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Article

Gout Pain Caused by Uric Acid Molecule and Its Solution Caused by Citric Acid Molecule: A Physicochemical Investigation

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ABSTRACT

The effect of relief from gout pain due to the restriction of precipitation of uric acid (UA) by citric acid (CA) has been studied through physicochemical study. Here, we have carried out the density (ρ) and viscosity (η) measurements of CA in w_1=0.00001, 0.00002, and 0.00003 mass fraction of aqueous UA binary mixtures at T=298.15K, 303.15K, 308.15K, and 313.15K and at pressure 1.013 bar. These measurements have been performed to ternary mixture (CA + UA + water) to derive some important parameters, namely, limiting apparent molar volume (φ_V^0), viscosity B-coefficients from extended Masson equation, and Jones–Dole equation, respectively. The refractive index (n_D) has been done on the same ternary mixtures at T=298.15K. Lorentz–Lorenz equation has used to evaluate molar refractive index (R_M) and limiting molar index (R_M^0). These parameters have been interpreted in terms of interactions of solute itself and with solvent.

Key words: Apparent molar volume, Citric acid, Molar refraction, Solute-solvent interactions, Uric acid, Viscosity B-coefficient.

1. INTRODUCTION

Gout is a very painful experience in our modern era. The underlying cause of gout is due to the crystallization of uric acid (UA), often related to relatively high levels in the blood of the human body. This can occur for number of reasons, including diet, genetic predisposition, or underexcretion of urate, the salts of UA. The remedial methods are both lifestyle changes and medications can decrease UA levels. Doctors are generally advised to reduce intake of food such as meat and seafood, limiting alcohol and consuming citrus fruits [1]. Citric acid (CA) is one of the major ingredients of citrus fruits. The chemistry of solutions deals with solutes and solvents and how solutes interact with solvents as they move about in solutions. So that we choose this biologically active compound, CA as a solute and aqueous UA as a solvent to examine the interaction between these two. Studies on the apparent molar volumes and viscosity B-coefficients at infinite dilution provide valuable information regarding solute-solute, solute-solvent, and solvent-solvent interactions [2]. The addition of solute could break or make the structure of a liquid [3-5] as viscosity being a property of the solution depending on the intermolecular forces, the structural aspects of the liquid can be inferred from the viscosity of solutions at different concentrations and temperatures.

CA, $C_6H_8O_7$ (CA), i.e., 2-hydroxypropane-1, 2, 3-tricarboxylic acid, is a tribasic, environmentally suitable and versatile chemicals. As it occurs in the metabolism of almost all living beings, its interactions in an aqueous solution are of great value to the biological scientists. In the pharmaceutical industry, CA is used as stabilizer in various formulations, as a drug component and as anticoagulant in blood for transfusions and also used as an acidifier in many pharmaceuticals. CA can be used as flavoring and preservative in food and beverages, especially soft drinks [6]. CA exists greater than trace amounts in a variety of vegetables, most notably citrus fruits. UA is a heterocyclic compound with the molecular formula $C_5H_4N_4O_3$ (UA), i.e., 7,9-Dihydro-1H –purine-2,6,8 (3H)-trione. It is a diprotic acid. It was first isolated from kidney stones in 1776 by Scheele [7]. UA is deprotonated at a nitrogen atom and uses a tautomeric keto/hydroxyl group as an electron-withdrawing group to increase the pK_a value while most organic acids are deprotonated by the ionization of a polar hydrogen-to-oxygen bond. In general, the water solubility of UA is low. This low solubility is significant for the etiology of gout. UA is a strong reducing agent and potent antioxidant. In humans, over half the anti-oxidant capacity of blood plasma comes from UA [8].

To the best of our knowledge, the studies in the present ternary solution systems have not been reported earlier. Therefore, in the present study, we have endeavored to make certain nature of interaction of solute itself (CA) and with cosolute (UA) in w_1=0.00001, 0.00002, and 0.00003 mass fraction of aqueous UA mixture at different temperatures (298.15–313.15) K with 5 intervals to explain various non-covalent interactions prevailing in the ternary systems under investigation.

2. EXPERIMENTAL SECTION

2.1. Source and Purity of Materials

CA monohydrate was purchased from HiMedia. UA was purchased from S D Fine-Chem. Ltd. The mass fraction purity of both was ≥0.99.

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The reagents were always placed in the desiccators over P_2O_5 to keep them in a dry atmosphere. These chemicals were used as received without further purification. The provenance and purity of the chemical used have been depicted in Table 1.

2.2. Apparatus and Procedure

Solubility of the UA in water (deionized, doubly distilled water with a specific conductance of 1.10^{-6} $S.cm^{-1}$) and the CA in aqueous UA had been checked precisely, before start of the experimental work and seen that CA soluble in all proportion of aqueous UA solution. The mother solutions of CA were prepared by mass (Mettler Toledo AG-285 with uncertainty 0.0003 g), and then, the working solutions (six sets) were prepared by mass dilution. The conversions of molarity into molality [9] had been done using experimental density values of respective solutions, and adequate precautions were taken to reduce evaporation losses during mixing and throughout the experiment.

The densities (ρ) of the solutions were measured by means of vibrating u-tube Anton Paar digital density meter (DMA 4500M) with a precision of ±0.00005 $g.cm^{-3}$ maintained at ±0.01 K of the desired temperature. It was calibrated by passing deionized, triple distilled water, and dry air [10].

The viscosities (η) were measured using a Brookfield DV-III Ultra Programmable Rheometer with fitted spindle size-42. The detail description has already been described earlier [11].

Refractive index (n_D) was measured with the help of a Digital Refractometer Mettler Toledo. The light source was LED, $\lambda = 589.3$ nm. The refractometer was calibrated twice using distilled water, and the calibration was checked after every few measurements [12a]. The uncertainty of refractive index measurement was ±0.0002 units.

The pH values of the experimental solutions were measured by a Mettler Toledo SevenMulti pH meter [12b]. The measurements were made in a thermostated water bath maintaining the temperature at 298.15K, 303.15K, 308.15K, and 313.15K with the uncertainty 0.01 K.

3. RESULT AND DISCUSSION

The physical parameters of binary mixtures in different mass fractions (w_1=0.00001, 0.00002, and 0.00003) of aqueous UA solutions at four different temperatures (298.15K, 303.15K, 308.15K, and 313.15K) and at 1.013 bar have been reported in Table 2. The experimental measured values of density, viscosity of CA as a function of concentration (molality), in different mass fractions of aqueous UA mixture at three above mentioned temperatures have been listed in Table 3. According to the pH data of ternary solution, CA in different mass fraction of aqueous UA is found within the range of 5.90–6.63 (Table 3), which is equivalent or higher than the value of pKa_3 value of CA (pKa_1=3.13 [13a]; pKa_2=4.76 [13a]; and pKa_3=6.39 [13b] and 6.40 [13c]). On the other hand, the estimated pKa value of the solution is greater than pKa_3 of CA (Table 3), and it predicts that the CA is dissociated at and above the pH. Thus, it clearly indicated that the CA is completely dissociated and exists as $3H^{+}$+Cit^{3-} form (Scheme 1) in ternary solutions, i.e.,

$$H_3Cit \rightleftharpoons 3H^{+}+Cit^{3-}$$

3.1. Apparent Molar Volume

Volumetric properties such as apparent molar volume (φ_V) and limiting apparent molar volume (φ_V^0) consider important tools for understanding of interactions taking place in solution systems. The apparent molar volume can be regarded to be the sum of the geometric volume of the central solute molecule and changes in the solvent volume due to its interaction with the solute around the peripheral or cosphere. Therefore, the apparent molar volumes (φ_V) have been determined from the solutions densities using the suitable equation [14], and the values are given in Table 4.

$$\varphi_V = M/\rho - 1000\,(\rho-\rho_0)/m\rho\rho_0 \tag{1}$$

Where M is the molar mass of the solute, m is the molality of the solution, and ρ and ρ_0 are the density of the solution and aqueous UA mixture, respectively.

The values of φ_V are positive and large for all the systems, signifying strong solute-cosolute interactions. The apparent molar volumes (φ_V) are found to decrease with increasing concentration (molality, m) of CA in the same mass fraction of aqueous UA at the same temperature. It is also found that apparent molar volumes (φ_V) increase with both increasing temperature as well as mass fraction of aqueous UA solution and varied with $\sqrt{m}$ and could be least-squares fitted to the extended Masson equation [15] from where limiting molar volume and φ_V^0 (infinite dilution partial molar volume) have been estimated and the values have been represented in Table 5.

$$\varphi_V = \varphi_V^0 + S_V^*\sqrt{m} + S_{VV}^{\neq}m \tag{2}$$

Here, φ_V^0 is the apparent molar volume at infinite dilution, and S_V^* and $S_{VV}^{\neq}$ are the experimental slope. At infinite dilution, each solute molecule is surrounded only by the solvent molecules and remains infinite distant from each other. As a consequence, that φ_V^0 is unaffected by itself interaction of solute molecules (either UA itself or CA), and it is a measure only of the solute-cosolute (UA-CA) interaction.

An inspection of Table 5 and Figure 1 shows that φ_V^0 is large and positive for all CA at all the studied temperatures, suggesting the presence of strong solute-cosolute interaction (Scheme 2). Comparing φ_V^0 with S_V^* and $S_{VV}^{\neq}$ values shows that the magnitude of φ_V^0 is greater than S_V^* and $S_{VV}^{\neq}$, suggesting that solute-cosolute interactions dominate over itself interaction of solute molecules in all solutions at all studied temperatures. Moreover, S_V^* values are negative at all temperatures indicating that the force of itself interaction of solute molecules is very poor. Positive and significant magnitude of $S_{VV}^{\neq}$ is indicating the ternary interaction of solute-cosolute-solute and cosolute-solute-cosolute (Scheme 3).

The variation of φ_V^0 with temperature is fitted to a polynomial of the following:

$$\varphi_V^0 = a_0 + a_1T + a_2T^2 \tag{3}$$

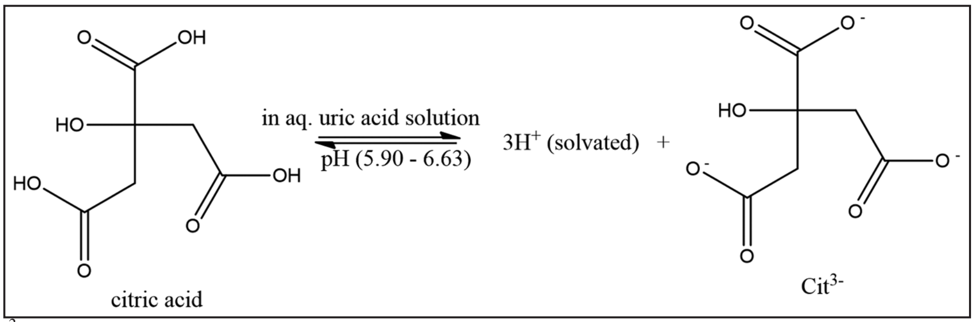
Table 1: Source and purity of the chemicals.

Chemical name	Source	Mass fraction purity	Purification method
Citric acid monohydrate	HiMedia	≥0.99	Used as procured
UA	SD Fine-Chem Ltd.	≥0.99	Used as procured

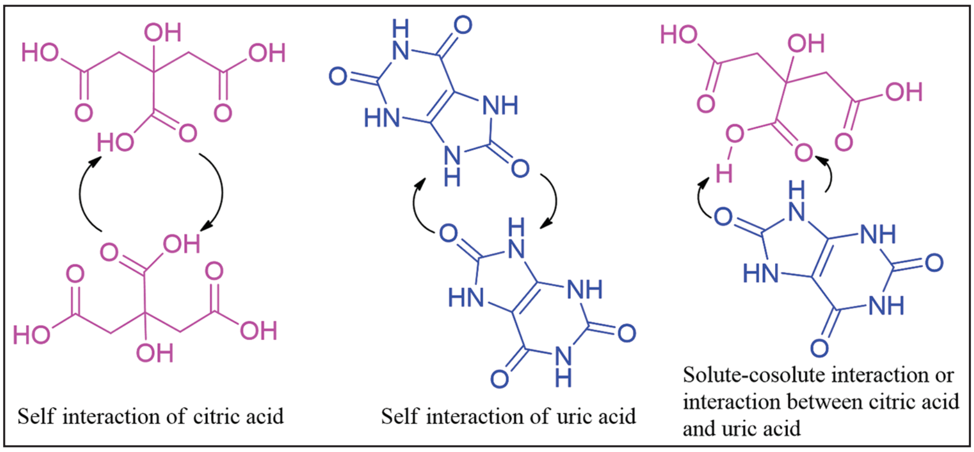
Table 2: Experimental values of density (ρ), viscosity (η), and pH at different temperatures, refractive index (n_D) at 298.15 K , and at pressure 1.013 bar of different mass fraction (w_1) of Aqueous UA mixtures*.

Aqueous UA mixture (w_1)	Temperature (K)	$\rho\times10^{-3}$/kg·m^{-3}	η/mP·s	n_D	pH
0.00001	298.15	0.99698	0.90	1.3316	6.58
	303.15	0.99558	0.82		6.50
	308.15	0.99401	0.73		6.41
	313.15	0.99209	0.63		6.33
0.00002	298.15	0.99704	0.90	1.3321	6.60
	303.15	0.99566	0.83		6.52
	308.15	0.99407	0.75		6.43
	313.15	0.99239	0.65		6.35
0.00003	298.15	0.99712	0.91	1.3327	6.63
	303.15	0.99573	0.84		6.53
	308.15	0.99414	0.76		6.44
	313.15	0.99244	0.66		6.36

*Standard uncertainties *u* are: u (ρ) =0.00002 kg·m^{-3}, u (η) =0.02 mP·s, u (n_D) =0.0002, u (pH) = 0.01 and u (T) =0.01K, (0.68 level of confidence)



Scheme 1: $3H^+$+ Cit^{3-} form of the citric acid in aqueous uric acid solutions.



Scheme 2: Plausible sites of interactions between solute-solute (citric acid-citric acid), cosolute-cosolute (uric acid-uric acid), and solute-cosolute molecules (citric acid-uric acid).

Where T is the temperature in K and a_0, a_1, and a_2 are the empirical coefficients depending on the solute and mass fraction of cosolute UA. Values of coefficients of the above equation for the CA in aqueous UA mixtures are reported in Table 6.

The limiting apparent molar expansibilities, φ_E^0, can be evaluated by the following equation:

$$\varphi_E^0 = (\delta\varphi_V^0/\delta T)_P = a_1+2a_2T \quad (4)$$

The limiting apparent molar expansibilities, φ_E^0, change in magnitude with the change of temperature. The values of φ_E^0 for different solutions of studied CA at T=298.15, 303.15, 308.15, and 313.15 K are reported in Table 7.

All the values of φ_E^0 as shown in the Table 7 are positive for CA in aqueous UA and studied temperature. This fact helps to explain the absence of caging or packing effect for the CA in solution [16].

Table 3: Experimental values of density (ρ) and viscosity (η), pH, and pKa of citric acid in different mass fractions of aqueous UA mixture (w_1) at three different temperatures at pressure 1.013 bar*.

^{a}m/mol·kg^{-1}	$\rho\times10^{-3}$/kg·m^{-3}	η/mP·s	pH	pKa	^{a}m/mol·kg^{-1}	$\rho\times10^{-3}$/kg·m^{-3}	η/mP·s	pH	pKa	^{a}m/mol·kg^{-1}	$\rho\times10^{-3}$/kg·m^{-3}	η/mP·s	pH	pKa
w_1=0.00001					**w_1=0.00002**					**w_1=0.00003**				
T=298.15 K					**T=298.15 K**					**T=298.15 K**				
0.0100	0.99721	0.91	6.51	6.87	0.0100	0.99723	0.92	6.53	6.92	0.0100	0.99727	0.92	6.56	6.99
0.0252	0.99789	0.92	6.42	7.17	0.0252	0.99791	0.93	6.44	7.21	0.0252	0.99794	0.93	6.47	7.27
0.0404	0.99896	0.93	6.32	7.20	0.0404	0.99894	0.94	6.34	7.24	0.0404	0.99894	0.95	6.37	7.30
0.0556	1.00021	0.93	6.23	7.16	0.0556	1.00021	0.95	6.25	7.20	0.0556	1.00014	0.96	6.28	7.26
0.0709	1.00149	0.94	6.14	7.09	0.0709	1.00155	0.96	6.16	7.13	0.0709	1.00152	0.97	6.19	7.19
0.0863	1.00303	0.95	6.06	7.01	0.0863	1.00307	0.97	6.08	7.05	0.0863	1.00312	0.98	6.10	7.10
T=303.15 K					**T=303.15 K**					**T=303.15 K**				
0.0101	0.99578	0.83	6.43	6.68	0.0101	0.99582	0.84	6.45	6.73	0.0101	0.99584	0.85	6.48	6.80
0.0252	0.99647	0.84	6.34	6.99	0.0252	0.99649	0.85	6.36	7.04	0.0252	0.99645	0.86	6.39	7.10
0.0404	0.99751	0.85	6.25	7.03	0.0404	0.99748	0.86	6.27	7.08	0.0404	0.99745	0.87	6.30	7.14
0.0557	0.99874	0.86	6.16	7.00	0.0557	0.99873	0.87	6.18	7.04	0.0557	0.99862	0.88	6.20	7.10
0.0710	1.00004	0.86	6.07	6.93	0.0710	1.00010	0.88	6.09	6.97	0.0710	1.00004	0.89	6.12	7.03
0.0864	1.00155	0.87	5.98	6.85	0.0864	1.00161	0.88	6.00	6.89	0.0864	1.00164	0.90	6.03	6.95
T=308.15 K					**T=308.15 K**					**T=308.15 K**				
0.0101	0.99416	0.74	6.35	6.44	0.0101	0.99419	0.76	6.37	6.49	0.0101	0.99421	0.77	6.39	6.55
0.0253	0.99481	0.75	6.25	6.80	0.0253	0.99482	0.77	6.27	6.84	0.0253	0.99477	0.78	6.29	6.88
0.0405	0.99577	0.75	6.16	6.84	0.0405	0.99580	0.77	6.18	6.89	0.0405	0.99573	0.79	6.20	6.93
0.0558	0.99706	0.76	6.07	6.82	0.0558	0.99703	0.78	6.09	6.86	0.0558	0.99693	0.80	6.11	6.90
0.0712	0.99839	0.77	5.98	6.75	0.0712	0.99842	0.79	6.00	6.79	0.0712	0.99836	0.80	6.02	6.83
0.0866	0.99990	0.77	5.90	6.67	0.0866	0.99995	0.80	5.92	6.71	0.0866	0.99991	0.81	5.94	6.75
T=313.15 K					**T=308.15 K**					**T=308.15 K**				
0.0101	0.99219	0.64	6.29	6.26	0.0101	0.99246	0.66	6.31	6.32	0.0101	0.99247	0.67	6.33	6.38
0.0253	0.99277	0.65	6.19	6.66	0.0253	0.99302	0.66	6.21	6.71	0.0253	0.99304	0.67	6.23	6.75
0.0406	0.99374	0.65	6.10	6.72	0.0406	0.99398	0.67	6.12	6.76	0.0406	0.99393	0.68	6.14	6.80
0.0559	0.99501	0.66	6.01	6.69	0.0559	0.99527	0.68	6.03	6.73	0.0559	0.99511	0.69	6.05	6.77
0.0713	0.99639	0.67	5.93	6.63	0.0713	0.99655	0.68	5.95	6.67	0.0713	0.99649	0.70	5.96	6.71
0.0867	0.99794	0.67	5.84	6.54	0.0867	0.99817	0.69	5.86	6.59	0.0867	0.99809	0.71	5.88	6.63

*Standard uncertainties u are: u (ρ) =0.00002 kg·m^{-3}, u (η) =0.02 mP·s, and u (T) =0.01K (0.68 level of confidence). ^{a}Molality has been expressed per kilogram of UA+water solvent mixture

The long-range structure-making and breaking capacity of the solute in mixed system can be determined by examining the sign of $(\delta\varphi_E^0/\delta T)_P$ developed by Hepler [17].

$$(\delta\varphi_E^0/\delta T)_P = (\delta^2\varphi_V^0/\delta T^2)_P = 2a_2 \quad (5)$$

The positive sign or small negative of $(\delta\varphi_E^0/\delta T)_P$ signifies that the molecule is a structure-maker; otherwise, it is a structure-breaker [18]. The perusal of Table 6 shows that $(\delta\varphi_E^0/\delta T)_P$ values of CA are all positive under investigation. It shows the more symmetric rearrangement of the interacting molecules (CA and UA) with the formation of H-bonding, Van der Waal forces, dipole-dipole interactions, etc. The plausible sites of different interactions playing in the ternary solution are shown in Scheme 2. This symmetric arrangement is signified the molecules of CA, and UA is definitely interacting with structure-making tendency in all of the studied solution systems. Table 6 also shows that the positive magnitude of $(\delta\varphi_E^0/\delta T)_P$ values of CA is depicting this structure-making tendency.

3.2. Viscosity

The experimental viscosity data for studied systems are listed in Table 3. The relative viscosity (η_r) has been calculated using extended Jones–Dole equation [19] for non-electrolytes.

$$(\eta/\eta_0-1)/\sqrt{m} = (\eta_r-1)/\sqrt{m} = A+B.\sqrt{m}+Dm \quad (6)$$

Where $\eta_r = \eta/\eta_0$ is the relative viscosity, η and η_0 are the viscosities of ternary solutions (CA + aqueous UA) and solvent (aqueous mixture of UA) respectively, and m is the molality of CA in ternary solutions.

Table 4: Apparent molar volume (φ_V) and $(\eta_r-1)/\sqrt{m}$ of citric acid in different mass fraction (w_1) of aqueous UA mixtures at three different temperatures*.

^{a}Molality/ mol·kg^{-1}	$\varphi_V\times10^6$/ m^{3}mol^{-1}	(ηr^{-1})/ √m/ kg$^{1/2}$mol$^{-1/2}$	^{a}Molality/ mol·kg^{-1}	$\varphi_V\times10^6$/ m^{3}mol^{-1}	$(\eta_r-1)/\sqrt{m}$/ kg$^{1/2}$mol$^{-1/2}$	^{a}Molality/ mol·kg^{-1}	$\varphi_V\times10^6$/ m^{3}mol^{-1}	$(\eta_r-1)/\sqrt{m}$/ kg$^{1/2}$mol$^{-1/2}$
w_1=0.00001				w_1=0.00002			w_1=0.00003	
	T=298.15 K			T=298.15 K		T=298.15 K		
0.0100	188.21	0.12	0.0100	191.71	0.13	0.0100	195.70	0.13
0.0252	174.27	0.14	0.0252	175.86	0.16	0.0252	177.85	0.16
0.0404	161.13	0.17	0.0404	163.12	0.18	0.0404	165.12	0.19
0.0556	151.87	0.18	0.0556	152.96	0.20	0.0556	155.68	0.21
0.0709	146.15	0.20	0.0709	146.14	0.23	0.0709	147.71	0.24
0.0863	139.38	0.22	0.0863	139.61	0.24	0.0863	139.95	0.26
	T=303.15 K			T=303.15 K			T=303.15 K	
0.0101	190.98	0.08	0.0101	194.99	0.08	0.0101	199.99	0.08
0.0252	175.40	0.11	0.0252	177.71	0.11	0.0252	182.12	0.12
0.0404	162.61	0.14	0.0404	165.36	0.14	0.0404	167.86	0.16
0.0557	153.36	0.15	0.0557	154.99	0.17	0.0557	158.27	0.18
0.0710	147.08	0.17	0.0710	147.35	0.19	0.0710	149.21	0.20
0.0864	140.53	0.19	0.0864	140.75	0.20	0.0864	141.21	0.23
	T=308.15 K			T=308.15 K			T=308.15 K	
0.0101	196.32	0.07	0.0101	199.32	0.06	0.0101	204.34	0.08
0.0253	179.13	0.10	0.0253	181.21	0.10	0.0253	186.03	0.12
0.0405	167.14	0.13	0.0405	167.89	0.13	0.0405	171.39	0.16
0.0558	155.62	0.15	0.0558	157.25	0.16	0.0558	160.35	0.19
0.0712	148.46	0.17	0.0712	148.88	0.18	0.0712	150.74	0.21
0.0866	141.69	0.18	0.0866	141.80	0.20	0.0866	143.10	0.23
	T=313.15 K			T=313.15 K			T=313.15 K	
0.0101	201.74	0.07	0.0101	204.70	0.04	0.0101	208.72	0.02
0.0253	184.40	0.11	0.0253	186.36	0.09	0.0253	187.56	0.08
0.0406	170.24	0.14	0.0406	171.70	0.12	0.0406	174.21	0.12
0.0559	158.30	0.17	0.0559	158.99	0.14	0.0559	162.83	0.15
0.0713	149.90	0.19	0.0713	151.87	0.17	0.0713	153.44	0.18
0.0867	142.44	0.21	0.0867	143.23	0.19	0.0867	144.76	0.22

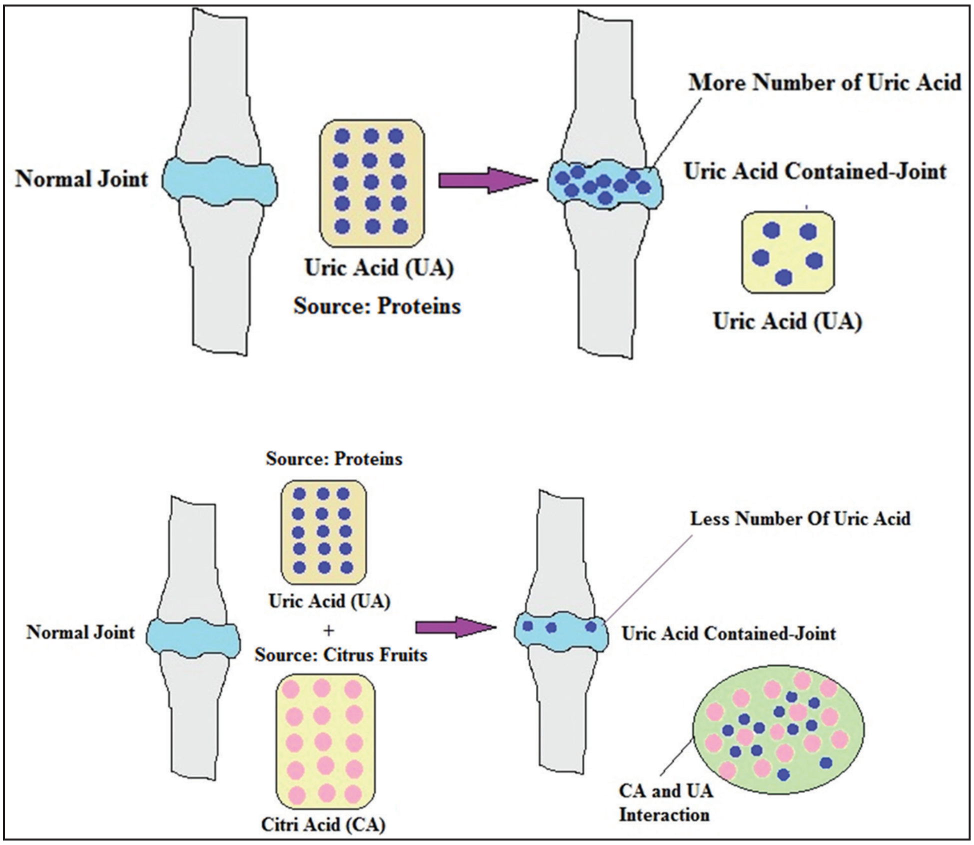
*Standard uncertainties u are: u (T) = 0.01K, the accuracy of φ_V is 1.75×10^{-6} m^3 mol^{-1} and $(\eta_r-1)/\sqrt{m}$ is 0.005 kg$^{1/2}$mol$^{-1/2}$ (0.68 level of confidence). ^{a}Molality has been expressed per kilogram of (UA+water) solvent mixture

Where A is known as Falkenhagen coefficient [20] as it is determined by the ionic attraction theory of Falkenhagen-Vernon and B is empirical constants known as viscosity B- coefficients, which are specifying to the interaction of solute itself and/or with cosolute molecules, respectively. The values of A-, B-, and D-coefficients are estimated by least-square polynomial method by plotting $(\eta_r-1)/\sqrt{m}$ against $\sqrt{m}$ with second order and reported in Table 4. It is observed from Table 4 that the values of the A-coefficient are found to decrease with increase in temperature. This fact indicates the presence of very weak solute-solute interaction and also in excellent agreement with those obtained from S_V* values.

The valuable information about the solvation of the solvated solutes and their effects on the structure of the cosolute UA in the local vicinity of the solute (CA) molecules in solutions has been obtained from viscosity B-coefficient [21]. It is found from Table 4 and Figure 2; the values of B-coefficient are positive and much higher than A-coefficient which signifies that solute-cosolute interaction is dominant over solute-solute and cosolute-cosolute interaction. It is also observed that the positive magnitude of viscosity B-coefficient increases with increasing temperature and also increases with an increase in mass fraction of aqueous UA mixture which suggests that solute-cosolute interaction is strengthened with the rise in temperature as well as the mass fraction of aqueous UA mixture. These results are in good agreement with those obtained from limiting apparent molar volume φ_V^0 values.

It is observed from Table 4 that the values of the *B*-coefficient of CA increase with temperature, i.e., the dB/dT values are positive. From Table 8, the small positive dB/dT values for the CA behave almost as structure-maker.

The free energy of activation of viscous flow per mole of solvent, $\Delta\mu_1^{0\neq}$, as proposed by Glasstone *et al*. [22] could be calculated from the following equation:



Scheme 3: Deposition of uric acid in joints in the absence of citric acid (top) and in the presence of citric acid (bottom).

Highlights

- Effect of relief from gout pain has been studied through physicochemical study study.
- Restriction of precipitation of uric acid by citric acid is causes relief from gout pain.
- A strong solute-cosolute interactions existss between citric acid and uric acid.
- Solute-cosolute interactions becomes stronger with increasing temperature.
- The process of crystallization and deposition of uric acid gets hampered in the presence of citric acid.

Table 5: Limiting apparent molar volume (φ_V^0), experimental slope (S_V^*), and viscosity A- and B-coefficient of citric acid in different mass fraction (w_1) of aqueous UA mixtures at three different temperatures*.

Mass fraction (w_1)	T/K	$\varphi_V^0 \times 10^6$/m^3 mol^{-1}	$S_V^* \times 10^6$/m^3 mol$^{-3/2}$ kg$^{1/2}$	$S_{VV}^{\#}$/m^3 mol^{-2} kg	B /kg mol^{-1}	A /kg$^{1/2}$ mol$^{-1/2}$	D /kg$^{3/2}$ mol$^{-3/2}$
0.00001	298.15	218.20	−307.10	129.83	0.30	0.08	0.56
	303.15	223.44	−339.72	194.74	0.48	0.03	0.14
	308.15	229.27	−339.97	139.42	0.59	0.01	0.03
	310.15	232.33	−339.53	100.13	0.70	0.00	−0.06
	313.15	235.52	−339.19	72.33	0.80	−0.01	−0.15
0.00002	298.15	223.89	−332.69	151.99	0.43	0.07	0.40
	303.15	228.36	−347.48	165.08	0.59	0.02	0.15
	308.15	234.17	−360.97	156.76	0.71	−0.01	0.08
	310.15	237.36	−366.01	141.98	0.78	−0.02	−0.05
	313.15	241.18	−372.21	132.41	0.84	−0.04	−0.17
0.00003	298.15	228.79	−344.90	147.05	0.51	0.07	0.39
	303.15	233.57	−343.32	99.36	0.73	0.01	0.05
	308.15	239.03	−350.76	79.37	0.82	−0.01	−0.01
	310.15	242.11	−371.00	60.01	0.93	−0.05	−0.10
	313.15	246.19	−390.71	59.69	1.08	−0.09	−0.19

*Standard uncertainties values of u are: u (T) = 0.01K

Table 6: Values of various coefficients and standard deviation of equation-3 for citric acid in different aqueous UA solutions*.

Aqueous UA mixture (w_1)	**$a^0\times10^6/m^3\ mol^{-1}$**	**$a_1\times10^6/m^3\ mol^{-1}K^{-1}$**	**$a_2\times10^6/m^3\ mol^{-1}K^{-2}$**	**$(\delta\varphi_E^0/\delta T)_P\times10^6/m^3\ mol^{-1}\ K^{-2}$**	**σ**
0.00001	814.79	−5.01	0.01	0.02	0.0002
0.00002	2249.69	−14.36	0.03	0.06	0.0003
0.00003	2102.48	−13.37	0.02	0.04	0.0001
Average standard deviation	4.2	0.013	0.0003	0.0001	

Table 7: Limiting apparent molar expansibilities (φ_E^0) for citric acid in different mass fraction of aqueous UA (w_1) at different temperature.

Aqueous UA mixture (w_1)	**$\varphi_E^0\times10^6/m^3\ mol^{-1}\ K^{-1}$**					**σ**
T/K	298.15	303.15	308.15	310.15	313.15	0.01
0.00001	0.953	1.053	1.153	1.201	1.253	0.0001
0.00002	3.529	3.829	4.129	4.277	4.429	0.0003
0.00003	−1.444	−1.244	−1.044	−0.941	−0.844	0.0002
Average standard deviation	0.003	0.003	0.002	0.002	0.001	

Table 8: Values of dB/dT, A_1, A_2 coefficients and standard deviation (σ) for the citric acid in different mass fraction of aqueous UA (w_1) at studied temperatures*.

Aqueous UA mixture (w_1)	**dB/dT**	**A_1**	**A_2**	**σ**
0.00001	0.031	−5.674	0.027	0.0003
0.00002	0.026	−4.676	0.022	0.0002
0.00003	0.035	−6.529	0.030	0.0002
Average standard deviation	0.002	0.015	0.003	

*Standard uncertainties values of u are: u (T)=0.01K

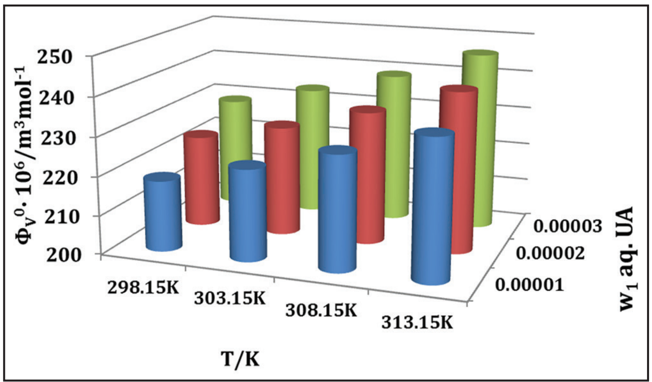


Figure 1: Plot of φ_V^0 as a function of different mass fraction (w_1) of aqueous uric acid solutions at different temperatures.

$$\eta_0 = (hN_A/V_1^0)\exp(\Delta\mu_1^{0\neq}/RT) \quad (7)$$

Where h, N_A, and V_1^0 are the Planck's constant, Avogadro's number, and partial molar volume of the solvent, respectively. The equation (7) can be rearranged as follows, we get

$$\Delta\mu_1^{0\neq} = RT\ln(\eta_0 V_1^0/hN_A) \quad (8)$$

Feakins *et al.* [23-25] suggested that if equations (6) and (8) are obeyed, then,

$$B = (V_1^0 - V_2^0) + V_1^0[(\Delta\mu_1^{0\neq} - \Delta\mu_2^{0\neq})/RT] \quad (9)$$

Where V_2^0 is the limiting partial molar volume (φ_V^0) of the solute and $\Delta\mu_2^{0\neq}$ is the ionic activation energy per mole of solute at infinite dilution. Rearranging the equation (9), we get

$$\Delta\mu_2^{0\neq} = \Delta\mu_1^{0\neq} + (RT/V_1^0)[B-(V_1^0 - V_2^0)] \quad (10)$$

From Table 8, it is evident that $\Delta\mu_2^{0\neq}$ values are all positive and much larger than $\Delta\mu_1^{0\neq}$, suggesting that interaction between solute (CA) and solvent (aqueous UA mixture) molecules in the ground state is stronger than in the transition state. According to free energy terms, the salvation of solute in the transition state is unfavorable.

The entropy of activation ($\Delta S_2^{0\neq}$) [24] for the solution has been calculated using relation:

$$\Delta S_2^{0\neq} = -d(\Delta\mu_2^{0\neq})/dT \quad (11)$$

Here, $\Delta S_2^{0\neq}$ has been obtained from the negative slope of the plots of $\Delta\mu_2^{0\neq}$ against T using a least-squares treatment.

The enthalpy of activation ($\Delta H_2^{0\neq}$) [24] has been obtained from the relation:

$$\Delta H_2^{0\neq} = \Delta\mu_2^{0\neq} + T\Delta S_2^{0\neq} \quad (12)$$

The values of $\Delta S_2^{0\neq}$ and $\Delta H_2^{0\neq}$ are also reported in Table 8.

It is evident from Table 9 that $\Delta\mu_1^{0\neq}$ is practically constant at all the mass fraction of the aqueous UA mixture, suggesting that $\Delta\mu_2^{0\neq}$ is mainly dependent on the viscosity coefficients and $V_1^0 - V_2^0$ terms. Positive $\Delta\mu_2^{0\neq}$ values at all studied temperature and solvent composition suggest that the process of viscous flow becomes difficult as the temperature and mass fraction of aqueous UA mixture increases. Therefore, the formation of transition state becomes less favorable. Feakins *et al.* [24] proposed that $\Delta\mu_2^{0\neq} > \Delta\mu_1^{0\neq}$ for solutes has positive B-coefficients and indicates stronger solute-solvent interactions, thereby suggesting that the formation of transition state is accompanied by the rupture and distortion of the intermolecular forces in the solvent structure [24,26].

Table 9: Values of V_1^0, $(V_1^0–V_2^0)$, $\Delta\mu_1^{0\neq}$, $\Delta\mu_2^{0\neq}$, $T\Delta S_2^{0\neq}$, and $\Delta H_2^{0\neq}$ and standard deviation (σ) for citric acid in different mass fraction (w_1) of aqueous UA mixture at different temperatures*.

Mass fraction	T/K	$V_10.10^6/m^3.mol^{-1}$	$(V_1^0–V_2^0).10^6$ $/m^3.mol^{-1}$	$\Delta\mu_1^{0\neq}/KJ.mol^{-1}$	$\Delta\mu_2^{0\neq}/KJ.mol^{-1}$	$T\Delta S_2^{0\neq}/KJ.mol^{-1}$	$\Delta H_2^{0\neq}/KJ.mol^{-1}$
w_1=0.00001	298.15	18.05	−200.15	9.19	78.41	−1468.09	−1389.68
	303.15	18.08	−205.36	9.11	104.93	−1492.71	−1387.78
	308.15	18.11	−211.17	8.97	121.61	−1517.33	−1395.72
	310.15	18.13	−214.27	8.85	138.02	−1527.18	−1389.16
	313.15	18.14	−217.38	8.73	154.44	−1541.95	−1387.51
w_1=0.00002	298.15	18.05	−205.84	9.20	96.77	−416.00	−319.23
	303.15	18.08	−210.28	9.14	120.99	−520.14	−399.15
	308.15	18.11	−216.06	9.04	139.50	−599.70	−460.20
	310.15	18.12	−219.55	8.93	150.52	−647.09	−496.57
	313.15	18.14	−223.04	8.82	161.55	−694.49	−532.94
w_1=0.00003	298.15	18.05	−210.74	9.22	108.18	−603.12	−494.94
	303.15	18.08	−215.49	9.17	141.55	−789.16	−647.61
	308.15	18.11	−220.92	9.07	155.65	−867.75	−712.10
	310.15	18.12	−224.49	8.96	175.92	−980.76	−804.84
	313.15	18.14	−228.05	8.85	196.19	−1093.76	−897.57
σ	0.01	0.03	7.22	0.08	10.85	10.57	0.65

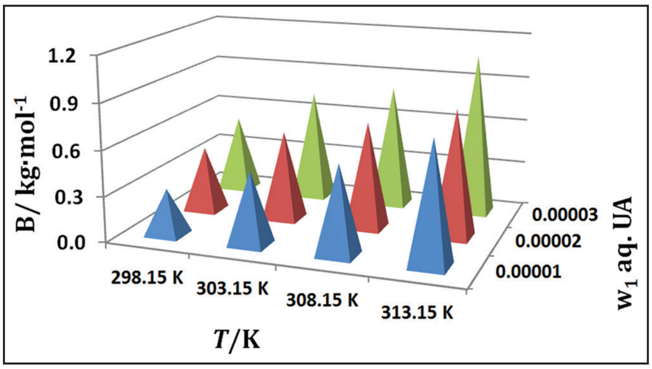


Figure 2: Plot of viscosity B-coefficient as a function of different mass fraction (w_1) of aqueous uric acid solutions at different temperatures.

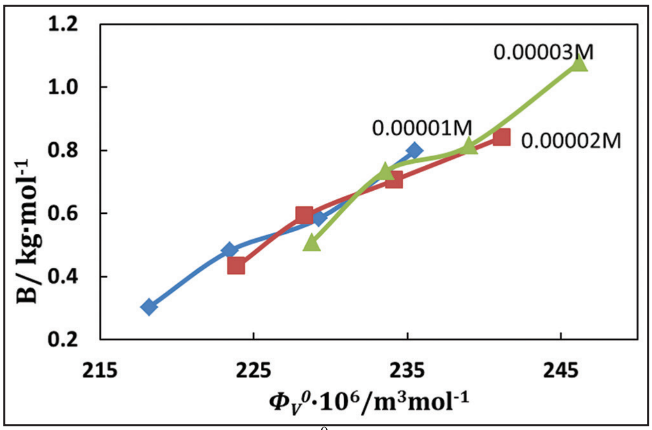


Figure 3: Plot of B against φ_V^0 of different mass fraction (w_1) of aqueous uric acid solutions at different temperatures.

The negative values of both $\Delta S_2^{0\neq}$ and $\Delta H_2^{0\neq}$ suggest that the formation of transition state is associated with bond-making and an increase in order. Although a detailed mechanism for this is not easily advanced, it may be suggested that the slip-plane is in the disordered state [24,27]. According to Feakins *et al*. model, as $\Delta\mu_2^{0\neq} > \Delta\mu_1^{0\neq}$, the solute (CA) behaves as structure makers. This again supports the behavior of dB/dT for the solute in aqueous UA mixture.

Furthermore, it is attractive to observe that there is a linear correlation between viscosity B-coefficients of the studied CA with the limiting apparent molar volumes (φ_V^0) in a different mass fraction of aqueous UA solutions (Figure 3). From the above fact, it means:

$$B = A_1 + A_2\varphi_V^0 \tag{13}$$

The coefficients A_1 and A_2 are listed in Table 8. As both viscosities, B-coefficient and limiting apparent molar volumes define the solute-solvent interaction in solution. The linear variation of viscosity B-coefficient and limiting apparent molar volume (φ_V^0) reflects the positive slope (or A_2).

It is evident from this study that there is a strong interaction between CA and UA and it becomes stronger with the rise in temperature. As molecules of UA are engaged with the CA's molecules, the accumulation among the UA molecules becomes less effective. Therefore, the process of crystallization and deposition of UA gets hampered in the presence of CA (Scheme 3). The above fact suggests that the relief of painful effect of gout can be achieved by consumption of more citrus fruits and by making warmth the affected area.

As we know that the gout is the disease occurred due to the crystallization of UA in the joint of human body. Therefore, the interaction of CA with UA in aqueous solution at human body temperature (37°C or 310.15K) is important. We have obtained the derived parameters such as limiting apparent molar volume (φ_V^0) and viscosity B-coefficient

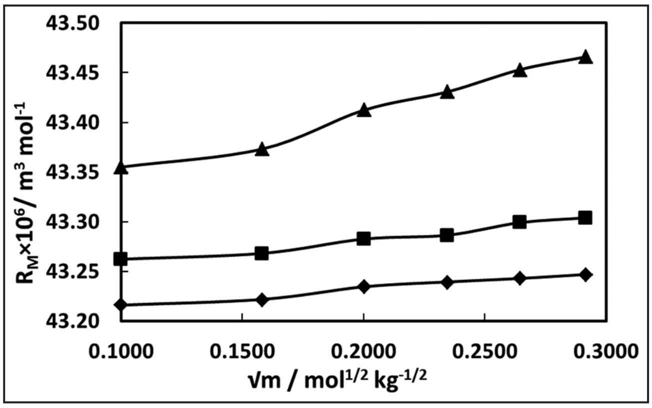


Figure 4: Plot of molar refractive index (R_M) against square root of concentration (√m) for citric acid in different mass fraction (w_1) at different temperatures.

by interpolation and presented in Table 5. The positive and significant magnitude of φ_V^0 and B-coefficient from Table 5 clearly indicates that the limiting apparent molar volume (φV^0), viscosity B-coefficient is increases with increasing mass fraction of citric acid, which indicates the positive effect of hampering in crystallization and deposition of UA in joint of the human body, and as a result, the presence of CA relieves the painful effect of gout. The effect also evidences from the values of free energy of activation ($\Delta\mu_1^{0\neq}$ and ($\Delta\mu_2^{0\#}$), entropy ($\Delta S_2^{0\neq}$), and enthalpy ($\Delta H_2^{0\neq}$) (Table 9). The positive values and increasing order of free energy of activation and negative magnitude and decreasing degree of entropy ($\Delta S_2^{0\neq}$) and enthalpy ($\Delta H_2^{0\neq}$) also suggest the positive effect for pain relief of gout in the presence of CA.

3.3. Refractive Index

The measurement of refractive index is also a suitable method for investigating the molecular interaction existing in solution. The molar refraction (R_M) (Figure 4) can be evaluated from the Lorentz–Lorenz relation [28]. The refractive index of a substance is defined as the ratio c_o/c, where c and c_o are the velocity of light in the medium and vacuum, respectively. Stated more simply that the refractive index of a compound describes its ability to refract light as it passes from one medium to another, and thus, the higher the refractive index of a compound, the more the light is refracted [29]. As stated by Deetlefs *et al*. [30], the refractive index of a substance is higher when its molecules are more tightly packed or in general when the compound is denser. Hence, as summarized in Table 10, we found that the refractive index and the molar refraction are higher for the studied CA in all the mass fraction of aqueous UA, indicating to the fact that the molecules are more tightly packed in the solution.

The limiting molar refraction (R_M^0) is estimated from the following equation (14) and presented in Table 10.

$$R_M = R_M^0 + R_S\sqrt{m} \qquad (14)$$

Accordingly, we found that the higher values of refractive index and RM^0 which representing the fact that the molecules of citric acid are more tightly packed and greater solute-solvent interaction with uric acid molecules than solute solvent interaction. This is also in good agreement with the results obtained from apparent molar volume and viscosity B-coefficients discussed above.

All the above-derived parameters suggest that there is a strong interaction between CA (solute) and UA (solvent) and these increases with a rise in temperature. The solute-solvent interaction is much greater than the solute-solute and solvent-solvent interactions.

Table 10: Refractive index (n_D), molar refraction (R_M), and limiting molar refraction (R_M^0) citric acid in different mass fraction of aqueous UA solutions at 298.15 K and at pressure 1.013 bar*.

[a]Molality/ mol·kg^{-1}	n_D	R_M×10^6/m^3 mol^{-1}	R_M^0×10^6/m^3 mol^{-1}
w_1=0.00001			
0.0100	1.3319	43.22	
0.0252	1.3322	43.22	
0.0404	1.3327	43.23	43.19±0.03
0.0556	1.3332	43.24	
0.0709	1.3337	43.24	
0.0863	1.3343	43.25	
w_1=0.00002			
0.0100	1.3323	43.26	
0.0252	1.3326	43.27	
0.0404	1.3331	43.29	43.23±0.03
0.0556	1.3337	43.29	
0.0709	1.3342	43.30	
0.0863	1.3348	43.30	
w_1=0.00003M			
0.0100	1.3331	43.35	
0.0252	1.3335	43.37	
0.0404	1.3342	43.41	43.28±0.02
0.0556	1.3349	43.43	
0.0709	1.3355	43.45	
0.0863	1.3362	43.47	

*Standard uncertainties u are: u (n_D)=0.0002 and u (T)=0.01K (0.68 level of confidence). [a]Molality has been expressed per kilogram of UA+water solvent mixture

4. CONCLUSION

It is evident from this study, that there is a strong interaction between citric acid and uric acid and it becomes stronger with rise in temperature. As molecules of uric acid are engaged with the citric acid molecules, the accumulation among the uric acid molecules becomes less effective. The Table S1 was given a strong evidence of enhances solubility of uric acid in the presence of citric acid. Therefore, the process of crystallization and deposition of uric acid gets hampered in presence of citric acid (Scheme 3). The above fact suggests that the relief of painful effect of gout can be achieved by consumption of more citrus fruits and by making warmth the affected area.

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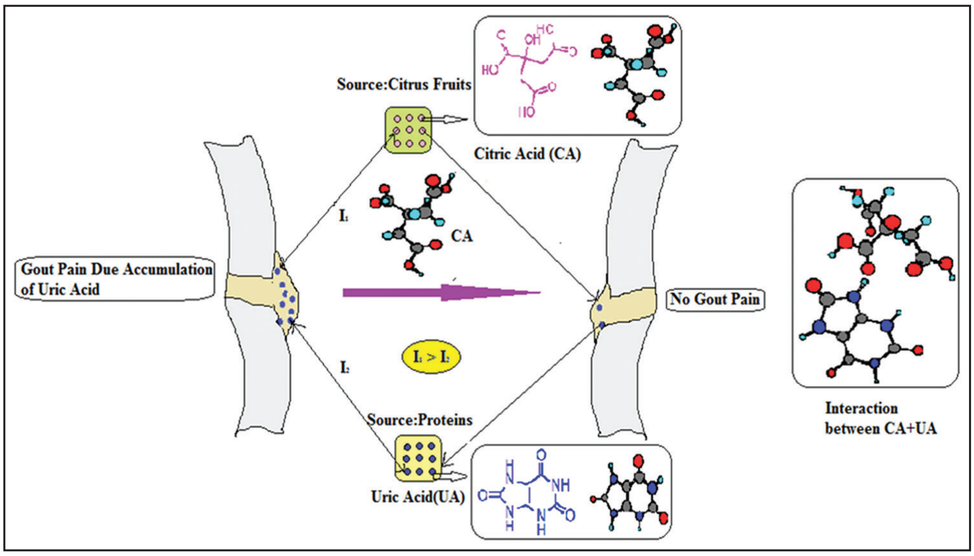
GRAPHICAL ABSTRACT



Gout pain due to accumulation of uric acid in the human body can be reduced by consuming more citrus fruits and making warmth the affected area. This fact has been explained by a physicochemical study (through solute-cosolute interaction).

no. F.4-10/2010 (BSR) regarding his active service for augmenting of research facilities to facilitate further research work.

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*Bibliographical Sketch

Professor (Dr.) Mahendra Nath Roy is Head of Chemistry in the University of North Bengal, Darjeeling. His research interests are in the areas of Host-Guest inclusion complex (Supramolecular chemistry), Ionic Liquids, Solution Thermodynamics, Surfactant, and Polymer Chemistry. His contribution has been recognized by the publication of a large number of high impact research articles (Total-262, International-202, and National-60), Books and (Total-6 [One book chapter], International-03, and National-03) and Chapters 01. He is the life member of ICS, ISC, CRSI, and JTR. He has been awarded one-time grant amounting Rs.-7.00 lakhs by UGC, New Delhi, under basic scientific research (BSR), Bronze Medal award from Chemical Research Society of India (CRSI) and Prof. Suresh C Ameta Award from Indian Chemical Society. He has excellently supervised 34 Ph.D. students to confer their Ph.D. degree and still he has been supervising outstandingly 8 (eight) Ph.D. students.

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SUPPORTING INFORMATION:

Table S1: Solubility chart.

Mass fraction of uric acid (w_1) in water	**Solubility at different temperature (K)**			
	298.15	**303.15**	**308.15**	**310.15**
0.1	Insoluble	Insoluble	Insoluble	Insoluble
0.01	Insoluble	Insoluble	Insoluble	Insoluble
0.001	Insoluble	Insoluble	Insoluble	Insoluble
0.0001	Insoluble	Insoluble	Insoluble	Insoluble
0.00001	Soluble	Soluble	Soluble	Soluble
0.00002	Soluble	Soluble	Soluble	Soluble
0.00003	Soluble	Soluble	Soluble	Soluble
0.00004	Partially soluble	Partially soluble	Partially soluble	Partially soluble
0.00005	Partially soluble	Partially soluble	Partially soluble	Partially soluble
0.00006	Insoluble	Insoluble	Partially soluble	Partially soluble
0.00007	Insoluble	Insoluble	Insoluble	Insoluble
0.00008	Insoluble	Insoluble	Insoluble	Insoluble
0.00009	Insoluble	Insoluble	Insoluble	Insoluble
Molal concentration of citric acid in (uric acid+water)				
w_1=0.00001				
0.010	Soluble	Soluble	Soluble	Soluble
0.025	Soluble	Soluble	Soluble	Soluble
0.040	Soluble	Soluble	Soluble	Soluble
0.055	Soluble	Soluble	Soluble	Soluble
0.070	Soluble	Soluble	Soluble	Soluble
0.086	Soluble	Soluble	Soluble	Soluble
w_1=0.00002				
0.010	Soluble	Soluble	Soluble	Soluble
0.025	Soluble	Soluble	Soluble	Soluble
0.040	Soluble	Soluble	Soluble	Soluble
0.055	Soluble	Soluble	Soluble	Soluble
0.070	Soluble	Soluble	Soluble	Soluble
0.086	Soluble	Soluble	Soluble	Soluble
w_1=0.00003				
0.010	Soluble	Soluble	Soluble	Soluble
0.025	Soluble	Soluble	Soluble	Soluble
0.040	Soluble	Soluble	Soluble	Soluble
0.055	Soluble	Soluble	Soluble	Soluble
0.070	Soluble	Soluble	Soluble	Soluble
0.086	Soluble	Soluble	Soluble	Soluble