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Electrolyte Effects on the Amino Acid Solubility in Water: Solubilities of Glycine, L-Leucine, L-Phenylalanine, and L-Aspartic Acid in Salt Solutions of (Na^+, K^+, NH_4^+)/(Cl^-, NO_3^-)

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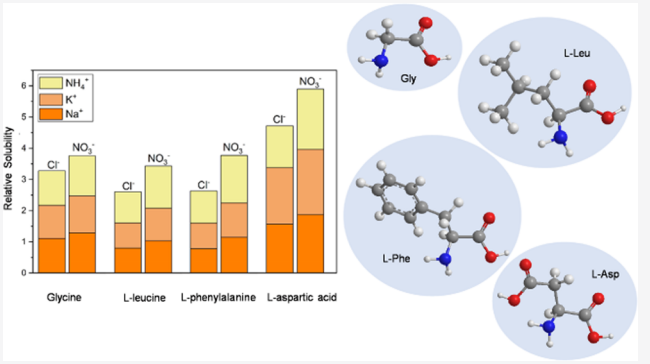
ABSTRACT: The solubilities of glycine, L-leucine, L-phenylalanine, and L-aspartic acid in aqueous solutions of the salts composed by combining Na^+, K^+, and NH_4^+ cations and Cl^- and NO_3^- anions were measured up to 2.0 salt molality at 298.2 K by the analytical gravimetric method. Using these data along with a review of literature information, encompassing all amino acids for which solubility is available in the studied aqueous electrolyte solutions, allowed us to interpret the effect of the functional groups of amino acids on their solubility. The four amino acids studied here showed higher solubility in aqueous solutions of salts with the nitrate anion. Except for L-aspartic acid with a polar side chain, amino acids with apolar side chains presented the highest salting-in effect in aqueous salt solutions with NH_4^+. The cations Na^+ and K^+ did not seem to establish relevant interactions with the amino acids and had little impact on their aqueous solubility.



1. INTRODUCTION

Proteins are complex molecules that exist in cells, acting as enzymes, hormones, transporters, and muscle fibers and playing essential roles in many biochemical processes. Proteins are also under attention because of their biological and pharmacological properties, helping to treat diseases like diabetes, cancer, hemophilia, among others.[1−4] Alongside this, knowledge of solubility is vital for extraction, drying, crystallization, or precipitation, usually applied to separate and purify proteins.[1,5] As aqueous electrolyte solutions are the natural environment of many biomolecules, it is also important to improve the understanding of the behavior of those organic compounds in this environment. Amino acids (AAs) can be used as model compounds (MCs), aiming to provide insights into the behavior of larger macromolecules. In this way, the direct study of the more complex protein/salt solutions is avoided, which has proven to be more complex due to their size, complex structure, global charge determination, and surface phenomena.

An extensive literature review on the solubility of AAs in electrolyte solutions is presented in Table S1 of the Supporting Information (SI). The AAs and salts studied in this work are highlighted with blue and bold letters and their intersection represents the studied aqueous systems, while the numbers are the references that indicate the aqueous ternary systems already published in the open literature. Table S1 considers all of the systems found in the literature without establishing a quality check or analysis of their consistency. As can be observed, the most studied AAs were glycine (Gly), alanine (Ala), valine (Val), and serine (Ser), and the salts were NaCl (by far), KCl, and $(NH_4)_2SO_4$. Even if relevant data on AA solubility in aqueous electrolyte solutions can be found, the gaps are evident, particularly for aromatic amino acids and for those presenting more than one amino or carboxylic group such as arginine (Arg) or L-aspartic acid (L-Asp). It is also significant that anions in the Hoffmeister series such as carbonate, perchlorate, and thiocyanate are seldom included in this type of study.

In line with the work on the topic being developed in our group,[5−10] this work considers the solubility of L-aspartic acid, L-phenylalanine (L-Phe), glycine, and L-leucine (L-Leu) in an aqueous inorganic solution containing the anions chloride or nitrate and the cations sodium, potassium, or ammonium. The amino acids belong to different categories: Gly and Leu have nonpolar and hydrophobic groups, Phe has nonpolar and

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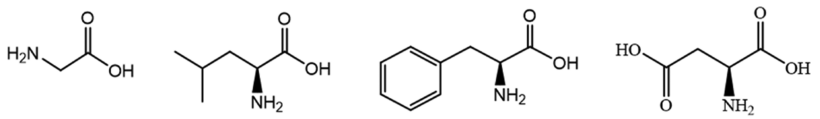

Figure 1. Chemical structure of (a) glycine, (b) L-leucine, (c) L-phenylalanine, and (d) L-aspartic acid.

hydrophobic aromatic side chains, and Asp has a second negatively charged hydrophilic carboxyl group.

From Table S1, a significant contribution is to fill the gaps, where Gly is included as a reference amino acid and NaCl as a reference salt to analyze the consistency of the data among different sources. The chemical structures of the chosen AAs in this work are given in Figure 1 (all other amino acids mentioned in this work are shown in Figure S1 of the Supporting Information).

2. EXPERIMENTAL SECTION

2.1. Chemicals. The source and purity of the used chemicals are given in Table 1. All of the AAs were used without further purification and stored in a desiccator to maintain the AAs dry. The salts were dried in an oven at 343.15 K for at least 24 h and, before use, cooled in the desiccator with silica gel. The solvents were prepared using deionized water (resistivity of 18.2 MΩ·cm, no particles with size of ≥0.22 μm, and total organic carbon < 5 ppb).

Table 1. Chemical Name, Source, CAS, and Mass Fraction Purity of the Compounds

chemicals	supplier	CAS	mass fraction purity
glycine (Gly)	Merck	56-40-6	≥0.997
L-leucine (Leu)	Merck	61-90-5	≥0.990
L-phenylalanine (Phe)	Merck	63-91-2	≥0.990
L-aspartic acid (Asp)	Alfa Aesar	56-84-8	≥0.980
sodium chloride	Fluka	7647-14-5	≥0.995
sodium nitrate	PanReac	7631-99-4	≥0.990
potassium chloride	PanReac	7447-40-7	≥0.995
potassium nitrate	PanReac	7757-79-1	≥0.990
ammonium chloride	PanReac	12125-02-9	≥0.995
ammonium nitrate	PanReac	6484-52-2	≥0.990

2.2. Experimental Procedure. The isothermal shake-flask method combined with the gravimetric analysis was chosen to perform the solubility measurements. The aqueous salt solutions were also prepared at a defined molality by gravimetry. The ternary system was prepared by adding AA (in slight excess to the expected saturation limit) into the equilibrium cell and a known amount of aqueous salt solution. Further, they were placed into the water bath at 298.2 K (± 0.1 K) and mixed with a magnetic stirrer for around 30 h to reach equilibrium. The speed of the mixing was maintained between 500−700 rpm in all of the experiments. Then, the mixing was stopped, and the solutions were left to rest for at least 12 h to precipitate the undissolved particles before sampling. Four samples (approximately 2−3 cm^3) were collected from the saturated ternary system using preheated plastic syringes with syringe filters (0.45 mm). The glass vessels with the samples were immediately weighed (Denver Instrument, ±0.0001 g). The drying followed two steps: first, the vessels were placed in the fume hood to evaporate water. After forming crystals, they were dried using the drying stove at 343.15 K. Before weighing the samples, they were first cooled in the desiccator with silica gel. The process was repeated every week until crystals were

Table 2. Solubilities (g of AA/1000 g of water) of the Amino Acids in Aqueous Solutions of Salts with Different Molalities at 298.2 K (Standard Deviation between Brackets)

		S_{AA} (g of AA/1000 g of water)			
salts	electrolyte molality (mol/kg)	glycine	L-leucine	L-phenylalanine	L-aspartic acid
no salt	0.000	238.332 (0.127)	21.544 (0.070)	28.347 (0.083)	5.140 (0.031)
NaCl	0.500	244.619 (0.874)	20.464 (0.047)	30.192 (0.093)	6.330 (0.178)
	1.000	252.847 (0.452)	19.674 (0.057)	25.783 (0.159)	7.155 (0.274)
	2.000	263.862 (0.229)	17.160 (0.205)	22.198 (0.245)	8.076 (0.122)
$NaNO_3$	0.500	256.830 (0.429)	22.977 (0.094)	30.983 (0.046)	6.452 (0.027)
	1.000	278.033 (0.329)	23.080 (0.088)	32.165 (0.041)	7.613 (0.009)
	2.000	305.871 (0.493)	22.300 (0.158)	32.506 (0.043)	9.607 (0.047)
KCl	0.500	243.174 (0.108)	21.236 (0.177)	28.115 (0.046)	6.343 (0.043)
	1.000	247.229 (0.240)	19.899 (0.048)	26.501 (0.149)	8.045 (0.177)
	2.000	252.281 (0.370)	17.440 (0.145)	23.181 (0.432)	9.318 (0.048)
KNO_3	0.500	253.178 (0.281)	22.894 (0.120)	31.397 (0.084)	6.732 (0.062)
	1.000	265.954 (0.270)	22.615 (0.110)	32.187 (0.155)	7.938 (0.081)
	2.000	284.801 (0.310)	22.588 (0.296)	31.266 (0.185)	10.780 (0.414)
NH_4Cl	0.500	245.097 (0.199)	22.591 (0.034)	29.763 (0.060)	6.002 (0.082)
	1.000	252.599 (0.342)	22.250 (0.093)	29.887 (0.043)	6.777 (0.063)
	2.000	264.662 (0.364)	21.407 (0.061)	29.297 (0.825)	6.871 (0.474)
NH_4NO_3	0.500	256.108 (0.606)	24.545 (0.129)	33.639 (0.206)	6.652 (0.034)
	1.000	274.534 (0.209)	26.586 (0.106)	37.468 (0.087)	7.835 (0.038)
	2.000	305.613 (0.355)	29.014 (0.077)	43.279 (0.108)	9.910 (0.089)

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Table 3. pH Range of Saturated Solutions of L-Aspartic Acid, Glycine, L-Phenylalanine, or L-Leucine in the Studied Aqueous Electrolyte Solutions at 298.2 K

	pH range in the ternary solution					
AAs	NaCl	$NaNO_3$	KCl	KNO_3	NH_4Cl	NH_4NO_3
Gly	5.97[a]−7.17	5.97[a] −6.30	5.97[a]−6.26	5.97[a]−6.33	5.97[a]−6.22	5.97[a]−6.17
Leu	5.77−5.98[a]	5.98[a]−6.09	5.75−5.98[a]	5.83−5.98[a]	5.56−5.98[a]	5.67−5.98[a]
Phe	5.48[a]−6.07	5.48[a]−5.66	5.48[a]−6.25	5.48[a]−5.60	5.42−5.48[a]	5.44−5.48[a]
Asp	2.76−2.77[a]	2.77[a]−2.81	2.77[a]−2.97	2.77[a]−3.11	2.77[a]−3.02	2.77[a]−3.18

[a]pH of the binary (amino acid + water) saturated solution.[13]

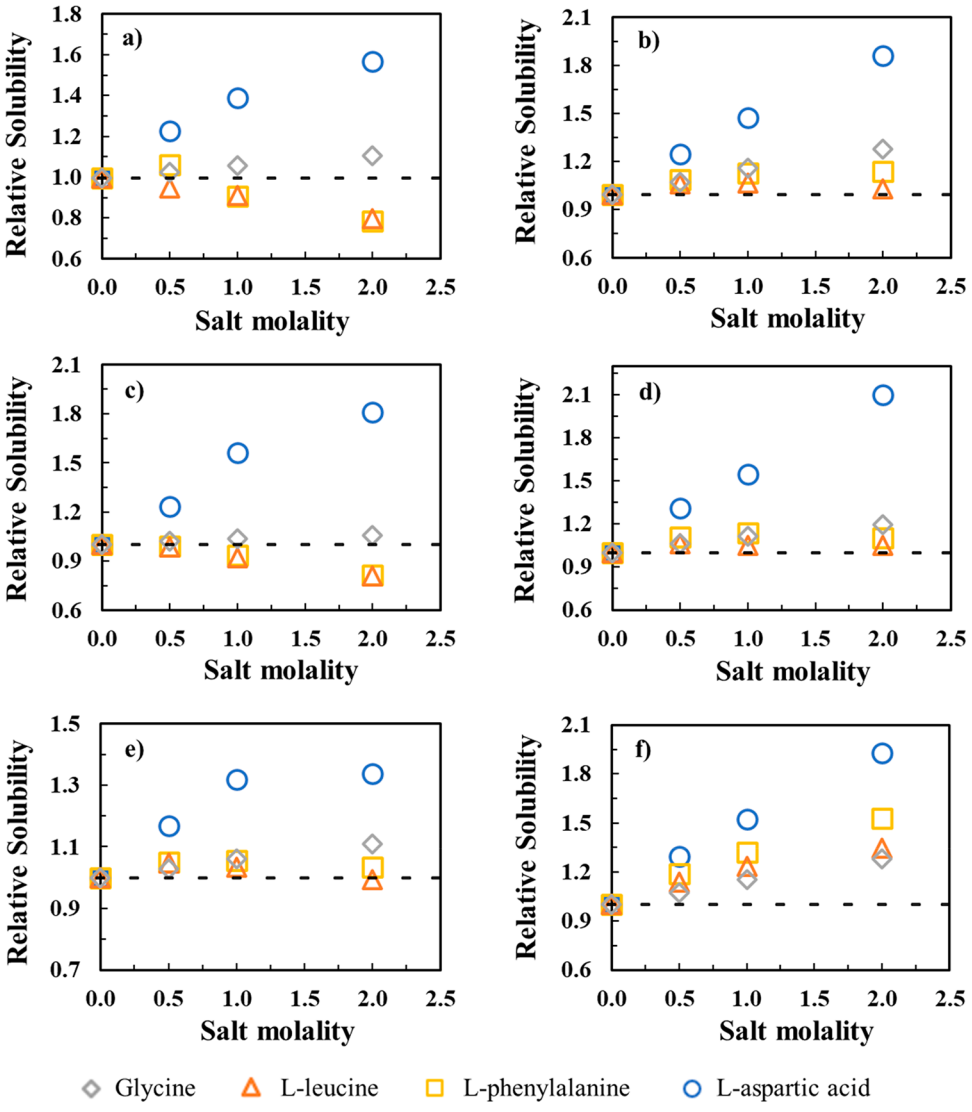

Figure 2. Relative solubility of glycine, L-leucine, L-phenylalanine, L-aspartic acid in aqueous (a) NaCl, (b) $NaNO_3$, (c) KCl, (d) KNO_3, (e) NH_4Cl, and (f) NH_4NO_3 solutions with different molalities at 298.2 K.

dried entirely, and a constant mass value was achieved. Each solubility value is an average of at least four different measurements.[6] A pH meter (WTW inoLab pH Level 1) and pH electrode (WTW SenTix 41) were used to measure the pH of solutions after each measurement, previously calibrated, at 298.2 K, and the estimated uncertainty is 0.05.

2.3. Solid-Phase Studies. The pure solid compounds as received from the supplier as well as solids settled in equilibrium with the saturated solution, after vacuum filtration and drying, were analyzed by powder and single-crystal X-ray diffraction.

Powder X-ray powder diffraction (XRD) data were collected on a X'Pert MPD Philips diffractometer, using Cu-Kα radiation (λ = 1.5406 Å), with a curved graphite monochromator, a set incident area of 10 mm^2, and a flat plate sample holder, in a Bragg−Brentano para-focusing optics configuration. Intensity data were collected by the step counting method (step 0.02° and time 5 s) in the range 5° < 2θ < 50°.

The cell parameters of suitable crystals of selected L-aspartic acid, L-phenylalanine, glycine, and L-leucine from the supplier, as well the samples obtained after crystallization with the different salts, were determined using a Bruker D8 QUEST

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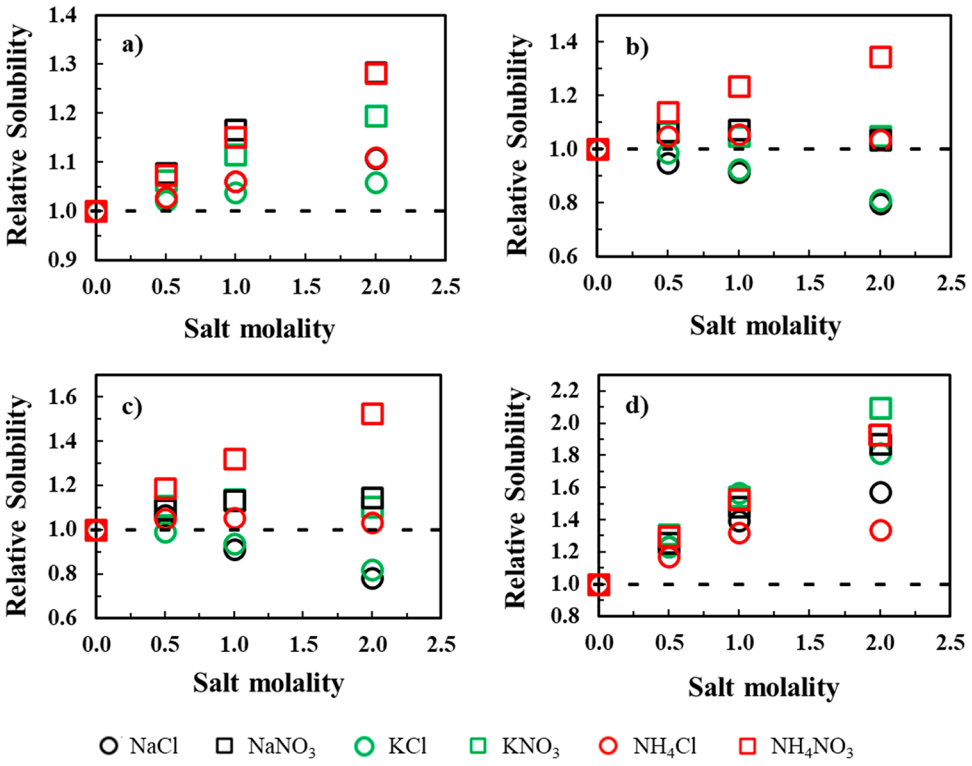

Figure 3. Relative solubility of (a) glycine, (b) L-leucine, (c) L-phenylalanine, and (d) L-aspartic acid in aqueous salt solutions with different molalities at 298.2 K.

diffractometer equipped with a Photon 100 area detector with monochromated Mo Kα radiation (λ = 0.71073 Å) and operating at 150(2) K. The selected crystals analyzed were placed at 40 mm from the photon 100 detector, and the spots were measured using different counting times (varying from 5 to 30 s).

3. RESULTS AND DISCUSSION

3.1. Experimental Data and Analysis. The solubilities of L-aspartic acid, L-phenylalanine, L-leucine, and glycine in the aqueous NaCl, $NaNO_3$, KCl, KNO_3, NH_4Cl, and NH_4NO_3 solutions with various salt molalities at 298.2 K are given in Table 2. The maximum coefficient of variation (standard deviation/average × 100) was 6.9% (system water/ammonium chloride/aspartic acid, 2 mol·kg^{-1} salt concentration), being lower than 1% in about 80% of cases.

Besides solubility, the pH of the saturated solutions was also measured at 298.2 K and is reported in Table 3. It is possible to conclude that all amino acids are in the zwitterionic form (dipolar ions) in the saturated solutions, as can be confirmed in the ChemSpider platform.[11,12]

The solid-phase studies are a strategy to examine any eventual changes in the crystallographic form of the amino acids that might impact the salting effects. First, the solids from the supplier were analyzed by single-crystal and powder X-ray diffraction. Glycine from the supplier presents a mixture of two phases: a monoclinic corresponding to the α-form and a hexagonal corresponding to γ-form (Figure S5), both already described in the literature. All of the other amino acids from the supplier show a single phase and are also well characterized in the literature. Table S2 of the SI presents the structure, cell parameters, CCDC code, and references relative to the crystal forms found. In all aqueous solutions of the six electrolytes, the glycine samples (Figure S6) crystallized only in the hexagonal crystal system, the γ-form. The crystalline form of the other amino acids (Figures S7−S9) investigated in some of the electrolyte solutions did not change compared to the structure found in the original solid from the supplier.

The absolute solubility values in all aqueous systems follow the rank Gly > Phe > Leu > Asp, which matches the solubility in pure water. Figure 2 shows the relative solubilities (ratio between the solubility of AA, expressed as the mass of the amino acid in 1 kg of water in aqueous salt solutions to that in pure water) of all of the studied AAs in different aqueous salt solutions at 298.2 K. The results show the relevance of the AA structural features (Figure 1). L-Aspartic acid, the most polar, shows a salting-in effect in all of the salt solutions. Leu, the most apolar hydrophobic AA in this study, generally presents the weakest salting-in effect or a salting-out effect, even if in most of the salt solutions, a very similar behavior is observed between Leu and Phe. The relative solubilities in all of the aqueous salt solutions follow the order Asp > Gly > Phe ≅ Leu, except the ammonium nitrate solution, where the ranking is Asp > Phe > Leu > Gly. Potassium chloride induces a salting-out effect over the whole salt concentration range in the solutions with Phe and Leu. The presence of sodium chloride leads to a salting-out effect in the solution with Leu. Besides, the addition of $NaNO_3$ causes an increase in the solubility of Phe. In all other cases, the solubility varies nonmonotonically with salt molality.

The effect of each salt on the relative solubility of the studied amino acids is shown in Figure 3. The solubilities of all of the AAs in aqueous salt solutions, with the nitrate anion, are higher than those in the solutions containing chloride anions (for the same cation). This is supported by the molecular dynamics simulations reported by Tomé et al.[8] It was concluded that the

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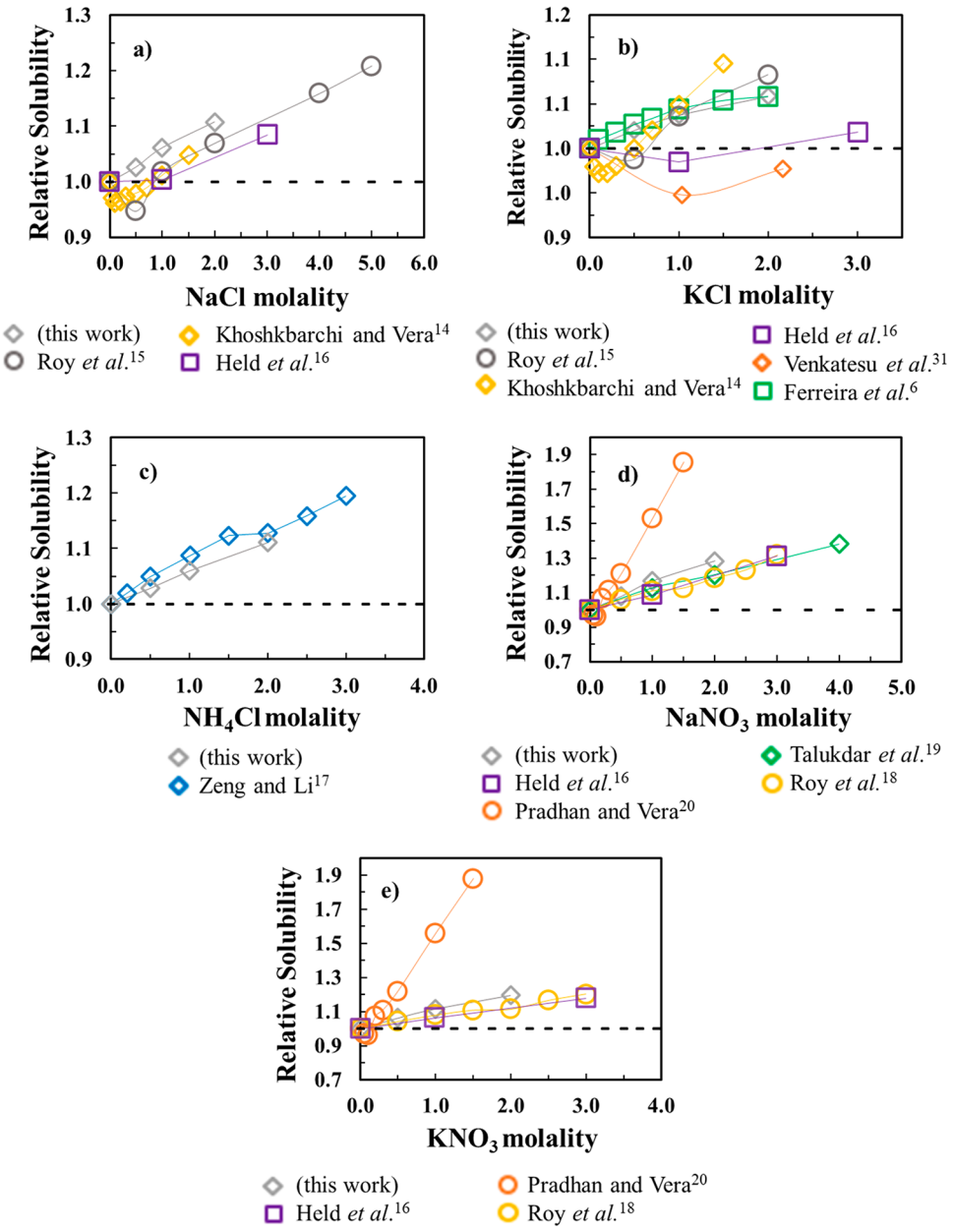

Figure 4. Relative solubility of glycine in aqueous salt solutions at 298.2 K. Lines are a guide to the eyes.

Cl^- anion has a much lower effect on the solubility of AAs and that it does not interact with the apolar groups of AAs. Considering the NO_3^- anion, it interacts more significantly with the hydrophobic groups of the AAs and thus contributes to increase the AA solubility. The effect of cations on the solubility of AAs was also studied in another work by the same author.[9] It was observed that monovalent cations, and particularly alkali cations, do not interact with the hydrophobic groups, and unlike the divalent cations, which interact strongly with the carboxylate groups of the AAs, for the monovalent cations, this binding is less favorable. The ammonium cation shows stronger interaction (through a combination of ion-induced dipole and dispersion interactions, promoting stabilization of the amino acids in water) than the sodium and potassium ions. It is worth mentioning that only for Asp, which presents two carboxylate groups, the ammonium nitrate salt does not present the highest salting-in effect compared to the nitrate salts of the alkali cations. The relative solubility of Phe and Leu follows the same order NH_4NO_3 > KNO_3 ≈ $NaNO_3$ ≈ NH_4Cl > KCl ≈ NaCl (evaluated at 2 molal). The relative solubility of Gly in the aqueous salt solutions with the nitrate and chloride anions follow the same ranking K^+ > NH_4^+ > Na^+, while for Asp, the order is found as KNO_3 > NH_4NO_3 ≈ $NaNO_3$ ≈ KCl > NaCl > NH_4Cl (evaluated at 2 molal).

As shown in Table S1, Gly is the most studied AA. For certain aqueous electrolyte solvents, there are even AA solubility data from different researchers, allowing us to check the reliability of the data measured in this work. The solubility data of Gly in aqueous KCl solution obtained in this work are consistent (Figure 4b) with the data of Ferreira et al.,[6] who checked their different results to those by Khoshkbarchi and Vera,[14] proving the reliability of their data recurring to experimental and theoretical approaches, and are also in agreement with Roy et al.[15] The results of Held et al.[16] are different from the results of this work. Similar differences were observed when the results in aqueous NaCl solutions

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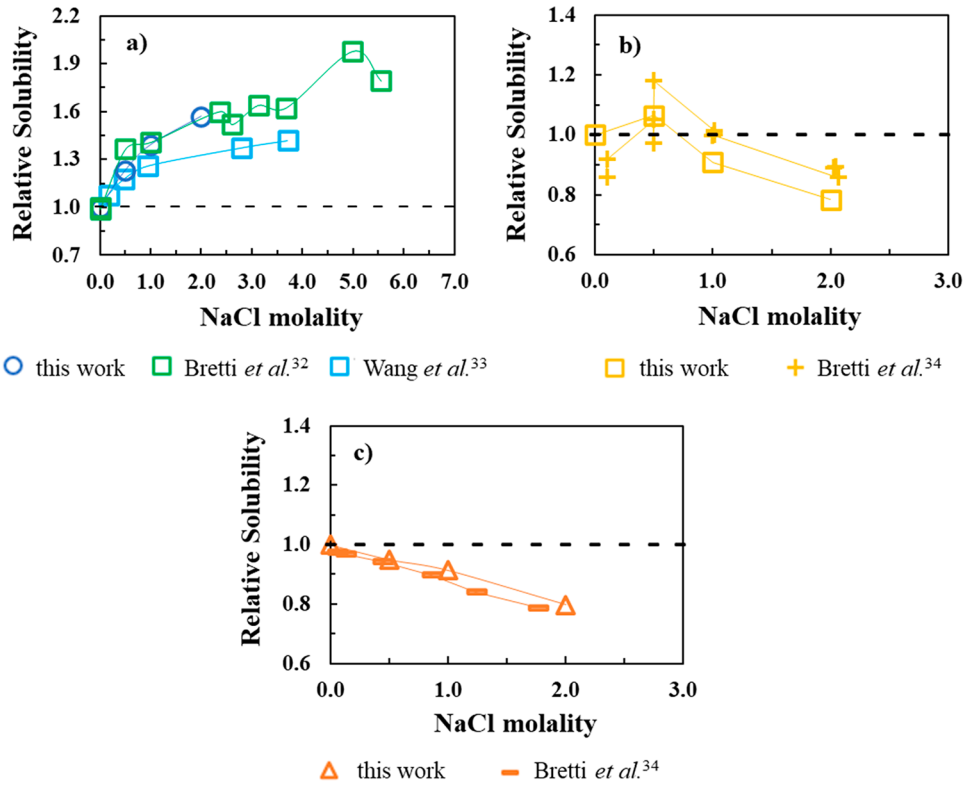

Figure 5. Relative solubility of a) L-aspartic acid, b) L-phenylalanine, and c) L-leucine in aqueous NaCl solutions at 298.2 K. Lines are a guide to the eyes.

were compared (Figure 4a), particularly the small salting-out effect at low salt molalities that was not observed in this work. The only work found with solubility data of Gly in aqueous NH_4Cl solution was the work by Zeng and Li,[17] in which the results were similar to the results from this work. Concerning the nitrate salts (Figure 4d,e), the relative solubility of Gly in aqueous $NaNO_3$ and KNO_3 solutions from this work is close to the data from Roy et al.,[18] Held et al.,[16] or Talukdar et al.[19] but quite different from Pradhan and Vera,[20] which shows much higher solubilities. The reason can be related to a particular detail of their experimental procedure; Pradhan and Vera dried their samples in the oven for 48 h, just at 308 K, and then weighed them, which most certainly was not enough to remove all water retained by the AA and salt crystals. It is worth mentioning that there are also other factors affecting solubility in this kind of study. Gly polymorphism is well known,[21−23] and the polymorph transformation of Gly in an aqueous solution can often occur.[24−28] For instance, Yang et al.[27] studied the transformation of the α-form to the γ-form, which occurs after 20 h. The presence of salts, as well as stirring speed, temperature, time, and pH clearly affect the transformation rate. Kitamura[29] developed important studies about strategies to control the crystallization of polymorphs, where these factors are also mentioned. Unfortunately, the solubility of Gly in NH_4NO_3 was presented just in one work[30] and not at 298.2 K. For some systems, not all solubility data found in the literature could be included due to the impossibility of accurately converting data from the units presented in these studies to those used here. For clarity, the relative solubility of glycine[15,31] in aqueous KCl solutions is not shown after a 3 molal concentration.

As can be observed from Table S1, for L-aspartic acid, not many solubility measurements were reported so far. Therefore, the results could be compared only in aqueous NaCl solutions, as presented in Figure 5a. Our data are very similar to Bretti et al.[32] and slightly higher than Wang et al.[33] at higher molalities. However, as the solubility studies in aqueous KCl solution were carried out only for the D-isomer of this AA,[33] no comparison could be provided. For Phe or Leu, data were also found in aqueous NaCl solutions.[34] A very good agreement is observed for Leu (Figure 5c) as well as for Phe (Figure 5b). However, in their work, Bretti et al.[34] indicate that the L-phenylalanine solubility in water at 298.15 K is 13.6 g/1000 g of water, while the literature values range from 25.2 to 30.6 g/1000 g of water.

3.2. Ion Effects on AA Solubility. Considering all of the experimental solubility data from this work and the literature, a set of patterns can be identified. To carry out this analysis, the information available was first divided into salts containing the monovalent K^+, Na^+, or NH_4^+ cations and evaluating the effect of the anions, since the impact of these cations on the solubility is minor compared to the anions. As shown in Figure 6 (the same color indicates the same anion, and it is limited to 3.0 salt molality for better reading), all salts induce a mild salting-in impact on Gly, except for KCH_3COO. This anion is a salting-out agent in the list of salts in the Hofmeister series. The effect of the studied salts is seen in a narrow range of the relative solubility of Gly, and some differences are most probably within the experimental error but give at least a qualitative view. For many salt aqueous solutions, more than one independent set of data are available, but not all were included as a consistency analysis was first carried out for a reliable interpretation (in SI3, this consistency analysis is briefly discussed). In addition, the results of some works could not be included as they were found in different units, or the solubility measurements were not provided at 298.2 K, or

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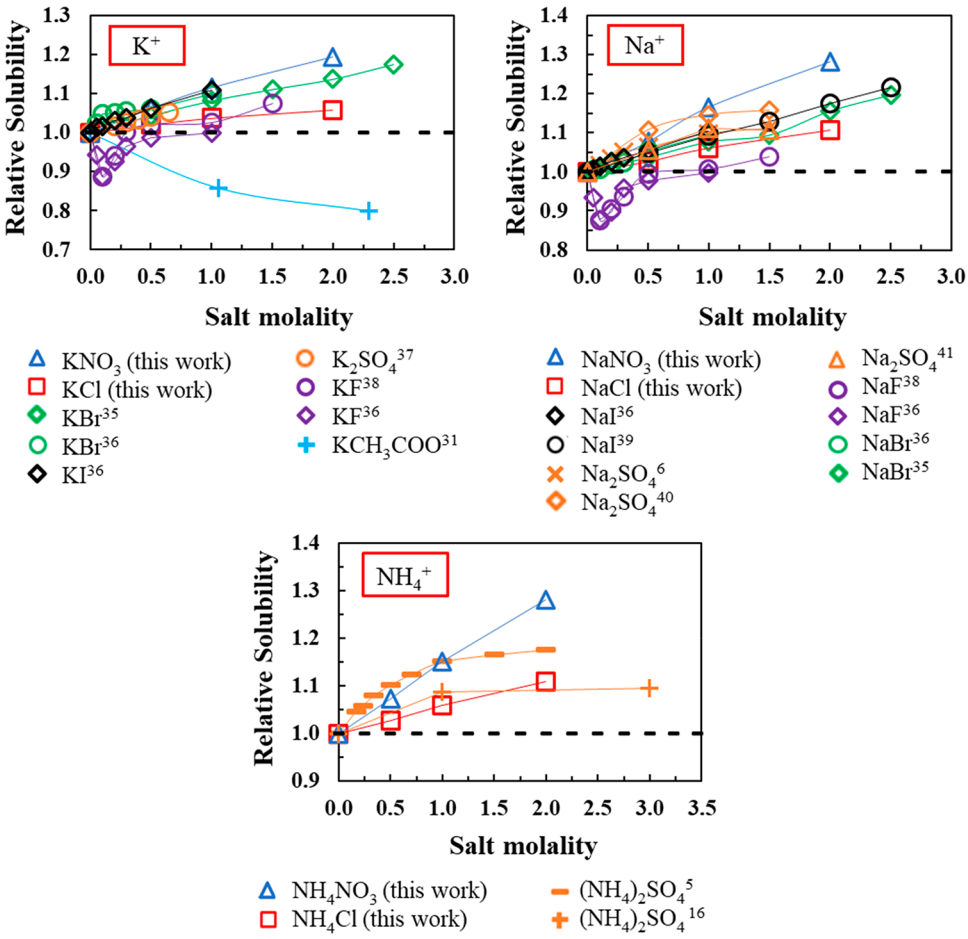

Figure 6. Ion effects on the relative solubility of glycine in aqueous salt solutions containing the K^+, Na^+, and NH_4^+ cations at 298.2 K. Lines are a guide to the eyes.

another isomer was studied. On the other hand, only the data measured here (and compared in Figure 4) were included for the salts studied experimentally in this work. It can be concluded that in the case of glycine, the salts with the nitrate anion present the highest salting-in effect (evaluated above 1 molal), followed by sulfate, iodide, bromide, chloride, and fluoride anions.

For alanine, the diversity of experimental data published is also significant, allowing us to see the effect of the additional methyl group in the amino acid side chain compared to Gly (the structures of all amino acids focused in this work are presented in Figure S1 of the Supporting Information). Figure 7 shows the relative solubility of DL-alanine in aqueous salt solutions with Na^+, K^+, or NH_4^+ cations. In comparison with Gly, the relative solubility of DL-alanine is lower in most of the aqueous electrolyte solutions, and a salting-out effect is observed, confirming the molecular dynamics results showing that the monovalent cations do not interact with hydrophobic moieties of the AAs. This change to Gly was more noticeable when DL-alanine was dissolved in aqueous KCl, NaCl, Na_2SO_4, NaF, $(NH_4)_2SO_4$, and K_2SO_4 solutions. Considering molecular dynamics studies,[8] it was found that SO_4^{2-} can interact only with small amino acids like glycine inducing the salting-in effect, while it does not interact with large nonpolar moieties and therefore shows a salting-out effect, also supporting the experimental observations. Consistent with glycine, the salts with the nitrate anions presented the highest salting-in effect (evaluated at 1.5 molal). Even if two independent and consistent sets of data are available, the salting-in magnitude seems too large, raising some doubts on the data quality. After nitrate, the ranking follows iodide ≈ bromide, chloride, and sulfate anions.

The relative solubility of DL-alanine is higher in aqueous salt solutions with the bromide and iodide anions compared to glycine. Moreover, the salts with the fluoride anion induce a different effect on the solubility of DL-alanine, a salting-in effect with the potassium cation, and a salting-out effect with the sodium cation. These differences with the potassium and sodium cations, and halogens, also open some questions about the quality of the results, emphasizing the need to have a structural analysis of the solid phase, identifying the AA crystallographic form in the electrolyte solutions, and performing a comparison to the original form of the supplier. The solubility of DL-alanine in the salt solutions with the ammonium cations is much less studied. In solutions of ammonium chloride or ammonium sulfate, the relative solubility is lower than that for glycine. At higher molalities, the sulfate anion induces a salting-out effect with DL-alanine, confirming the trend mentioned before.

The same type of analysis has been attempted for valine. However, some sets of published data (referenced in Table S1) do not follow the expected trends. Where sometimes a very mild salting-in effect is expected, a strong effect stands out. In aqueous Na_2SO_4 solutions, all of the AAs, except glycine

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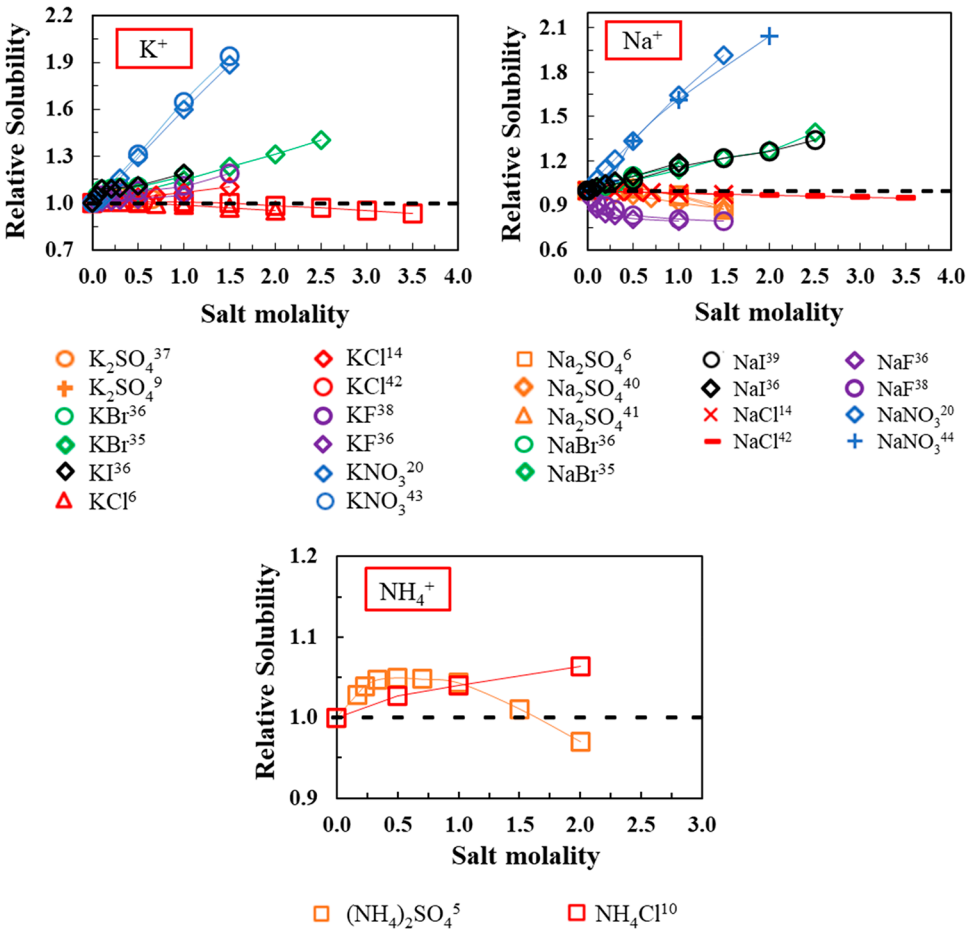

Figure 7. Ion effects on the relative solubility of DL-alanine in aqueous salt solutions containing the K^+, Na^+, and NH_4^+ cations at 298.2 K. Lines are a guide to the eyes.

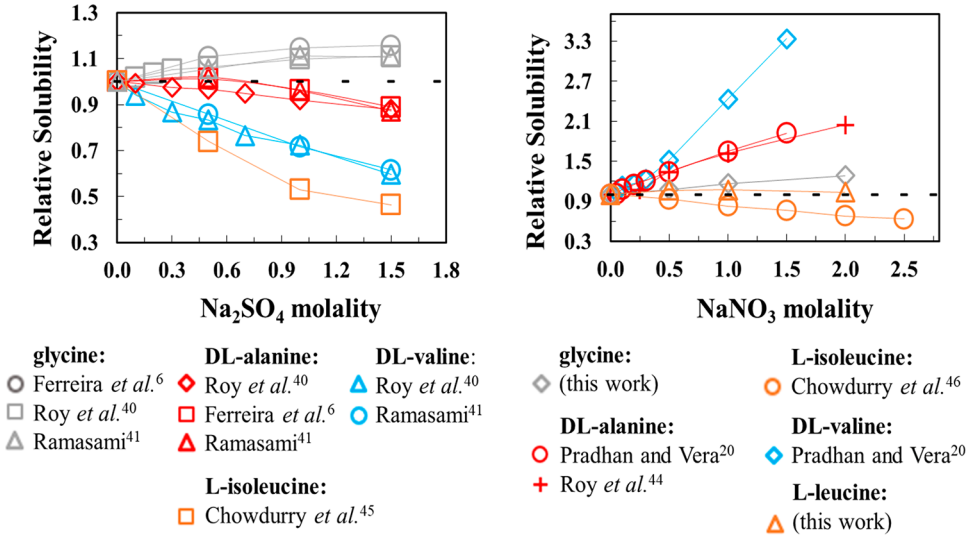

Figure 8. Relative solubility of glycine, DL-alanine, DL-valine, L-isoleucine and L-leucine in aqueous Na_2SO_4 and $NaNO_3$ solutions. Lines are a guide to the eyes.

(Figure 8), show a salting-out effect, and the ranking is DL-alanine < DL-valine < L-isoleucine (L-Ile), which is in agreement with the expected order, also derived from molecular dynamics studies. In the case of $NaNO_3$ solutions, even if nitrate has a more salting-in character than sulfate, DL-valine and DL-alanine systems show a salting-in effect that seems too intense. The rank is DL-valine > DL-alanine > glycine > L-leucine > L-isoleucine, which is not consistent as DL-valine and DL-alanine are AAs with larger apolar groups than glycine, and it would be expected to have valine positioned somewhere in the middle between alanine and leucine, as the size of the hydrocarbon chain is the main effect on the solubility change. This analysis

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sheds some light on the importance of checking the data consistency before drawing general rules, concerning the impact of the different anions on AA solubility. The quality of the experimental information available seems, in some cases, not good enough to support heuristic rules.

3.3. Effect of the AA Structure. For a given salt, its impact on the AA solubility can be explored in terms of the structural features of AA. Figure 9 illustrates the relative

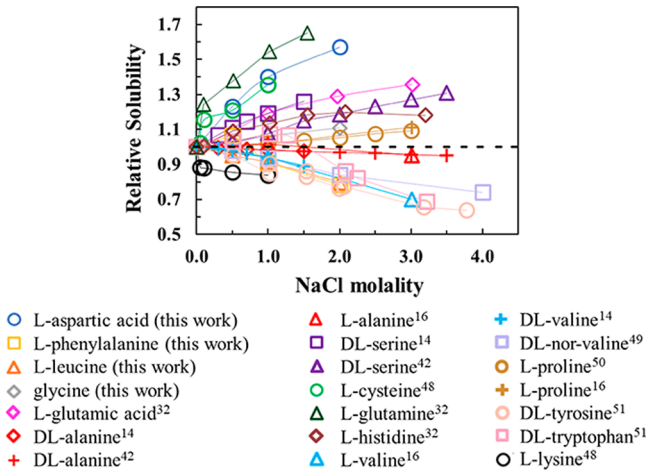

Figure 9. Relative solubility of different AAs in aqueous NaCl solution at 298.2 K. Lines are a guide to the eyes.

solubility of different AAs in aqueous NaCl solutions (by far, the most studied aqueous salt solution), highlighting the relevance of the functional group on the relative solubility change. The AA showing the highest salting-in effect is L-glutamine (L-Gln), whose structure is similar to glutamic acid (Glu), where one −COOH group is replaced by an amide group. The presence of these two −COOH groups in L-aspartic acid contributes to the high salting-in effect, while L-glutamic acid,[32] with an additional CH_2 group, still presents an evident salting-in effect but with a smaller magnitude.[24] Between these two AAs, the polar hydrophilic −OH group of DL-serine increases the polarity of the hydrocarbon backbone, increasing its solubility,[47] while the relative solubility of L-cysteine (L-Cys) is higher than DL-serine. L-cysteine possesses an −SH group, probably contributing greatly to the salting-in magnitude, and it has been proven that in aqueous salt solutions, L-cysteine forms soluble complexes with the salts inducing the salting-in effect.[48] Next to serine is histidine (His), a basic AA, which has an imidazole side chain. Glycine, the simplest AA, and L-proline (L-Pro), which has a cyclic structure with the NH group in the cycle, show almost no salting-in effect, and DL- and L-alanine show the smallest salting-out effect. The addition of successive CH_2 groups to alanine induces stronger salting-out effect in DL- and L-valine, DL-nor-valine (DL-Nva), and L-leucine. L-phenylalanine, an aromatic AA, shows a hybrid behavior. Though L-lysine (L-Lys) has an additional amino group, it also contains the longer alkyl side chain, conferring a more hydrophobic character to the structure, resulting in the highest salting-out effect. Finally, although DL-tryptophan (DL-Trp) has a polar NH group in its cyclic structure and DL-tyrosine (DL-Tyr) has a polar OH group, they present large aromatic hydrophobic groups in their structures, thus being salted-out in aqueous NaCl solution, with DL-tryptophan showing a hybrid behavior.

The solubility dependence of AAs in the aqueous KCl solutions can be observed in Figure 10. In good agreement

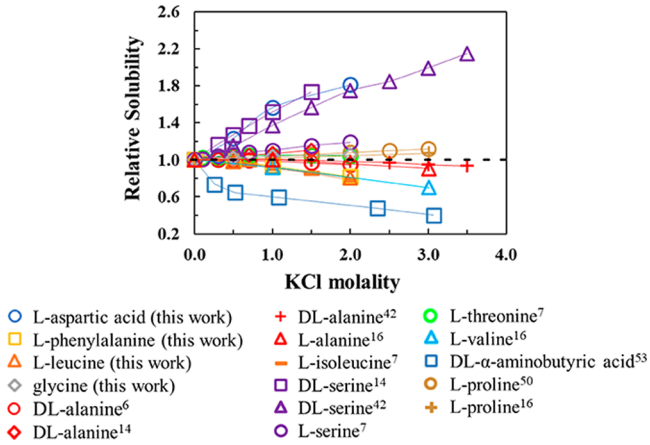

Figure 10. Relative solubility of different AAs in aqueous KCl solution at 298.2 K. Lines are a guide to the eyes.

with the NaCl analysis, L-aspartic acid presents the highest salting-in effect, glycine and L-proline present a very weak salting-in effect, DL and L-alanine present a very slight salting-out effect, L-valine, L-phenylalanine, and L-leucine also show a salting-out effect. For the same reasons as expressed in Figures 8 and 9, the data available for DL-valine[14] and DL-nor-valine[49] or L-glutamic acid[52] were not considered in the discussion. The very similar results obtained for DL-serine by Khoskhbarchi and Vera[14] and Roy et al.[42] indicate a much stronger salting-in behavior in KCl solutions if compared to NaCl solutions, raising some doubts not only from the fundamental interpretation derived from the physical chemistry of the solutions and molecular simulation but also because for L-serine, Ferreira et al.[7] found a salting-in effect of the same dimension as the same author found for DL-serine in aqueous NaCl solutions. Compared to serine, threonine (Thr) has an additional aliphatic CH_3 group, which causes a very relevant reduction in the salting-in effect observed in serine. DL-α-aminobutyric acid (DL-α-Abu) is the AA presenting the highest salting-out effect, unexpectedly stronger then L-leucine.

Figure 11 shows the relative solubility in aqueous $NaNO_3$ solutions at 298.2 K. Except DL-nor-valine and L-proline, which, in these aqueous solutions, show similar salting magnitude as

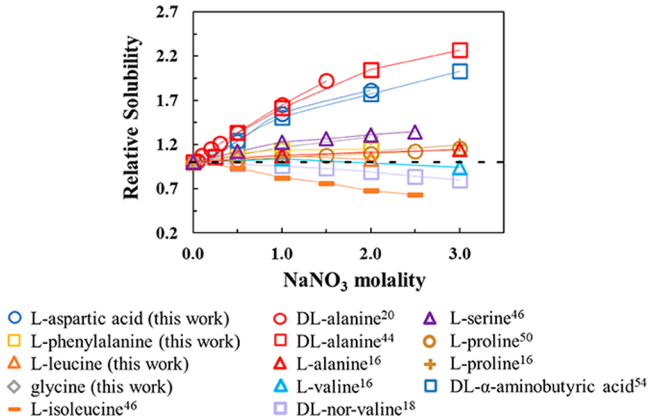

Figure 11. Relative solubility of different AAs in aqueous $NaNO_3$ solution at 298.2 K. Lines are a guide to the eyes.

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in the chloride salt solutions, an increase in the relative solubility was observed for all other amino acids, confirming the higher salting-in character of the nitrate anion in comparison to chloride. The results show a massive increase in the relative solubility of DL-alanine, which is too large in comparison with the L-isomer. The same was observed in the case of the serine isomers (Figure S4), and only the data of L-serine are left in Figure 11. Considering the results of L-isomers, it can be concluded that after aspartic acid, the AA with the highest salting-in effect is L-serine. With the addition of methyl groups to glycine, the relative solubilities of AAs with larger apolar groups decrease, and it follows: Gly > L-Ala > L-Val ≈ L-Leu > DL-nor-Val > L-Ile. DL-α-aminobutyric acid, which has one more methyl group than alanine, seems to be in the right place compared to the results of alanine but, like in KCl aqueous solutions, show an unexpected salting magnitude considering the results of other nonpolar aliphatic AAs. L-Phe with an aromatic group showed the highest salting-in effect among the AAs with apolar groups.

The dependence of the relative solubilities of AAs on the molality of aqueous KNO_3 solution is shown in Figure 12. The

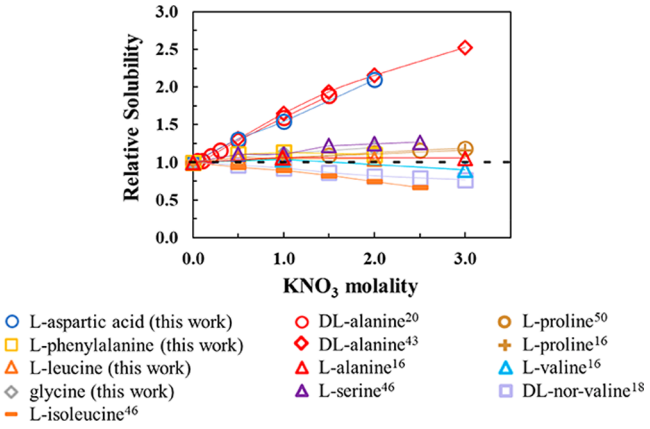

Figure 12. Relative solubility of different AAs in aqueous KNO_3 solution at 298.2 K. Lines are a guide to the eyes.

similarities found with the $NaNO_3$ solutions again reaffirm how monovalent cations do not significantly affect the solubility of the amino acids. In both solutions with the nitrate anion, all of the AAs with polar and apolar functional groups follow the same order with very similar magnitudes. Compared to KCl, the relative solubilities of all of the AAs increased, and even alanine, leucine, and phenylalanine, which suffer salting-out in solutions with the chloride anions, show slight salting-in results in these nitrate solutions.

The available data for glycine, DL-alanine, DL-serine, DL-valine, and L-isoleucine, shown in Figure S10 of the supporting information, confirm the difficulty to establish, with enough confidence, a rationale about the effect when changing the cation while fixing the anion (NaF/KF) or the opposite (NaF/NaBr).

4. CONCLUSIONS

The study of the solubility of L-aspartic acid, L-phenylalanine, glycine, and L-leucine in aqueous NaCl, KCl, NH_4Cl, $NaNO_3$, KNO_3, and NH_4NO_3 solutions at 298.2 K was carried out between 0 and 2 mol/kg. For the systems measured in this work, the critical analysis showed, generally, very high consistency with data from the literature. Except for NH_4NO_3, the relative solubility followed the order Asp > Gly > Phe ≥ Leu, while the observed salting-in effect in aqueous NH_4NO_3 solution was as follows Asp > Phe > Leu > Gly. In accordance with the position of the anions in the Hoffmeister series, the nitrate salt shows higher salting-in effects. Evaluated at 2 molal, the relative solubility of Phe and Leu follows the same order NH_4NO_3 > KNO_3 ≈ $NaNO_3$ ≈ NH_4Cl > KCl ≈ NaCl. For glycine, the relative solubility in the aqueous salt solutions with the nitrate and chloride anions follows the same ranking K^+ > NH_4^+ > Na^+, while for Asp, the order found is KNO_3 > NH_4NO_3 ≈ $NaNO_3$ ≈ KCl > NaCl > NH_4Cl. This ranking also shows that for these monovalent cations, ammonium induces the highest salting-in effect for apolar aliphatic AA while it is worse for acidic AAs such as aspartic acid.

To establish patterns on the effect of the anion and specific structural features of the AA, an extensive database on the solubility of amino acids in aqueous electrolyte solutions has been constituted. The collected data, some very recent, show important differences and inconsistencies, suggesting that editorial policies to check data need to be improved in some journals. It is also strongly recommended that the solid-phase analysis (e.g., X-ray diffraction) of the original AA and the AA settled in the saturated solutions is included to identify eventual crystal structure changes during the solid−liquid equilibrium measurements.

Considering the effect of anions on the solubility of glycine and alanine, when combined with the monovalent cations Na^+, K^+, and NH_4^+, generally, the Hoffmeister series is verified. Acetate is a strong salting-out agent, while nitrate anion presents the highest salting-in effect, followed by iodide, bromide, chloride, and fluoride anions. A major difference is observed with the sulfate anion, which is a salting-in agent to glycine and a salting-out agent for AA when the alkyl-chain length increases, as also explained by molecular dynamics.

Finally, analyzing the effects of NaCl and KCl in a wide variety of AAs, their maximum salting-in effect is observed over acidic AA, followed by polar and neutral AAs such as serine and cysteine. Concerning the salting-out effect, it is not only maximum over basic AA such as lysine but also in apolar aliphatic AA with large alkyl chains. In both salts, glycine, the cyclic proline, and alanine present the least significant salting-in/out effect. Generally, $NaNO_3$ and KNO_3 salts induce the salting-in effect in all AAs but follow a ranking quite similar to the chloride salts, with the smallest effects being observed for AAs such as glycine, proline, and phenylalanine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.iecr.1c04562.

Literature review on the salting effect on the AA solubility in aqueous salt solutions (SI1); chemical structures of amino acids listed in this work (SI2); consistency analysis of the solubility data (SI3); solid-phase studies (SI4); solubility of different AAs in the same salt solutions (SI5) (PDF)

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Notes

The authors declare no competing financial interest.

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