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Physicochemical study on molecular interactions in ternary aqueous solutions of the pharmaceutically active ionic liquid cetylpyridinium salicylate and amino acid/glycylglycine at different temperatures

Zhenning Yan *, Xingxing Cao, Meng Sun, Lulu Zhang

College of Chemistry, Zhengzhou University, Zhengzhou, Henan 450001, PR China

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ABSTRACT

The pharmaceutically active form of an ionic liquid, cetylpyridinium salicylate ([CetPy][Sal]), was synthesized, and the intermolecular interactions of [CetPy][Sal] with amino acids (glycine, L-alanine, L-valine, and L-leucine) and glycylglycine (AAGG) in aqueous media were investigated by measuring the density, conductivity and UV–visible spectra at different temperatures. The measured density data was used to compute the apparent molar volume at infinite dilution, $V^0_{2,\varphi}$, the hydration number, n_H, the transfer volume, $\Delta_t V^0$, and the apparent molar expansibility at infinite dilution, $E_{\varnothing}{}^{o}$, of AAGG in aqueous [CetPy][Sal] solution. The measured electrical conductivity was used to calculate the critical micelle concentration, *cmc*, and the relative thermodynamic quantities for the micellization of [CetPy][Sal] in an AAGG solution, i.e. the changes in the Gibbs free energy, the enthalpy, and the entropy. The binding constants between [CetPy][Sal] and AAGG were derived from UV–vis spectroscopic data. The aforementioned properties were analyzed in terms of the molecular interactions and structural changes existing in the studied ternary solutions of (AAGG + [CetPy][Sal] + water).

1. Introduction

Numerous researchers worldwide are intensively studying ionic liquids in pharmaceutically active forms (API-ILs). API-ILs are the third generation ILs that can be easily synthesized by combining appropriate active cations and anions. These ionic liquids exhibit improved characteristics and biological activities [1,2] compared with the corresponding prodrugs. For example, ionic liquids of ampicillin salts have potent antiproliferative effects against various tumor cell lines [3]. A methotrexate (MTX) based API-IL produced with the proline ethyl ester exhibits the desired in vitro antitumor activity and is more soluble than free MTX and its sodium salt in both water and simulated body fluids [4]. M. Goto et al. synthesized a new API-IL comprising *N*-methyl-2-pyrrolidonium as a cation and ibuprofen as an anion. This API-IL has enhanced ability to penetrate skin and accumulate in the target tissues of pig skin [5]. Some API-ILs have the applications in drug delivery [6].

Studying the intermolecular interactions between API-ILs and biomolecules is essential for modeling the performance and elucidating the molecular mechanism of API-ILs [7]. Amino acids and dipeptides are the basic structural entities of proteins. Studying the interactions between these compounds and API-ILs can provide a wealth of information concerning solute-solvent and solute-cosolute interactions on protein. However, few such studies have been performed. Shekaari and coworkers made a great contribution to this respect [8–13]. They developed the synthesis of six API-ILs using 1-butyl (1-hexyl or 1-octyl)-3-methylimidazolium as cations and salicylate/ibuprofenate as anions, and investigated the thermodynamic properties of aqueous solutions of (API-ILs + amino acids), such as density, sound velocity, viscosity, conductivity and refractive index. All these properties were analyzed in the terms of the molecular interactions between API-ILs and amino acids. In the present work, a new API-IL, cetylpyridinium salicylate ([CetPy][Sal]), was synthesized, and the interactions of [CetPy][Sal] with selected amino acids and glycylglycine (AAGG) were studied by volumetric, conductometric and UV–vis absorption spectroscopy methods. [CetPy][Sal] has a high affinity for human serum and is effective as an antimicrobial pharmaceutical [14]. The experimentally measured densities were utilized to compute the apparent molar volume, the apparent molar volume at infinite dilution, the transfer volume and the hydration number. The measured conductivity was used to determine the micellization conditions for aqueous [CetPy][Sal] with added AAGG. A UV spectroscopy study of ternary systems was also carried out. All the calculated quantities were analyzed in terms of the possible molecular interactions present in the ternary solutions. This

* Corresponding author.
E-mail address: yanzzn@zzu.edu.cn (Z. Yan).

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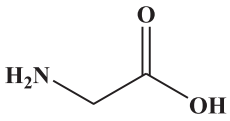
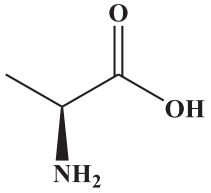
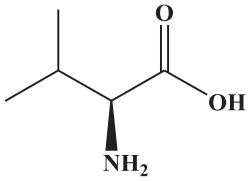
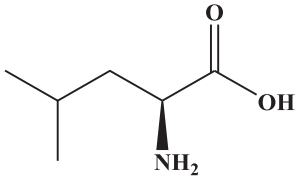
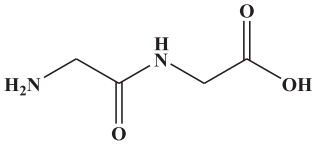
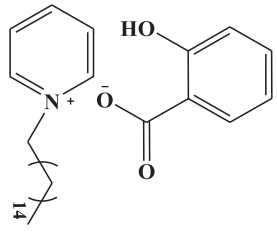
Table 1
Specification of the studied chemicals.

Chemical	CAS No.	Source	Purity (mass fraction)	Structure	Purification method
Glycine	56–40-6	J&K Chemicals, China	>0.99		Dried over P_2O
L-alanine	56–41-7	J&K Chemicals, China	>0.99		Dried over P_2O
L-valine	72–18-4	J&K Chemicals, China	>0.99		Dried over P_2O
L-leucine	61–90-5	J&K Chemicals, China	>0.99		Dried over P_2O
Glycylglycine	556–50-3	Sigma-Aldrich, USA	>0.99		Dried over P_2O
$CetPyCl·H_2O$	6004-24-6	Aladdin Chemicals, China	0.98		None
Sodium salicylate	54–21-7	J&K Chemicals, China	0.99		None
[Cetpy][Sal]		Synthesized	>0.96		Rotary/evaporator and vacuum
Dichloromethane	75–09-2	J&K Chemicals, China	0.999		None
Potassium chloride	7447-40-7	Sigma-Aldrich, USA	0.99999		Drying

investigation provides useful data for exploring the pharmaceutical profile and performance of API-ILs.

2. Experimental

2.1. Chemicals

A detailed description for the current materials is specified in Table 1. The investigated amino acids and glycylglycine were vacuum dried over P_2O_5 before use. The mixed solution was prepared with fresh distilled and deionized water (conductance $< 1\ \mu S \cdot cm^{-1}$).

2.2. Synthesis of [CetPy][Sal]

Cetylpyridinium salicylate was prepared according to the literature method [15]. Typically, cetylpyridinium chloride (0.0112 mol) and sodium salicylate (0.0112 mol) were weighed separately and dissolved in a 20 ml acetone and water (1:1) mixture. The reaction mixture was stirred overnight at room temperature. The solution was then extracted with dichloromethane, the organic phase was washed with water several times, the remaining water in the organic phase was removed with anhydrous magnesium sulfate, and the organic solvent was removed by rotary evaporation after filtration. The obtained sample was dried under vacuum at 80 °C to obtain the final product (a white waxy solid). The synthesized [CetPy][Sal] was characterized by ^1H and ^{13}C NMR (Bruker DPX, 400 MHz), and the NMR spectra are shown in Fig. S1 in the Supplementary Material. The water content for [CetPy][Sal] was about 510 ppm, as determined using a Karl–Fischer titrator (Metrohm 815). The structure of [CetPy][Sal] is graphically depicted in Table 1.

2.3. Apparatus and methods

A Sartorius BP 211D analytical balance was used to weigh the samples to a precision of ± 0.01 mg. The standard uncertainty in the

molality of the solution is $u(m) = 2.0\times10^{-4}$ mol·kg^{-1}. We utilized a vibrating-tube digital densimeter (Anton Paar DMA 4500 M) to measure the density of the solutions at temperatures from 293.15 to 308.15 K. The precision in density is 1.0×10^{-5} g·cm^{-3}. Before each series of measurements was made, the densimeter was calibrated according to the instructions in the instrument manual by using doubly distilled deionized water and dry air in the investigated temperature range. The instrument was automatically thermostatted within ±0.01 K using the built-in Peltier technique. Triplicate measurements of each data point were done to obtain the average density. Uncertainty calculations were carried out following the procedure described in JCGM100: 2008 [16]. Taking into account the purity of the materials and the uncertainty of the instrument, the combined expanded uncertainty in the density was estimated to be $u(\rho) = 2.8\times10^{-4}$ g·cm^{-3}.

The conductivity of the ternary mixtures was obtained by utilizing a Thermo Orion digital conductivity meter (145A+) in the temperature range of 293.15–313.15 K. The instrumental measurement has a relative uncertainty of ± 3%. Prior to performing the experimental measurements, the conductivity cell was calibrated by alignment in a standard KCl solution. A DC-2006 circulated water thermostat manufactured by Hengping Shanghai Ltd. was used to sustain the temperature within ±0.02 K.

The UV–vis absorbance of sample solutions containing different [CetPy][Sal] concentrations and 1.0×10^{-4} mol·kg^{-1} AAGG was measured at room temperature. The absorbance data was collected on a UV–vis spectrometer (Lambda 365, PerkinElmer) at wavelengths of 190 to 350 nm using a 1 cm silica cuvette.

3. Results and discussion

3.1. Volumetric properties of amino acids and glycylglycine

3.1.1. Apparent molar volumes at infinite dilution and hydration number

The experimentally measured densities (ρ) of different AAGG concentrations in 0.005 and 0.010 mol·kg^{-1} [CetPy][Sal] solutions are presented in Table S1 of the Supplementary Material. Fig. 1a shows that the ρ values become large with the increased concentrations of [CetPy][Sal] in the solutions, which implies the presence of interactions between AAGG and [CetPy][Sal]. These interactions will result in the molecular structure of solute and [CetPy][Sal] getting more close [17]. Fig. 1a and b clearly show that density increases with the AAGG concentration. This trend reflects structural enhancement in water in the presence of biomolecules. In addition, ρ decreases with the ascension of temperature. This phenomenon implies that the kinetic energy of the molecules is strengthened with temperature.

Using the obtained ρ values of the ternary mixtures, apparent molar volumes of AAGG have been derived first based on Eq. (1) [18]:

$$V_{2,\varphi} = \mathrm{M}/\rho - 1000(\rho-\rho_0)/(\mathrm{m}\rho\rho_0) \quad (1)$$

The symbol ρ_o stands for the densities of ([CetPy][Sal] + water) mixed solvent, and m and M denote the molality and molar mass of AAGG, respectively. Table S1 presents the resulting values of $V_{2,\varphi}$. The results clearly show that $V_{2,\varphi}$ value increases with temperature.

The apparent molar volume at infinite dilution, $V^0_{2,\varphi}$ was computed from the least squares fit given by Eq. (2) [19]:

$$V_{2,\varphi} = V^0_{2,\varphi} + S_V \cdot m \quad (2)$$

Here, S_V is the slope of the regressed equation. The linear relationship of $V_{2,\varphi}$ vs. m for glycine/glycylglycine in a 0.005 mol·kg^{-1} aqueous [CetPy][Sal] solution is plotted in Fig. 2 as an example. The evaluated $V^0_{2,\varphi}$ and the corresponding standard deviation are presented in Table 2. The $V^0_{2,\varphi}$ values of AAGG in [CetPy][Sal] aqueous solution increase with the [CetPy][Sal] concentration and temperature. This trend implies the dehydration of amino acids and glycylglycine, indicating enhanced solute-solvent interactions. Furthermore, the $V^0_{2,\varphi}$ values decrease in the following order: leucine > valine > alanine > glycine. This behavior is attributed to the increasing molar mass and hydrophobicity of the amino acids. The [CetPy][Sal]-amino acid interactions are enhanced by the longer alkyl side chain of the amino acids.

The hydration behavior of AAGG in [CetPy][Sal]+water mixtures was further analyzed by calculating the hydration number n_H using Millero's method [20], as described in the Supplementary Material. Table 3 and Fig. 3 show that the $n_H$values decrease with increased [CetPy][Sal] molarity and temperature. This result confirms that [CetPy][Sal] and high temperature result in the dehydration of the

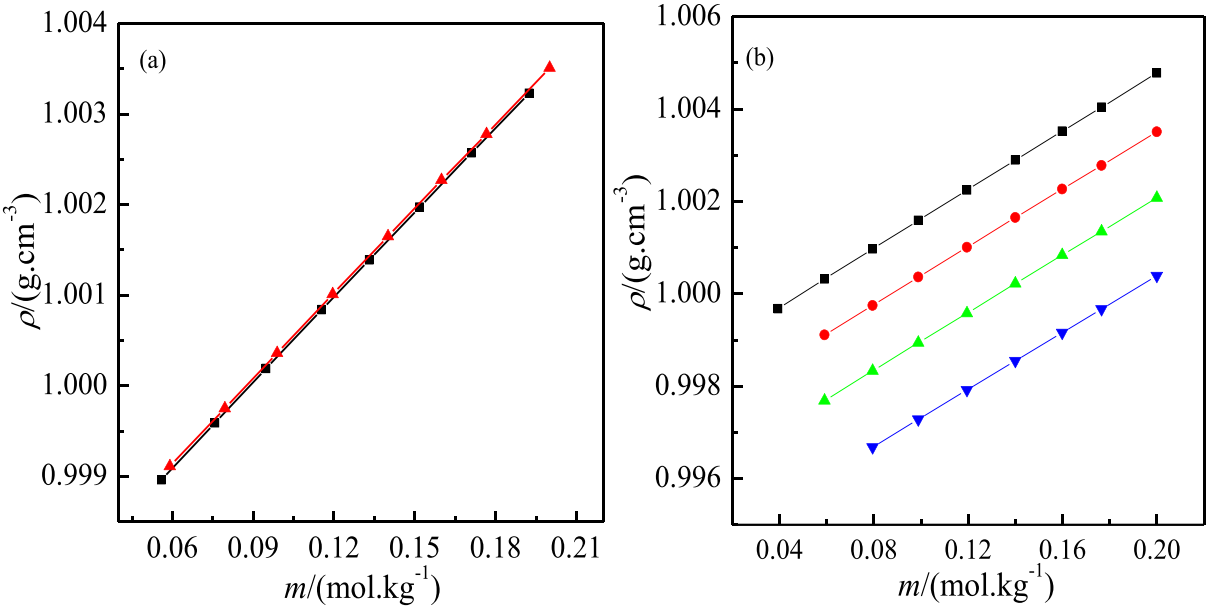


Fig. 1. (a) Density data of glycine in (■) 0.005 mol·kg^{-1} and (▲) 0.010 mol·kg^{-1} [CetPy][Sal] solutions vs. molality of glycine at 298.15 K; (b) Density data of glycine in 0.010 mol·kg^{-1} [CetPy][Sal] solution vs. molality of glycine at (■) 293.15 K, (●) 298.15 K, (▲) 303.15 K and (▼) 308.15 K.

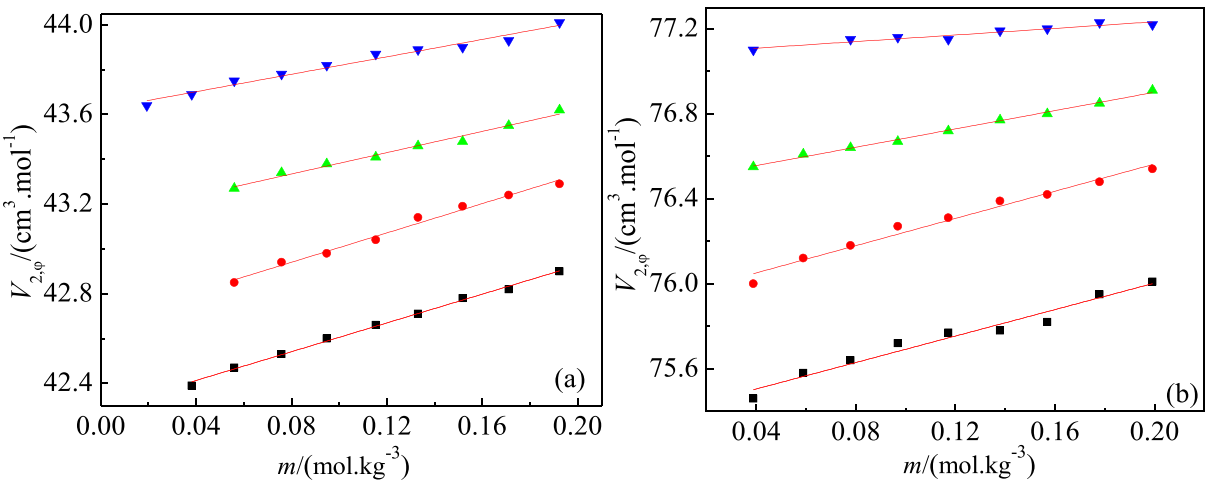


Fig. 2. Apparent molar volumes vs. molality of (a) glycine and (b) glycylglycine in aqueous 0.005 mol·kg^{-1} [CetPy][Sal] solutions at (■) 293.15 K, (●) 298.15 K, (▲)303.15 K and (▼) 308.15 K.

Table 2
Apparent molar volume at infinite dilution, $V^0_{2,\varphi}$ of AAGG in aqueous [CetPy][Sal] solution at different temperatures and pressure $p = 101$ kPa.[a]

	$V^0_{2,\varphi}$/(cm^3·mol^{-1})			
	293.15 K	298.15 K	303.15 K	308.15 K
0.005 mol·kg^{-1} [CetPy][Sal]				
glycine	42.28±0.01	42.68±0.02	43.14±0.02	43.62±0.01
L-alanine	59.34±0.01	59.76±0.01	60.11±0.02	60.58±0.01
L-valine	89.93±0.01	90.30±0.01	90.69±0.02	91.07±0.01
L-leucine	106.31±0.02	106.89±0.01	107.32±0.02	107.99±0.01
glycylglycine	75.38±0.03	75.92±0.03	76.47±0.01	77.08±0.01
0.010 mol·kg^{-1} [CetPy][Sal]				
glycine	42.36±0.01	42.74±0.02	43.31±0.02	43.75±0.01
L-alanine	59.59±0.02	60.01±0.01	60.39±0.01	60.85±0.01
L-valine	89.95±0.01	90.46±0.03	90.83±0.01	91.32±0.01
L-leucine	106.51±0.01	107.09±0.03	107.62±0.01	108.30±0.01
glycylglycine	75.55±0.01	75.96±0.02	76.55±0.01	77.12±0.01

[a] Standard uncertainties u are: $u(T) = 0.01$ K, $u(p) = 5$ kPa.

Table 3
Values of hydration number, n_H $n_H$of AAGG in aqueous [CetPy][Sal] solution at different temperatures and pressure $p = 101$ kPa.[a]

	n_H			
	293.15 K	298.15 K	303.15 K	308.15 K
0.005 mol·kg^{-1} [CetPy][Sal]				
glycine	9.40	8.71	7.64	6.95
L-alanine	3.49	3.15	2.72	2.39
L-valine	4.91	4.50	3.91	3.52
L-leucine	1.84	1.55	1.27	1.00
glycylglycine	6.36	5.81	5.03	4.50
0.010 mol·kg^{-1} [CetPy][Sal]				
glycine	9.37	8.69	7.59	6.91
L-alanine	3.41	3.08	2.64	2.33
L-valine	4.91	4.45	3.87	3.46
L-leucine	1.77	1.49	1.19	0.93
glycylglycine	6.30	5.80	5.01	4.49

[a] Standard uncertainties u are: $u(T) = 0.01$ K, $u(p) = 5$ kPa.

amino acids/glycylglycine, which further supports the conclusions drawn from the $V^0_{2,\varphi}$ values.

3.1.2. Transfer volume

The transfer volume, $\Delta_t V^0$, from water to the aqueous [CetPy][Sal] solutions was computed as follows:

$$\Delta_t V^0 = V^0_{2,\varphi}\ (\text{aqueous [CetPy][Sal]}) - V^0_{2,\varphi}\ (\text{pure water}) \quad (3)$$

The values of $V^0_{2,\varphi}$ (pure water) for AAGG were taken from the literature [21–23]. The estimated $\Delta_t V^0$ values are listed in Table 4. The $\Delta_t V^0$ values are negative and increase with the enhancing temperature and concentration of [CetPy][Sal]. This effect has also been observed for amino acids in many ionic liquid solutions, such as [Emim][Br] [24], 3-HPAF ionic liquid [25], [Phpi][BF_4] [26], [Emim][HSO_4] [27], and [Bmim][BF_4] [28] solutions. The cosphere overlap model [29] can be used to explain the above mentioned effect. The following interactions may occur between AAGG and [CetPy][Sal]:

(a) ionic-polar group interactions between ions of [CetPy][Sal] and polar groups ((NH_3^+,COO^-) and (CH_2CONH)) of AAGG;
(b) ionic-apolar group interactions between ions of [CetPy][Sal] and hydrophobic side chains of AAGG as well as between charged groups of AAGG and hydrophobic side chains of [CetPy][Sal]; and.
(c) apolar-apolar group interactions between hydrophobic groups of [CetPy][Sal] and hydrophobic side chains of AAGG.

In accordance with the cosphere overlap model [29], the negative $\Delta_t V^0$ values are indicative of potent interactions (b) and (c). Apolar-apolar group interactions can be heightened by the interactions of alkyl groups in AAGG with the large hydrophobic aliphatic chain in [CetPy][Sal]. Furthermore, the $\Delta_t V^0$ values become less negative as the molality of [CetPy][Sal] increases, implying the enhancement of ionic-polar group interactions.

3.1.3. Apparent molar expansibility at infinite dilution

The results presented above show that the $V^0_{2,\varphi}$ values are sensitive to temperature. This temperature dependence can be represented as

$$V^0_{2,\varphi} = v_1 + v_2(T-273.15) + v_3(T-273.15)^2 \quad (4)$$

where v_1, v_2 and v_3 are the parameters. The temperature derivative of Eq. (4) gives the apparent molar expansibility at infinite dilution, $E^o_\varnothing$:

$$E^o_\varnothing = \left(\partial V^0_{2,\varphi}/\partial T\right)_p = v_2 + 2v_3(T-273.15) \quad (5)$$

Eq. (5) can also be utilized to compute $(\partial E^o_\varnothing/\partial T)_p$, which reflects the structure-forming or structure-breaking features of amino acids/glycylglycine [30].

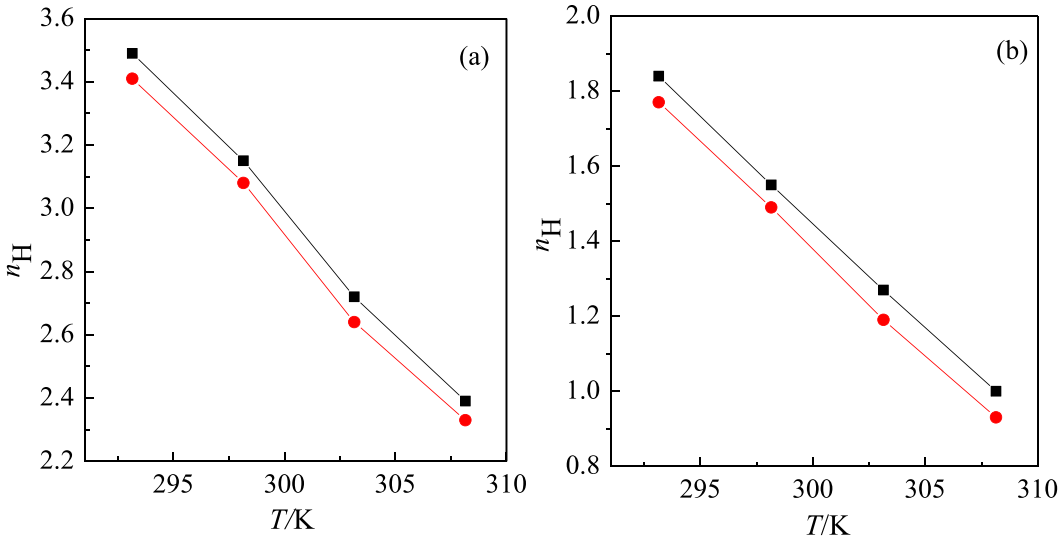


Fig. 3. Hydration number n_H of alanine (a) and leucine (b) vs. temperature in aqueous (■) 0.005 mol·kg^{-1} and (●) 0.010 mol·kg^{-1} [CetPy][Sal] solutions.

Table 4
Transfer volumes, $\Delta_t V^0$ of AAGG in aqueous [CetPy][Sal] solution at different temperatures and pressure $p = 101$ kPa.[a]

	$\Delta_t V^0$ (cm^3·mol^{-1})			
	293.15 K	298.15 K	303.15 K	308.15 K
0.005 mol·kg^{-1} [CetPy][Sal]				
glycine	−0.62	−0.56	−0.52	−0.26
L-alanine	−0.63	−0.60	−0.58	−0.39
L-valine	−0.61	−0.57	−0.53	−0.41
L-leucine	−0.82	−0.80	−0.75	−0.40
glycylglycine	−0.41	−0.24	−0.18	−0.11
0.010 mol·kg^{-1} [CetPy][Sal]				
glycine	−0.54	−0.50	−0.36	−0.13
L-alanine	−0.38	−0.35	−0.30	−0.12
L-valine	−0.59	−0.41	−0.39	−0.16
L-leucine	−0.62	−0.60	−0.45	−0.09
glycylglycine	−0.24	−0.20	−0.10	−0.07

[a] Standard uncertainties u are: $u(T) = 0.01$ K, $u(p) = 5$ kPa.

Table 5
Partial molar expansibility at infinite dilution, $E^0_\varnothing$ and $(\partial E^0_\varnothing/\partial T)_p$ values of AAGG in aqueous [CetPy][Sal] solutions.[a]

	$E^0_\varnothing$/(cm^3·mol^{-1}·K^{-1})				$(\partial E^0_\varnothing/\partial T)_p$/ (cm^3·mol^{-1}·K^{-2})
	293.15 K	298.15 K	303.15 K	308.15 K	
0.005 mol·kg^{-1} [CetPy][Sal]					
glycine	0.0776	0.0856	0.0936	0.1016	0.0016
L-alanine	0.0739	0.0789	0.0839	0.0889	0.0010
L-valine	0.0747	0.0757	0.0767	0.0777	0.0008
L-leucine	0.0959	0.1049	0.1139	0.1229	0.0018
glycylglycine	0.1025	0.1095	0.1165	0.1235	0.0014
0.010 mol·kg^{-1} [CetPy][Sal]					
glycine	0.0858	0.0918	0.0978	0.1038	0.0012
L-alanine	0.0772	0.0812	0.0852	0.0892	0.0008
L-valine	0.0848	0.0888	0.0928	0.0918	0.0008
L-leucine	0.1030	0.1130	0.1230	0.1330	0.0020
glycylglycine	0.0820	0.0980	0.1140	0.1300	0.0032

[a] Standard uncertainties u are: $u(T) = 0.01$ K, $u(p) = 5$ kPa.

$$\left(\partial E^o_\varnothing/\partial T\right)_p = \left(\partial^2 V^0_{2,\varphi}/\partial T^2\right)_p = 2v_3 \tag{6}$$

The calculated $E^o_\varnothing$ and $(\partial E^o_\varnothing/\partial T)_p$ values are reported in Table 5. Note that the $E^o_\varnothing$ values are all positive. This phenomenon implies the presence of interactions between the solute and solvent. Furthermore, increasing the temperature and molarity of [CetPy][Sal] causes $E^o_\varnothing$ to increase (Table 5), corresponding to the easier release of electrostricted water from loose hydration layers of small biomolecules and a subsequent expansion in volume. The positive sign of $(\partial E^o_\varnothing/\partial T)_p$ indicates the structure-forming behavior of AAGG in the investigated cases [30].

3.2. Conductivity properties

3.2.1. Critical micelle concentration of [CetPy][Sal]

The long alkyl chains in [CetPy][Sal] enable the formation of micellar aggregates in pure water and (AAGG + water) systems. The conductivity was measured to analyze the micellization conditions for [CetPy][Sal]. The measured conductance (Table S2) was used in Eq. (7) to calculate the critical micelle concentration (*cmc*) [31,32]:

$$f(c) = f(0) + S_1 c + \Delta c(S_2 - S_1)\ln\left(\frac{1 + e^{(c-c_0)/\Delta c}}{1 + e^{-c/\Delta c}}\right) \tag{7}$$

where $f(0)$ is the conductivity at the [CetPy][Sal] concentration c=0, S_1 and S_2 are the slopes for the lower and upper *cmc* values, respectively. Δc is the width of a sudden transition in $f(c)$. c_0 is [CetPy][Sal] concentration at the midpoint of the transition, which corresponds to the *cmc*. The obtained *cmc* is shown in Table 6. Saraiva et al. [33] measured the *cmc* value of [CetPy][Sal] in water using fluorescence assay at room temperature. There is no significant deviation between our *cmc* value in water and the literature value of 0.19 mmol.dm^{-3}. The calculated *cmc* in water is much smaller than that of cetylpyridinium chloride, 0.99 mmol·kg^{-1} [15]. This fact is not surprising because salicylate anion has been reported to promotes the micellization of some cationic surfactants [14,33,34]. This behavior is mainly attributed to -OH group being located at the *ortho*-position in [Sal]$^-$. The strong hydrophobicity of [Sal]$^-$ relative to Cl$^-$ also contributes to this behavior.

The influence of the concentration of AAGG and temperature on the *cmc* values of [CetPy][Sal] is shown in Fig. 4. The *cmc* increases with temperature. This phenomenon could be attributed to the deformation of the water structure under intensified molecular motion [35]. Fig. 4 also shows that the *cmc* decreases upon AAGG addition. These results indicate that the addition of small biomolecules to an aqueous solution promotes the micellization of [CetPy][Sal]. This

Table 6
Various micellization and thermodynamic parameters of [CetPy][Sal] in AAGG-water mixed media at different temperatures [a].

m/(mol·kg^{-1})	T/K	cmc/(mmol·dm^{-3})	α	ΔG_m^0/(kJ·mol^{-1})	ΔH_m^0/(kJ·mol^{-1})	ΔS_m^0/(J·mol^{-1}·K)	$\Delta\Delta G_m^0$/(kJ·mol^{-1})
water							
0.00	293.15	0.15	0.7466	−39.17	−11.82	93.29	
	298.15	0.16	0.7181	−40.54	−11.85	96.24	
	303.15	0.17	0.7150	−41.12	−11.59	97.41	
	308.15	0.18	0.6798	−42.75	−11.58	101.16	
	313.15	0.19	0.6781	−43.32	−11.22	102.49	
glycine + water							
0.05	293.15	0.14	0.5832	−44.52	−14.71	101.70	−5.35
	298.15	0.15	0.5734	−45.35	−16.02	98.36	−4.81
	303.15	0.16	0.5582	−46.36	−17.48	95.29	−5.24
	308.15	0.18	0.5770	−46.08	−18.57	89.28	−3.33
	313.15	0.19	0.5557	−47.33	−20.25	86.46	−4.01
0.10	293.15	0.13	0.5571	−45.60	−15.67	102.12	−6.43
	298.15	0.14	0.5570	−46.12	−15.25	103.54	−5.58
	303.15	0.15	0.5718	−46.16	−14.62	104.04	−5.04
	308.15	0.16	0.5616	−47.02	−14.20	106.52	−4.27
	313.15	0.17	0.5832	−46.84	−13.40	106.78	−3.52
L-alanine + water							
0.05	293.15	0.13	0.5729	−45.10	−15.49	100.99	−5.93
	298.15	0.14	0.5783	−45.43	−15.02	102.00	−4.89
	303.15	0.15	0.5655	−46.36	−14.69	104.49	−5.24
	308.15	0.16	0.5562	−47.19	−14.25	106.91	−4.44
	313.15	0.17	0.5805	−46.93	−13.43	106.98	−3.61
0.10	293.15	0.12	0.5636	−45.68	−16.87	98.27	−6.51
	298.15	0.13	0.5614	−46.24	−16.38	100.16	−5.70
	303.15	0.14	0.5597	−46.80	−15.82	102.21	−5.68
	308.15	0.15	0.5677	−47.06	−15.09	103.75	−4.31
	313.15	0.16	0.5970	−46.61	−14.08	103.87	−3.29
L-valine + water							
0.05	293.15	0.12	0.5565	−45.90	−16.95	98.74	−6.73
	298.15	0.13	0.5632	−46.18	−16.36	100.02	−5.64
	303.15	0.14	0.5590	−46.82	−15.83	102.25	−5.70
	308.15	0.15	0.5776	−46.73	−14.98	103.03	−3.98
	313.15	0.16	0.5800	−47.17	−14.25	105.12	−3.85
0.10	293.15	0.11	0.6186	−44.22	−17.66	90.61	−5.05
	298.15	0.12	0.5995	−45.30	−17.28	93.97	−4.76
	303.15	0.13	0.6141	−45.30	−16.41	95.30	−4.18
	308.15	0.14	0.5412	−48.19	−16.46	102.95	−5.44
	313.15	0.15	0.5529	−48.32	−15.45	104.96	−5.00
L-leucine + water							
0.05	293.15	0.11	0.5589	−46.13	−18.42	94.51	−6.96
	298.15	0.12	0.5667	−46.35	−17.68	96.16	−5.81
	303.15	0.13	0.5703	−46.72	−16.92	98.29	−5.60
	308.15	0.14	0.5501	−47.89	−16.36	102.32	−5.14
	313.15	0.15	0.5922	−47.00	−15.03	102.09	−3.68
0.10	293.15	0.10	0.5503	−46.74	−20.33	90.12	−7.57
	298.15	0.11	0.5321	−47.79	−19.76	94.02	−7.25
	303.15	0.12	0.5488	−47.72	−18.63	95.96	−6.60
	308.15	0.13	0.5458	−48.31	−17.67	99.43	−5.56
	313.15	0.14	0.5400	−49.01	−16.64	103.36	−5.69
glycylglycine + water							
0.05	293.15	0.10	0.5956	−45.28	−19.69	87.29	−6.11
	298.15	0.11	0.5726	−46.47	−19.21	91.42	−5.93
	303.15	0.12	0.5869	−46.47	−18.14	93.44	−5.35
	308.15	0.13	0.5639	−47.70	−17.45	98.18	−4.95
	313.15	0.14	0.5538	−48.54	−16.48	102.38	−5.22
0.10	293.15	0.08	0.5313	−48.15	−19.28	98.49	−8.98
	298.15	0.09	0.5242	−48.78	−22.80	87.14	−8.24
	303.15	0.10	0.5532	−48.24	−25.90	73.68	−7.12
	308.15	0.11	0.5076	−50.22	−30.59	63.70	−7.47
	313.15	0.13	0.4768	−51.42	−35.38	51.23	−8.10

[a] m is the molality of AAGG in water. Standard uncertainties u are $u(T) = 0.02$ K, $u(P) = 5$ kPa, $u(m) = 0.0002$ mol·kg^{-1}, $u(cmc) = (0.003–0.008)$ mol·dm^{-3}, $u(\Delta G_m^0) = 0.02$ kJ·mol^{-1}, $u(\Delta H_m^0) = 0.06$ kJ·mol^{-1}, $u(\Delta S_m^0) = 0.1$ J·mol^{-1}·K, $u(\Delta\Delta G_m^0) = 0.03$ kJ·mol^{-1}.

behavior may be attributed to the electrostatic attraction between polar groups of AAGG and the cationic $[CetPy]^+$ of API-IL, which decreases the electrostatic repulsive forces between the charged heads of $[CetPy]^+$. Consequently, micellization is promoted, and the counterions are liberated from the aggregate. The length of the alkyl chain of AAGG also affects the *cmc*. The *cmc* increases in the order: glycylglycine < leucine < valine < alanine < glycine < water. This result has been previously reported in the literature [36–39]. This decrease in the *cmc* upon AAGG addition is due to the breaking of the hydration film of [CetPy][Sal] because of the interactions between AAGG and [CetPy][Sal]. The entropy value of the studied system increases, and hence, micelles can easily form.

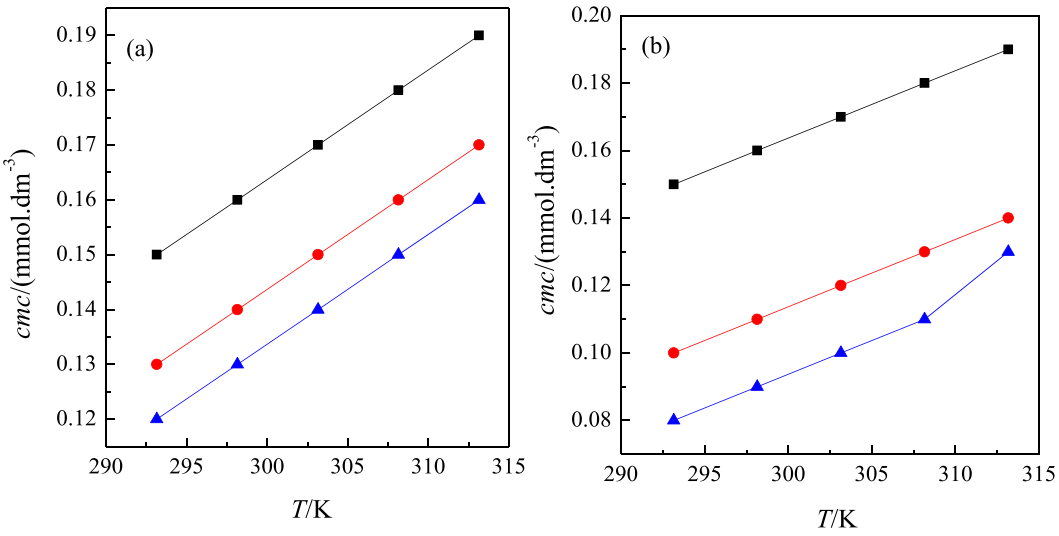


Fig. 4. Variation in critical micelle concentration of [CetPy][Sal] in water (■) and aqueous alanine (a) and glycylglycine (b) solutions with temperature and molality of alanine and glycylglycine: (●) 0.05 mol·kg^{-1}, (▲) 0.10 mol·kg^{-1}.

3.2.2. Thermodynamics of [CetPy][Sal] micellization

Standard thermodynamic quantities of micellization were computed using the following relations based on the mass action model:

$$\Delta G_m^0 = (2-\alpha)\ RT\ \ln X_{cmc} \tag{8}$$

$$\Delta H_m^0 = -(2-\alpha)\ RT^2\ d\ln X_{cmc}/dT \tag{9}$$

$$\Delta S_m^0 = \left(\Delta H_m^0 - \Delta G_m^0\right)/\mathrm{T} \tag{10}$$

where ΔG_m^0, ΔH_m^0 and ΔS_m^0 are changes in the standard Gibbs free energy, the enthalpy, and the entropy for micellization, respectively. The *cmc* appears as a molecular fraction (X_{cmc}). The term ($d\ln X_{cmc}/dT$) can be obtained using the following second-degree polynomial equation:

$$\ln X_{cmc} = k_1 + k_2\mathrm{T} + k_3 T^2 \tag{11}$$

The calculated thermodynamic quantities are presented in Table 6. In all the studied cases, ΔG_m^0 value is negative. The negative ΔG_m^0 indicates that the aggregation process is spontaneous. To further explore the impact of AAGG addition on the micellization of [CetPy][Sal], the Gibbs free energy of transfer, $\Delta\Delta G_m^0 = \Delta G_m^0$(in a mixed solvent) -$\Delta G_m^0$ (in water), was calculated. The gotten results in Table 6 show that $\Delta\Delta G_m^0$ values in the aqueous AAGG solution are negative. This result implies that the micelle formations are more favorable in the presence of the AAGG than in water. More negative ΔG_m^0 values signify that the dehydration of [CetPy][Sal] occurs at high temperatures, which is a major driver for the formation of micelles [40]. The negative value of ΔH_m^0 shows that micelle formation is exothermic. Micellization becomes more exothermic in the presence of biomolecules in aqueous solution. The large positive ΔS_m^0 values state that the micellization process is entropy-driven, that is, the transfer of the hydrophobic group from the solvent to the micellar interior provides the driving force for the [CetPy][Sal] micellization. The negative ΔH_m^0 and positive ΔS_m^0 values show that electrostatic interactions play an important role, in addition to hydrophobic interactions, in micelle formation [41].

3.3. UV–vis spectroscopy

To elucidate the intermolecular interactions in the studied systems, UV–vis absorption measurements were performed in the mixed solutions with a fixed AAGG concentration of 1.0×10^{-4} mol·kg^{-1}. Fig. S2 illustrates the absence of an absorption peak in the 190–350 nm range in the amino acid solutions, whereas strong absorption peaks appear at ~190 nm for the glycylglycine solutions. In the presence of [CetPy][Sal], three absorbances were observed at approximately 200, 260 and 295 nm. In the UV absorption spectra, the absorbance increases and the UV absorption at 200 nm is shifted to higher wavelengths as the [CetPy][Sal] concentration increases. These changes are indications of significant AAGG-[CetPy][Sal] interactions. The UV absorption data at 200 nm was used with the Scott equation to calculate the binding constant (K_b) between AAGG and [CetPy][Sal] [42].

$$\frac{C_D C_m l}{\Delta A} = \frac{C_m}{\varepsilon_m - \varepsilon_0} + \frac{1}{(\varepsilon_m - \varepsilon_0)K_b} \tag{12}$$

Here ΔA and (ε_m-ε_0) are the differences in the absorbance and molar extinction coefficient, respectively, with and without [CetPy][Sal]. C_m and C_D are the concentrations of [CetPy][Sal] and AAGG, respectively, and C_D is 1.0×10^{-4} mol·kg^{-1}. The K_b value is evaluated from the ratio of the intercept to the slope of the straight lines of ($C_D C_m l/\Delta A$) against C_m as shown in Fig. S3. The K_b values for the association of [CetPy][Sal]-AAGG (glycine, alanine, valine, leucine, and glycylglycine) are 3472, 3537, 3934, 4474 and 4530 m^3·mol^{-1}, respectively. These K_b values show that increasing the side-chain length of an amino acids increases the binding appetency of the amino acid towards [CetPy][Sal]. The order of the strength of the AAGG and [CetPy][Sal] interactions is attributed to the difference in the hydrophobicities of the corresponding alkyl chains. This result agrees with the results of the volumetric studies.

4. Conclusions

A pharmaceutically active ionic liquid [CetPy][Sal] was synthesized and the volumetric, conductometric and UV–vis spectra properties were determined for ternary aqueous solutions containing [CetPy][Sal] and amino acids/glycylglycine (AAGG). The experimental data was used to calculate several parameters, such as the apparent molar volume at infinite dilution, the hydration number, the transfer volume, the apparent molar expansibility at infinite dilution of AAGG, the critical micelle concentration, relative thermodynamic properties of [CetPy][Sal] and the binding constant between AAGG and [CetPy][Sal]. These thermodynamic properties depend upon the temperature, composition, and size of the AAGG alkyl chain. The hydrophilic-hydrophobic and hydrophobic-hydrophobic interactions between AAGG and [CetPy]

[Sal] increase with the cosolute concentration. The presence of [CetPy][Sal] and high temperature result in the dehydration effect on AAGG. The increase in alkyl chain length of AAGG enhances solute-solvent interactions in the present ternary solutions. The critical micelle concentrations of [CetPy][Sal] increase with temperature and decrease with the addition AAGG. The micellization process is spontaneous and exothermic. Both hydrophobic interactions and electrostatic interactions play an important role in the formation of micelle process.

Credit authorship contribution statement

Zhenning Yan: Methodology, Validation, Formal analysis, Data curation, Writing - review & editing, Writing - original draft, Project administration, Funding acquisition. **Xingxing Cao:** Conceptualization, Validation, Formal analysis, Writing - review & editing. **Meng Sun:** Validation, Investigation, Formal analysis. **Lulu Zhang:** Validation, Visualization, Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the results reported in this paper.

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Appendix A. Supplementary data

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