



Aqueous nicotine solutions: pH-measurements and salting-out effects – Analysis of the effective Gibbs energies of hydration and ionic strengths of the solutions

NIKOLA D. GROZDANIĆ^{1#}, MARTA S. CALADO², MIRJANA LJ. KIJEVČANIN^{1#},
SLOBODAN P. ŠERBANOVIĆ^{1#} and ZORAN P. VIŠAK^{2*}

¹Faculty of Technology and Metallurgy, University of Belgrade, Karnegijeva 4, 11120
Belgrade, Serbia and ²Centro de Química Estrutural, Instituto Superior Tecnico,
Universidade de Lisboa, Av. Rovisco Pais 1, 1049-001 Lisboa, Portugal

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Abstract: This work is a continuation of previous studies on phase demixing – salting-out effects – in aqueous nicotine solutions. Thus, pH measurements were performed, allowing a brief analysis of the existing hydrogen bond interactions. Salting-out effects – the related experimental cloud point shifts – provoked by the addition of two inorganic salts, potassium nitrate and sodium sulfate, which have not hitherto been studied, were determined. Analysis of the current and previously reported salting-out/or salting-in phenomena in nicotine aqueous solutions was performed. In this respect, five studied salts were included: four inorganic salts (sodium chloride, potassium nitrate, sodium sulfate and trisodium phosphate (Na₃PO₄)), and ionic the liquid 1-ethyl-3-methylimidazolium ethyl sulfate ([C₂mim][EtSO₄], commercial name ECOENG212[®]). Based on pH measurements, the effective Gibbs energies of hydration and the ionic strengths of the respective ternary solutions were calculated and plotted against the related cloud-point shifts caused by the addition of the salts. For the studied salts, the results and diagram obtained within this work may be used to predict the cloud-points shifts, based on the related quantities of the salts added and/or the molar Gibbs energies of hydration and/or ionic strengths requested in each case.

Keywords: inorganic salts; ionic liquids; pH measurements of solutions.

INTRODUCTION

Nicotine is an extremely toxic alkaloid¹ that is completely soluble in water at ambient temperatures.^{2,3} It is widely present in tobacco (dust) and the related industrial (aqueous) wastes – thus, nicotine and its aqueous solutions represent a

* Corresponding author. E-mail: zoran.visak@ist.utl.pt

Serbian Chemical Society member.

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dangerous threat to the environment and human health.^{1,4-6} On the other hand, nicotine recently started to appear, albeit with concerns, as a potentially useful drug for the treatment of some neurodegenerative diseases.⁷⁻⁹ Therefore, these issues impose the need not only for nicotine separation/extraction, but also for its purification or recovery. However, common organic (toxic) solvents still play the main role in such applications.¹⁰⁻¹⁴ Thus, it has become an emerging necessity to develop methods that are more environmentally friendly.

In previous studies,^{6,15} the potential use of ionic liquids and inorganic salts as the media for eventual sustainable treatment of nicotine and its aqueous solutions were investigated and discussed. In this respect, the salting-out effects, which revealed the very complex nature of the studied aqueous nicotine solutions, were particularly considered.⁶

In this work, the aforementioned studies and the reported salting-out effects - cloud point shifts - provoked by the addition of another two inorganic salts, sodium nitrate and sodium sulfate, were continued. Moreover, both the current and previously reported⁶ salting-out and salting-in phenomena were analyzed. Thus, five salting-out media were scrutinized: four inorganic salts (NaCl, KNO₃, Na₂SO₄ and Na₃PO₄) and the ionic liquid 1-ethyl-3-methylimidazolium ethyl sulfate ([C₂mim][EtSO₄], commercial name ECOENG212[®]).

The pH values for the (nicotine+water) binary solutions and for the ((nicotine+water)+salt) systems were measured. Based on these measurements a brief analysis of the hydrogen bond interactions was given. Moreover, the effective Gibbs energy of hydration and ionic strength were calculated for the respective ternary solutions and the diagrams showing their relation to the related cloud-point shifts were constructed. These results enabled the prediction of the cloud-points shifts, for each salt included, based on the related quantities of the salts applied and/or the molar Gibbs energies of hydration or ionic strengths necessary for each shift to be achieved.

EXPERIMENTAL

Chemicals

Ionic liquid 1-ethyl-3-methyl imidazolium ethyl sulfate, [C₂mim][EtOSO₃] (ECOENG 212[®]), was purchased from Solvent Innovation (Merck), with a stated purity > 98 mass % (water and chloride content 153 and 404 ppm, respectively). Nicotine, sodium chloride, potassium nitrate and sodium sulfate were obtained from Sigma-Aldrich, with the stated purities: > 99, 99.5, ≥ 99 and ≥ 99 mass %, respectively. Trisodium phosphate (Na₃PO₄) was acquired from Riedel de Haën with a stated purity of 96 mass %.

ECOENG212[®] was subjected to vacuum (0.1 Pa) at moderate temperature (60 °C), several days prior to the experiments. This procedure was primarily applied to reduce significantly the presence of volatile compounds (solvents) in the ionic liquid but also to dry it. The water contents after the drying procedure were very low, below 90 ppm, as determined by coulometric Aquapal Karl-Fischer titration. Thus, the presence of water was not considered in the subsequent preparation of the aqueous solutions. As in previous studies^{6,15} and according to

recommendations from literature,¹⁶ the stated chloride contents were taken as acceptable and no further reduction was performed. Considering the possibility of the anion hydrolysis,^{6,17} which would lead to acidity increase,⁶ the pH of the used ECOENG212[®] was checked and the values were far from acidic (pH 6.50–6.90).

Nicotine was dried using 3Å molecular sieves for at least 48 h ahead of the experiments and the Karl–Fischer titrations revealed water contents of 100 ppm.

Solutions were prepared gravimetrically using a Mettler AT201 analytical semi-micro-balance with a stated accuracy (repeatability) of $\pm 2 \times 10^{-5}$ in mass fraction. Doubly distilled and deionized Millipore water (Millipore Co. equipment, Bedford, MA) was used to prepare the solutions.

pH Measurements

Current pH measurements were performed at room temperature, using an InoLab Multi 720 pH meter (WTW GmbH, Germany). The device was calibrated each time prior to the experiments using two different buffers having pH values of 7.00 (Technischen puffer WTW STP 7) and 10.00 (Technischen puffer WTW STP 10). Fresh Millipore water was always used for the measurements.

Liquid–liquid equilibria – cloud-point shift determination

The liquid–liquid equilibria experiments performed herein were related to the determination of cloud-point shifts due to salt addition (salting-out effects) to the (nicotine+water) solutions initially having a near-critical concentration of nicotine (the mole fraction of nicotine was 0.0708). In this respect, a dynamic, visual method was used – in the studied solutions, the turbidity (cloud-point) that indicates the beginning of phase demixing was observed by eye, while heating a homogeneous solution. The experiments were performed in a Pyrex-glass cell, introduced by Domanska¹⁸ and applied in several studies thereafter.^{6,19–25} A description of the cell, its application and the procedure of the cloud-point observation were described in details in earlier contributions.^{6,22,23} The uncertainties in the determination of the cloud-point temperatures (T_{cp}), estimated from repeated measurements, were ± 0.4 K. A 2-L glass beaker filled with ethylene glycol, as a thermostatic liquid, was used as a thermostat bath in all the experiments. Temperature was monitored using a Pt100 temperature probe, having an accuracy of ± 0.03 K.

RESULTS

The pH values determined for the studied (nicotine+water) solutions, without any added buffer, are presented in Table I. In order to keep the concept of water as a solvent and, thus, its ion product applicable, the measurements were performed in the nicotine concentration range up to 85 % by mass.²⁶ This table also gives the pH-dependent percentage (P) of unprotonated nicotine molecules (Nic⁰ – free base) and protonated nicotine (both Nic⁺ and Nic²⁺) given as:²⁷

$$P(\text{Nic}^0) = \frac{100}{\frac{[\text{H}^+]^2}{K_{a2}K_{a1}} + \frac{[\text{H}^+]}{K_{a2}} + 1} \quad (1)$$

In Eq. (1), $[\text{H}^+]$ is the concentration of the protons in the solution, calculated from the related pH values in Table I; K_{a1} and K_{a2} are the acid dissociation

equilibrium constants having the values $10^{-3.41}$ and $10^{-8.01}$, respectively, according to the pK_a values cited in the literature.²⁸ These constants refer to the following equilibria:

$$K_{a1} = \frac{[\text{Nic}^+][\text{H}^+]}{[\text{Nic}^{2+}]} \quad (2)$$

that is related to the acid dissociation of the nicotine dication:



and to:

$$K_{a2} = \frac{[\text{Nic}^0][\text{H}^+]}{[\text{Nic}^+]} \quad (3)$$

that refers to the acid dissociation of the nicotine monocation:



The percentage of the protonated nicotine is then calculated by the expression:

$$P(\text{Nic}^+ + \text{Nic}^{2+}) = 100 - P(\text{Nic}^0) \quad (4)$$

TABLE I. pH Values of the studied (nicotine+water) solutions, at 298.15 K, and the percentages of nicotine that exists in the solutions as the free base $P(\text{Nic}^0)$; w_{Nic} and x_{Nic} are the mass and mole fraction of nicotine in the aqueous solutions, respectively; ρ is density of the studied nicotine aqueous solutions and c is the related molar concentration of nicotine. The pH of the Millipore water used for the preparation of these solutions was 6.81

w_{Nic}	x_{Nic}	$\rho / \text{kg m}^{-3a}$	$c / \text{mol dm}^{-3}$	pH	$[\text{H}^+] \times 10^{11}$	$P(\text{Nic}^0)^b$	$P(\text{Nic}^+ \text{ and } \text{Nic}^{2+})$
0.0002	2.2×10^{-5}	997.13	0.0012	9.10	79.4	92.48	7.52
0.0007	7.6×10^{-5}	997.13	0.0042	9.55	28.2	97.20	2.80
0.0019	0.0002	997.13	0.0114	9.95	11.2	98.86	1.14
0.0045	0.0005	997.33	0.0277	10.10	7.94	99.19	0.81
0.0103	0.0012	997.61	0.0633	10.25	5.62	99.43	0.57
0.0478	0.0055	999.93	0.2947	10.38	4.17	99.58	0.42
0.1401	0.0178	1006.31	0.8690	10.48	3.31	99.66	0.34
0.2001	0.0270	1010.46	1.2463	10.50	3.16	99.68	0.32
0.4071	0.0708	1024.55	2.5708	10.38	4.17	99.58	0.42
0.6012	0.1433	1034.09	3.8319	10.10	7.94	99.19	0.81
0.7055	0.2100	1035.28	4.5019	9.85	14.1	98.58	1.42
0.8012	0.3074	1031.69	5.0872	9.62	24.0	97.60	2.40
0.8501	0.3860	1027.49	5.3832	9.52	30.2	97.00	3.00

^aDensities of the (nicotine+water) solutions were calculated using experimental data;^{3b} nicotine as a free base is an unprotonated form (Nic^0) of this alkaloid represented by its neutral molecule

The experimental cloud-point temperatures, at a pressure of 0.1 MPa, as a function of the salt compositions in the present ternary solutions are given in Table II. Following the previous procedure, the salts were added to the initial

(water+nicotine) solution of a near-critical nicotine concentration ($(X_S)_T = 0$; $X_{\text{Nic}} = 0.0708$ in mole fractions).⁶

TABLE II. Ternary solutions (nicotine+water+salt) at a pressure of 0.1 MPa: liquid phase demixing temperatures (cloud-points, T_{cp}) and their negative shifts (ΔT_{cp}) as a function of the salt compositions. $(x_S)_T$ and $(x_{\text{Nic}})_T$ are mole fractions of salt and nicotine in the ternary solutions, respectively. The salts were added to the initial (nicotine+water) solution of near-critical nicotine concentration ($(x_S)_T = 0$; $x_{\text{Nic}} = 0.0708$ in mole fractions). Standard NIST uncertainties were, in mole fraction, $u(x) = 3 \times 10^{-4}$ and in temperature $u(T) = \pm 0.4$ K

Salt: KNO ₃				Salt: Na ₂ SO ₄			
$(x_S)_T$	$(x_{\text{Nic}})_T$	T_{cp} / K	$\Delta T_{\text{cp}} / \text{K}$	$(x_S)_T$	$(x_{\text{Nic}})_T$	T_{cp} / K	$\Delta T_{\text{cp}} / \text{K}$
0.0000	0.0000	335.0	0.0	0.0000	0.0000	335.0	0.0
0.0087	0.0702	326.3	-8.7	0.0008	0.0707	328.2	-6.8
0.0131	0.0699	322.2	-12.8	0.0013	0.0707	323.1	-11.9
0.0181	0.0695	317.0	-18.1	0.0019	0.0707	318.4	-16.6
0.0247	0.0690	310.6	-24.4	0.0023	0.0706	314.7	-20.4
0.0286	0.0688	306.3	-28.7	0.0027	0.0706	311.3	-23.7

The values of the molar Gibbs energies of hydration of each ion species i at 298.15 K and 0.1 MPa, $(G_i)_{\text{hyd}}$, both for the solutions studied herein and previously,⁶ are presented in Table III. The values of $(G_i)_{\text{hyd}}$ for $[\text{C}_2\text{mim}]^+$, HPO_4^{2-} and $[\text{EtSO}_4]^-$ at 298.15 K – to the best of our knowledge not available in the literature – were calculated using the related ionic radii and applying the calculation procedure set by Marcus.²⁹ The radii for $[\text{C}_2\text{mim}]^+$ (0.303 nm)³⁰ and HPO_4^{2-} (0.238 nm)³¹ were taken from the literature. However, no reported values for the radius of $[\text{EtSO}_4]^-$ could be found. Thus, the radius was calculated either *i*) using the radius for SO_4^{2-} (0.230 nm)³¹ and the contributions for the CH_3^- and CH_2^- groups given by Bondi³² or *ii*) by applying the procedure based on the McGowan volumes,³³ given by Zhao *et al.*³⁴ – see the Supplementary Material to this paper for details. Both approaches gave very similar values of the anion radius: *i*) 0.280 and *ii*) 0.282 nm.

TABLE III. Molar Gibbs energies of hydration at 298.15 K and 0.1 MPa, $(g_i)_{\text{hyd}}$, of the ion species present in the studied salts (this work and from the literature⁶)

Ion	$(G_i)_{\text{hyd}} / \text{kJ mol}^{-1}$	Ion	$(G_i)_{\text{hyd}} / \text{kJ mol}^{-1}$
Na ⁺	-385	Cl ⁻	-270
K ⁺	-305	NO ₃ ⁻	-275
$[\text{C}_2\text{mim}]^+$	-53.2	SO ₄ ²⁻	-1145
$[\text{EtSO}_4]^+$	-139.7	PO ₄ ³⁻	-2835
OH ⁻	-345	HPO ₄ ²⁻	-1125.3

For the other ions in Table III, the experimental values of the molar Gibbs energies of hydration at 298.15 K and 0.1 MPa taken from the literature²⁹ were included.

In Table IV, for all these hitherto studied solutions, the cloud-point temperatures, T_{cp} , are given as a function of the effective Gibbs energies of hydration, $(\Delta G_{eff})_{hyd}$, of the salts and ionic strength increase of the solutions, ΔI . The last two properties were calculated as follows:

$$(\Delta G_{eff})_{hyd} = \frac{1}{n_T} \sum_i n_i (G_i)_{hyd} \quad (5)$$

$$\Delta I = \sum m_i z_i^2 \quad (6)$$

In the equations above, n_i , n_T , m_i and z_i are number of moles of each ion, total number of moles in the ternary solution, molal concentration of every present ion and its formal charge, respectively. $(G_i)_{hyd}$ is molar Gibbs energy of hydration of each ion i as explained above with the values given in Table III.

TABLE IV. Cloud-point temperatures (T_{cp}), at a pressure of 0.1 MPa, as a function of the effective Gibbs energies of hydration $(\Delta G_{eff})_{hyd}$ of the studied salts and of ionic strength of the respective solutions

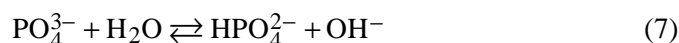
$(\Delta G_{eff})_{hyd} / \text{kJ mol}^{-1}$	$\Delta I / \text{mol kg}^{-1} \text{ a.c.u.}^2$	T_{cp} / K
Salt: NaCl		
0.000	0.000	335.0 ^a
1.954	0.212	329.3 ^a
2.861	0.311	326.3 ^a
4.232	0.461	323.2 ^a
5.768	0.630	318.5 ^a
9.822	1.079	309.5 ^a
10.939	1.204	306.3 ^a
12.764	1.409	301.1 ^a
Salt: Na ₂ SO ₄		
0.000	0.000	335.0 ^b
1.430	0.168	328.2 ^b
2.439	0.287	323.1 ^b
3.398	0.400	318.4 ^b
4.155	0.489	314.7 ^b
4.845	0.571	311.3 ^b
Salt: KNO ₃		
0.000	0.000	335.0 ^b
5.168	0.621	326.3 ^b
7.776	0.939	322.2 ^b
10.763	1.306	317.0 ^b
14.707	1.797	310.6 ^b
17.019	2.087	306.3 ^b
Salt: Na ₃ PO ₄		
0.000	0.000	335.0 ^a
0.633	0.062	330.4 ^a
1.416	0.152	327.4 ^a

TABLE IV. Continued

$(\Delta G_{\text{eff}})_{\text{hyd}} / \text{kJ mol}^{-1}$	$\Delta I / \text{mol kg}^{-1} \text{ a.c.u.}^2$	T_{cp} / K
Salt: Na_3PO_4		
2.019	0.217	323.7 ^a
2.757	0.297	320.1 ^a
2.912	0.314	319.4 ^a
Salt: $[\text{C}_2\text{mim}][\text{EtSO}_4]$		
0.0000	0.000	335.0 ^a
1.513	0.583	339.8 ^a
5.692	2.246	343.3 ^a
7.453	2.970	340.3 ^a
10.159	4.111	334.6 ^a
12.276	5.028	329.7 ^a
14.775	6.141	321.6 ^a
15.953	6.676	318.2 ^a
19.255	8.218	305.8 ^a
22.051	9.572	296.2 ^a

^aCloud-point taken from the literature;⁶ ^bcloud-point obtained within this work

It is known that the inorganic salts NaCl , KNO_3 and Na_2SO_4 are practically completely dissociated in their aqueous solutions and the same is postulated for ECOENG212[®].³⁵ However, in order to confirm experimentally that these expectations stand in the presence of nicotine, the pH values of the studied (nicotine+water+salt) solutions were measured at distinct salt compositions. The changes in pH upon addition of the aforementioned salts to (nicotine+water) solutions confirmed their complete dissociation. Namely, the percentages of the change in pH were, on average, 1.24 (NaCl), 0.19 (KNO_3), 2.01 (Na_2SO_4) and 2.5 % (ECOENG212[®]). Thus, the values of n_i and m_i of the actual ions needed in Eqs. (5) and (6) were calculated using the respective stoichiometry. However, the large increase of pH observed when Na_3PO_4 was included (17.47 %) imposes that the equilibrium:



has to be taken into account. The equilibrium constant for hydrolysis is $K_b = 2.24 \times 10^{-2}$, while the other two dissociation reactions can be neglected. Therefore, PO_4^{3-} , HPO_4^{2-} and OH^- exist in the solutions and their molal concentrations were calculated using the aforementioned value of K_b .

A low molar entropy of hydration^{36,37} imposes a weak temperature dependence of the molar Gibbs energies of hydration – this was true for all the ions of the studied inorganic salts and could be reasonably assumed for those of ECOENG212[®]. Therefore, the values of $(G_i)_{\text{hyd}}$ at 298.15 K were used for the calculations of the effective Gibbs energies of hydration at the other temperatures presented in Table IV.

Figure 1 compares the liquid phase demixing data from Table II and from a previous study,⁶ whereas Figs. 2 and 3 give cloud-point temperature as a function of the ionic strength increase in different salts and in ECOENG212[®], all along with the fittings.

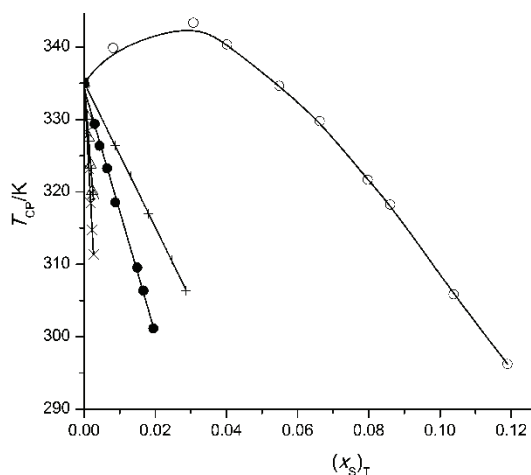


Fig. 1. Cloud-point temperatures (T_{cp}) as a function of the composition of different salts in the ternary (nicotine+water+salt) solution ($(x_s)_T$): Δ – Na_3PO_4 (literature data⁶), \times – Na_2SO_4 (data from this work), \bullet – NaCl (literature data⁶), $+$ – KNO_3 (data from this work) and \circ – ECOENG212[®] (literature data⁶). The salts were added to the initial binary (nicotine+water) solution of near-critical nicotine concentration ($(x_s)_T = 0$ and $x_{\text{Nic}} = 0.0708$). The lines represent the fittings of the experimental data.

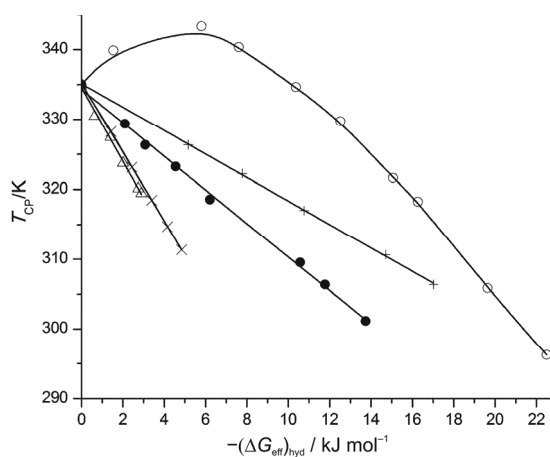


Fig. 2. Cloud-point temperatures (T_{cp}) as a function of the effective Gibbs energy of hydration ($(\Delta G_{\text{eff}})_{\text{hyd}}$): Δ – Na_3PO_4 , \times – Na_2SO_4 , \bullet – NaCl , $+$ – KNO_3 and \circ – ECOENG212[®]. The salts were added to the initial binary (nicotine+water) solution of near-critical nicotine concentration ($(x_s)_T = 0$ and $x_{\text{Nic}} = 0.0708$). The lines represent the fittings of the experimental data.

Table V presents the effective Gibbs energies of hydration calculated for ternary (nicotine+water+salt) solutions of a given composition ($(x_s)_T = 0.0006$, $(x_{\text{Nic}})_T = 0.07075$, Eq. (5)) and the related negative cloud-point shifts (ΔT_{cp}) obtained from the linear fits of the data from Table II and from the previous study.⁶ Thus, the obtained ΔT_{cp} vs. $(\Delta G_{\text{eff}})_{\text{hyd}}$ data are shown in Fig. 4. In respect to ECOENG212[®], both procedures of the radius calculation (see above) gave also very similar values of $(\Delta G_{\text{eff}})_{\text{hyd}}$ ($-0.7507 \text{ kJ mol}^{-1}$ in the first case and

$-0.7408 \text{ kJ mol}^{-1}$ in the second) and, for practical reasons, only the first point is included in Fig. 4.

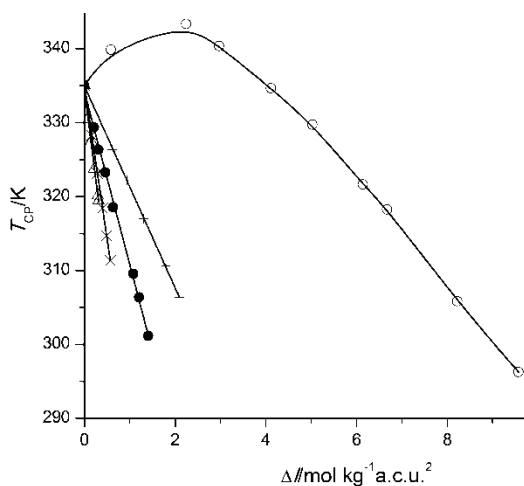


Fig. 3. Cloud-point temperatures (T_{cp}) as a function of the ionic strength increase (Δ): Δ – Na_3PO_4 , \times – Na_2SO_4 , \bullet – NaCl , $+$ – KNO_3 and \circ – ECOENG212[®]. The salts were added to the initial binary (nicotine+water) solution of near-critical nicotine concentration ($(x_S)_T = 0$ and $x_{\text{Nic}} = 0.0708$). The lines represent the fittings of the experimental data.

TABLE V. Effective Gibbs energies of hydration, $(\Delta G_{\text{eff}})_{\text{hyd}}$, and the related negative cloud-point shifts, ΔT_{cp} , for the studied salts in (nicotine+water+salt) solutions of the given composition (ternary salt mole fraction was $(x_S)_T = 0.0006$ and that of nicotine $(x_{\text{Nic}})_T = 0.07075$)

Salt	$-(\Delta G_{\text{eff}})_{\text{hyd}} / \text{kJ mol}^{-1}$	$\Delta T_{cp} / \text{K}$
Na_3PO_4	1.849	-10.1
Na_2SO_4	1.086	-5.3
NaCl	0.423	-1.0
KNO_3	0.357	-0.6
ECOENG212 [®]	0.112	1.5

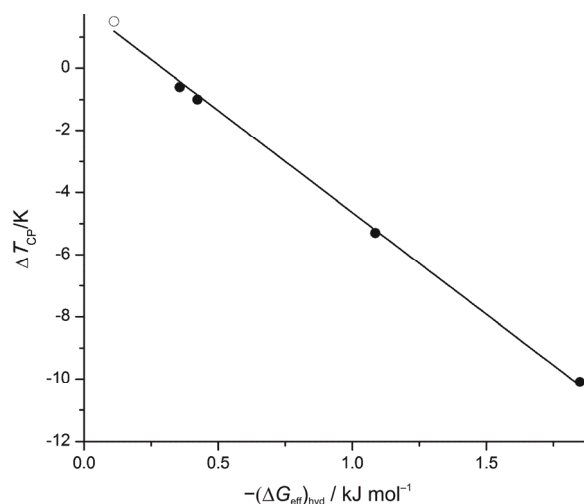


Fig. 4. Generalized graph: cloud-point shifts (ΔT_{cp}) as a function of the effective Gibbs energy of hydration $(\Delta G_{\text{eff}})_{\text{hyd}}$ (for the (nicotine+water+salt) solution of a given composition ($(x_S)_T = 0.004$, $(x_{\text{Nic}})_T = 0.07051$): \bullet – the points related to the four inorganic salts studied herein and \circ – the point related to ECOENG212[®]. The latter was excluded from the linear regression given in the graph.

DISCUSSION

It is well-known and described in the literature that nicotine can exist in three forms in its aqueous solutions: as a free base (unprotonated, neutral molecule Nic^0), singly protonated (monocation Nic^+) and doubly protonated (dication Nic^{2+}).^{12,27,38–40} The first protonation ($\text{p}K_{\text{b}} = 5.99$ or $\text{p}K_{\text{a}} = 8.01$) occurs on the nitrogen atom (Nsp^3) of the nicotine *N*-methylpyrrolidine ring, while the second one occurs on the nitrogen (Nsp^2) in the pyridine ring ($\text{p}K_{\text{b}} = 10.59$ or $\text{p}K_{\text{a}} = 3.41$).²⁸ In other words, the much higher basicity of the pyrrolidine nitrogen compared to that of the pyridine one implies that the presence of the monocation, created by the protonation of the pyridine nitrogen, can be neglected.³⁹ However, it was also emphasized that the percentage of protonated nicotine is dependent on the pH of the solution.^{38,40} Thus, Table I shows that the pH values of the (nicotine+water) solutions allowed that the major part of the nicotine remained as the free base. As the nicotine concentration was increased, the pH first increased, then exhibited a maximum and finally decreased, see Fig. 1. Both experimental⁴¹ and simulation studies⁴² imply that the network of hydrogen bonds between nicotine and water is a complex dynamic structure that depends on the protonation of nicotine that mainly occurs at the pyrrolidine nitrogen.^{38,40} Briefly, it appears that this protonation – as an overall effect – even reinforces the hydrogen bond network by introducing one more (a two-fold) binding site and stabilizing the structure of the bonds *via* the specific interactions between water and the charged pyrrolidine ring.⁴² Although any extrapolation to higher nicotine mole fractions is as yet uncertain, Table I shows a behavior that agrees with the aforementioned findings. Namely, in aqueous nicotine solutions with a nicotine content over ≈ 36 mol %, generally homogeneous at any temperature (see the nicotine+water temperature–composition “closed loop” phase diagram reported in literature³), protonation is increasingly present. The percentage of protonated nicotine follows an abrupt, practically linear increase with increasing nicotine composition, which commenced when the near-critical concentration of nicotine (0.0708 mole fraction) was surpassed. From the interaction point of view only, this analysis certainly concurs with a very good solubility of nicotine in water, depicted in the large areas of complete miscibility in its phase diagram.

Figure 1 showed that KNO_3 was the inorganic salt that provoked the worst salting-out effect, reasonably poorer than that of NaCl , determined previously,⁶ probably due to the lower hydration abilities of the constituting ions. On the contrary, the achievement of Na_2SO_4 was exceptionally good and very similar, although slightly inferior, to that of Na_3PO_4 . This occurrence could have been expected since salts of doubly- and triply-charged anions are excellent water-structuring (kosmotropic) salts, having highly negative effective Gibbs energies of hydration.^{36,43}

The effective Gibbs energies of hydration or ionic strengths necessary for each salting-out effect (cloud-point shift) of each salt added to the aforementioned initial binary (nicotine+water) solution are depicted in Figs. 2 and 3, respectively. These figures indicate that a change in ionic strength strongly affected the liquid phase demixing behavior.

On the other hand, as reported and discussed previously,⁶ ECOENG212[®] changes its behavior from salting-in, at lower concentrations (chaotropic behavior prevails, provided by the non-polar alkyl side chains), to salting-out at higher concentrations, (kosmotropic behavior becomes dominant, due to the polar part of the ions). Thus, it has to be added in larger quantities in order to afford Gibbs energies of hydration and/or ionic strengths able to provoke a significant cloud-point decrease. Nevertheless, the fact that ECOENG212[®] is a molten salt (wide liquid range), completely soluble in water and that it is a relatively low-priced ionic liquid speak in favor of its use for the present purposes.

Figure 4, in relation to Table V, shows which effective Gibbs energy of hydration is required in order to achieve a certain temperature shift in nicotine aqueous solution after adding an exact quantity (0.06 mole fraction in the ternary solution) of salt in general. For the four studied inorganic salts, the linear regression was very good ($R^2 = 0.999975$), which could have been expected from the linear form in the mole fractions of Eq. (5) and generally the very good linear fits of T_{cp} by ternary composition ($(x_S)_T$) of the added inorganic salts, see Fig. 1. Actually, the results of this work and a previous study,⁶ as well as the salting-out effects studied in the other aqueous solutions such as those of ionic liquids³⁶ and poly(ethylene glycol)⁴⁴ indicate, although still with caution, that the linear dependence shown in Fig. 1 is not a sheer coincidence but something that might reasonably be expected, once the experiments were performed carefully. If this assumption is accepted, Fig. 4 could be considered as a general graph for (nicotine+water) solutions and, thus, shows two interesting features: *i*) which effective Gibbs energy of hydration is expected to provoke a null cloud-point shift and *ii*) what is the salting-in effect that could be anticipated applying a salt that would give a null effective Gibbs energy of hydration. – in principle, this could occur since there are some ions that possess null or positive molar Gibbs energy of hydration.²⁹

However, the point related to ECOENG212[®], which was included in Fig. 4 but not in the regression since the ionic (van der Waals) radius of its anion, necessary to obtain $(\Delta G_{eff})_{hyd}$, was calculated and not taken from literature, see the text above and the Supplementary Material to this paper. Moreover, the positive shift for the given composition in the case of ECOENG212[®] was not obtained by linear but polynomial fit of the related cloud-point–composition curve (see Fig. 1). These could be the reasons for the worse agreement to a linear regression compared to the other four points.

Thus, Figs. 1–4 demonstrate which solutions should be prepared in order to expect certain salting-out effects (T_{cp} shifts) and which effective Gibbs energies of hydration and/or ionic strength are required to achieve them.

The results show that small quantities of inorganic salts, actually extremely small in the case of the salts with polyvalent ions, provide effective Gibbs energies of hydration and ionic strengths sufficient to allow strong salting-out effects and abrupt decreases in the cloud-point.

CONCLUSIONS

The pH measurements of (nicotine+water) solutions showed that the bulk of nicotine molecules therein exist in the neutral, unprotonated form. This study also demonstrated that the presence of the protonated form rapidly increases as the critical concentration of nicotine in water is surpassed. Moreover, as stated above, in nicotine solutions with a nicotine content over ≈ 36 mol %, the percentage of the protonated form steadily increases.

Analyses in literature clearly show that the hydrogen bonded network of nicotine with water is very stable and strong in both neutral and protonated form of its molecule. In fact, the overall effect of the protonation of nicotine is the strengthening of this network, which is in agreement with the results obtained in the present study.

The inorganic salts studied herein appeared as very efficient salting-out media – added in very small quantities they provided effective Gibbs energies of hydration and ionic strengths sufficient to allow large negative cloud-point shifts.

The results of this work may be useful as a guide in future applications of the studied salts in treating aqueous nicotine solutions.

SUPPLEMENTARY MATERIAL

Calculation of the McGowan volumes and the Pauling ionic radius are available electronically from <http://www.shd.org.rs/JSCS/>, or from the corresponding author on request.

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ИЗВОД

ВОДЕНИ РАСТВОРИ НИКОТИНА: pH МЕРЕЊА И „SALTING OUT“ ЕФЕКТИ – АНАЛИЗА ЕФЕКТИВНЕ ГИБСОВЕ ЕНЕРГИЈЕ ХИДРАТАЦИЈЕ И ЈОНСКЕ ЈАЧИНЕ РАСТВОРА

НИКОЛА Д. ГРОЗДАНИЋ¹, MARTA S. CALADO², МИРЈАНА Љ. КИЈЕВЧАНИН¹, СЛОБОДАН П. ШЕРБАНОВИЋ¹
и ЗОРАН П. ВИШАК²

¹Технолошко–металуршки факултет, Универзитет у Београду, Караџијева 4, 11120 Београд и ²Centro de Química Estrutural, Instituto Superior Técnico, Universidade Técnica de Lisboa, Av. Rovisco Pais 1, 1049-001 Lisboa, Portugal

Рад је наставак претходне студије о немешљивости фаза у воденим растворима никотина. pH мерења су дала кратку анализу интеракција постојећих водоничних веза. Одређивани су “salting out” ефекти изазвани додавањем две неорганске соли, калијум-нитрата и натријум-сулфата, који нису разматрани раније. У овој као и претходној студији, анализирани су “salting out or in” ефекти у воденим растворима никотина за четири неорганске соли: натријум-хлорид, калијум-нитрат, натријум-сулфат и натријум-фосфат као и за јонску течност 1-етил-3-метилимидазолијум етил-сулфат ([C₂mim][EtSO₄], комерцијални назив ECOENG212[®]). За разматране соли, резултати и добијени дијаграми у овом раду могу да се узму за предсказивање померања тачака замућења, на основу количине додатих соли, Гибсове енергије хидратације и јонске јачине.

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