperatures.

2. Experimental

2.1. Materials

The chemicals used in the present study i.e. uracil, cytosine, thymine, uridine, cytidine and thymidine have been procured from Sisco Research Laboratories (SRL), India and caffeine has been obtained from Sigma-Aldrich India, and were stored in vacuum desiccator over $CaCl_2$ before use. The HPLC analysis and the water content determined by Karl-Fisher analysis of these chemicals have been discussed elsewhere [13,14]. CHNS analysis was carried out to judge the purity of chemicals using FLASH 2000 Organic Elemental Analyser, USA. The percentage

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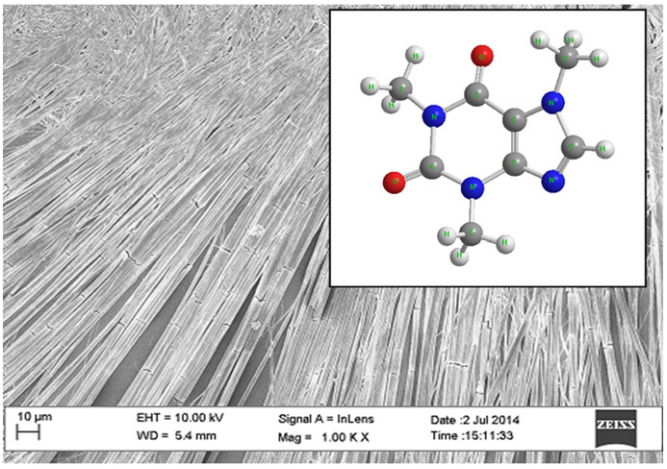


Scheme 1. (a) Scanning electron microscopic image and 3-D molecular structure (inset) of caffeine.

content of carbon, nitrogen and hydrogen (Table 1) were in excellent agreement with the calculated values using molecular formulae.

2.2. Instrumentation and methods

Solutions were prepared on mass basis using Mettler balance having an accuracy of ±0.01 mg in Milli-Q water having resistivity of 18.2 MΩ cm. The water content observed from Karl-Fisher analysis has also been taken into account during molality calculations.

2.2.1. Density

The densities of solutions were measured using vibrating-tube digital densimeter (model DMA 60/602, Anton Paar, Austria) attached with a constant temperature bath having temperature stability within ±0.01 K. The calibration and working of densimeter has been discussed elsewhere [13]. The standard uncertainty in the densities, u (d) is $4{\cdot}10^{-3}$ kg m^{-3}.

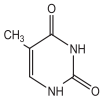
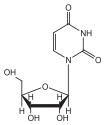
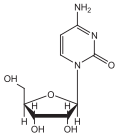
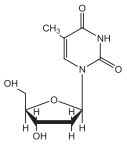
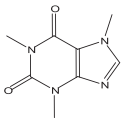
2.2.2. Viscosity

Viscosities of the solutions were measured by a suspended level Micro Ubbelohde viscometer placed in a constant temperature bath having temperature stability within ±0.01 K. Flow time measurements were performed using an automatic efflux time measurement unit (SCHOTT AVS 350) with a resolution of ±0.01 s. The average of at least six readings was used as the final efflux time. The viscometer was calibrated with Milli-Q water. The efflux time data for water were collected at T/K = (288.15, 298.15, 308.15 and 318.15). The viscosities for water at different temperatures were taken from the literature [15]. The measured viscosities of aqueous solutions of glycine at 298.15 K agreed well with the literature values [16]. The standard uncertainty in viscosity, u (η) is ±0.012 mPa s (by taking 1% uncertainty in water which is used for calibrating the apparatus [17]).

2.2.3. Isothermal Titration Calorimetry

Isothermal Titration Calorimeter (MicroCal iTC$_{200}$, USA) having a temperature stability within ±0.005 K was used to measure the enthalpies of dilution, q. An automated instrument controlled syringe having volume capacity of 40 μL and stirring at 500 rpm, was used for carrying out titrations into the sample cell containing 200 μL of the respective solvent. Each titration experiment consisted of 19 consecutive injections (2 μL each) with duration of 4 s and 120 s time interval.

Table 1
Chemicals used in this study with their structures, molar mass (M), source (SRL = Sisco Research Laboratories, India), CAS number, mass fraction moisture content (w) and CHNS analysis.

Chemical name	Structures	M	Source	CAS no	[a]w	CHNS Calculated%	CHNS Observed %
Uracil		112.09	SRL	66-22-8	0.005 (0.0005)	C (42.82); N (24.98); H (3.57)	C (42.60); N (24.96); H (3.51)
Cytosine		111.10	SRL	71-30-7	0.01 (0.00045)	C (43.20); N (37.80); H (4.50)	C (42.85); N (37.87); H (4.44)
Thymine		126.12	SRL	65-71-4	0.01 (0.0007)	C (47.58); N (22.20); H (4.76)	C (46.77); N (22.06); H (4.65)
Uridine		244.20	SRL	58-96-8	0.005 (0.0005)	C (44.23); N (11.47); H (4.91)	C (44.30); N (11.63); H (4.92)
Cytidine		243.22	SRL	65-46-3	0.01 (0.0006)	C (44.40); N (17.27); H (5.34)	C (44.44); N (17.33); H (5.33)
Thymidine		242.23	SRL	50-89-5	0.01 (0.00075)	C (49.54); N (11.56); H (5.78)	C (49.64); N (11.70); H (5.74)
Caffeine		194.20	SIGMA	58-08-2	0.005	C (49.43); N (28.84); H (5.15)	C (49.54); N (28.86); H (5.18)

[a] As reported by the suppliers and in parenthesis are given the mass fraction water content obtained from the Karl-Fisher analysis.