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Supporting Information

Using coarse-grained molecular dynamics to rationalize biomolecule solubilization mechanisms in ionic liquid-based colloidal systems

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Table S1. QAILS-GA aqueous solutions considered in this work.[a,b]

Simulation	Systems	[QAILS] (wt %)	[GA] (wt %)	GA net charge	PW	Na	Time (µs)	AN
1	$[N_{1,1,1,14}]$Cl control	10.02	-	-	23250	-	1	38
2	$[N_{1,1,1,14}]$Cl + Prot. GA	9.99	0.29	0	23250	-	0.5	28
3	$[N_{1,1,1,14}]$Cl + Deprot. (-1) GA	10.01	0.29	-1	23150	25	0.5	29
4	$[N_{1,1,1,14}]$Cl + Deprot. GA (-3)	10.00	0.28	-3	23050	75	0.5	33
5	$[N_{1,1,1,14}]$Cl + Prot. GA	9.79	2.28	0	23250	-	1	45
6	$[N_{1,1,1,14}]$Cl + Deprot. (-1) GA	9.66	2.24	-1	23150	200	1	56
7	$[N_{1,1,1,14}]$Cl + Deprot. (-3) GA	9.37	2.13	-3	23050	600	1	56
8	$[N_{4,4,4,14}]$Cl control	10.02	-	-	33750	-	1	45
9	$[N_{4,4,4,14}]$Cl + Prot. GA	10.00	0.20	0	33750	-	1	100
10	$[N_{4,4,4,14}]$Cl + Deprot. (-1) GA	10.01	0.20	-1	33650	25	1	63
11	$[N_{4,4,4,14}]$Cl + Deprot. (-3) GA	10.08	0.20	-3	33250	75	1	125
12	$[N_{4,4,4,14}]$Cl + Prot. GA	9.86	1.60	0	33750	-	1	71
13	$[N_{4,4,4,14}]$Cl + Deprot. (-1) GA	9.76	1.58	-1	33650	200	1	-
14	$[N_{4,4,4,14}]$Cl + Deprot. (-3) GA	9.63	1.53	-3	33250	600	1	-
15	$[N_{4,4,4,4}]$Cl control	10.05	-	-	22000	-	1.5	-
16	$[N_{4,4,4,4}]$Cl + Prot. GA	10.02	0.31	0	22000	-	1.5	-
17	$[N_{4,4,4,4}]$Cl + Deprot. (-1) GA	10.00	0.30	-1	22000	25	2.1	-

18	[$N_{4,4,4,4}$]Cl + Deprot. (-3) GA	9.95	0.30	-3	22000	75	1.5	-
19	[$N_{4,4,4,4}$]Cl + Prot. GA	9.81	2.40	0	22000	-	1.5	-
20	[$N_{4,4,4,4}$]Cl + Deprot. (-1) GA	9.64	2.35	-1	22000	200	1.5	-
21	[$N_{4,4,4,4}$]Cl + Deprot. (-3) GA	9.30	2.22	-3	22000	600	1.5	-

[a] All systems contain 25 GA molecules for the first set of three runs (for example 2-4), and 200 for the higher concentration set (for example 5-7). PW and Na correspond to the number of beads used.

[b] Systems 1,8 and 15 (shaded) are used as controls for analysis and are composed by the QAILS and PW, in similar conditions as the ones containing GA.

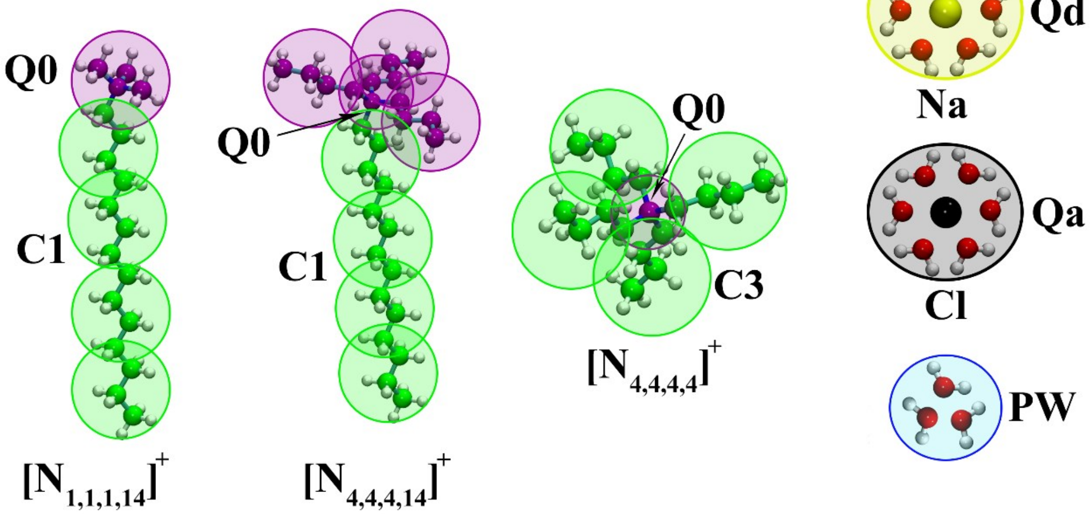

Figure S1. Coarse-grain mapping scheme for $[N_{1,1,1,14}]^+$ and $[N_{4,4,4,14}]^+$ and $[N_{4,4,4,4}]^+$ QAILS cations, chloride and sodium ions (surrounded by six implicit water molecules) and water. Each bead label corresponds to the type according to the MARTINI model framework.

A. Validation of a novel GA-CG model

A detailed GA-CG model for the three different ionization states were carefully developed. The partial charges calculated for the GA-AA versions in both ionization states are depicted in **Figure S2**. The partial charges were obtained using CHELPG in vacuum with the B3LYP / 6-311+G(d,p) level of theory. The electronic density was also shown to highlight the charge density of each region (**Figure S3**). The CG validation was carried out for Prot. GA and Deprot. GA (-1) GA versions to cover the different ionization states representing realistic GA aqueous solutions. The RDF profiles and SDF images were used to compare hydration of GA in both, the AA and CG level, as shown in **Figures S4** and **S5**, respectively.

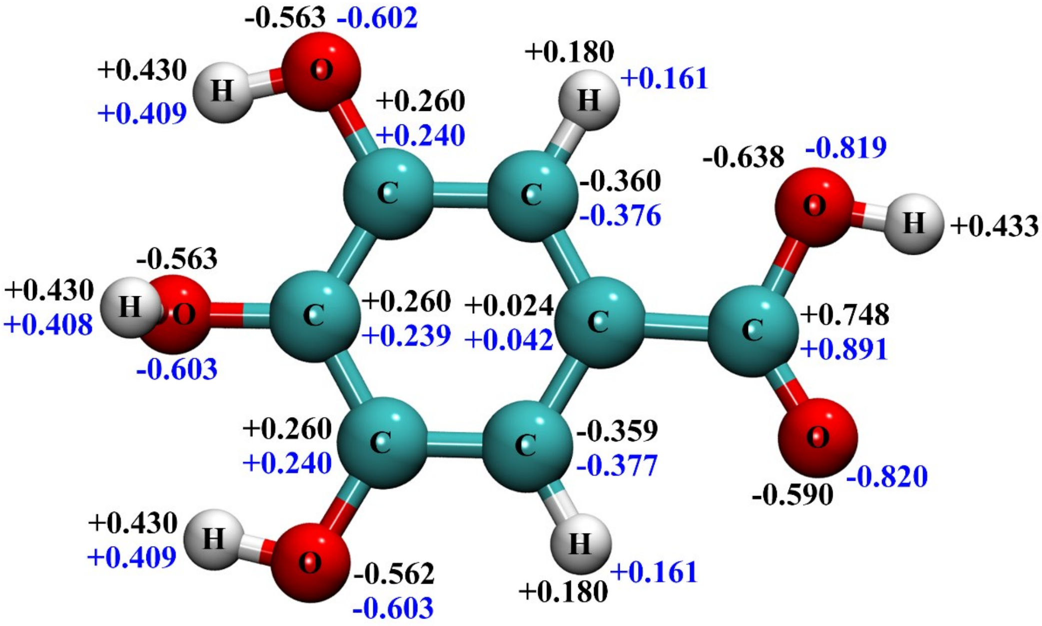

Figure S2. Atomic partial charges for the GA-AA structure. The charges are presented in black for Prot. GA and blue for Deprot. GA (-1).

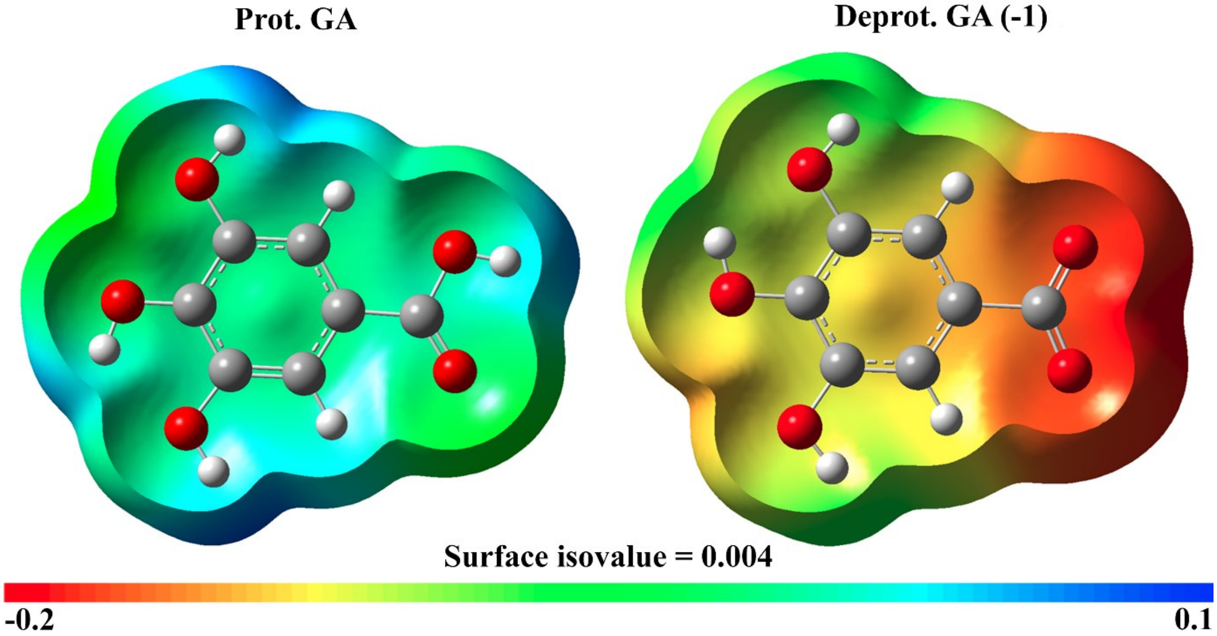

Figure S3. The electrostatic potential mapping of the protonated GA is displayed on the left and deprotonated version is on the right. Blue colours indicate positive charges while red ones represent negative ones.

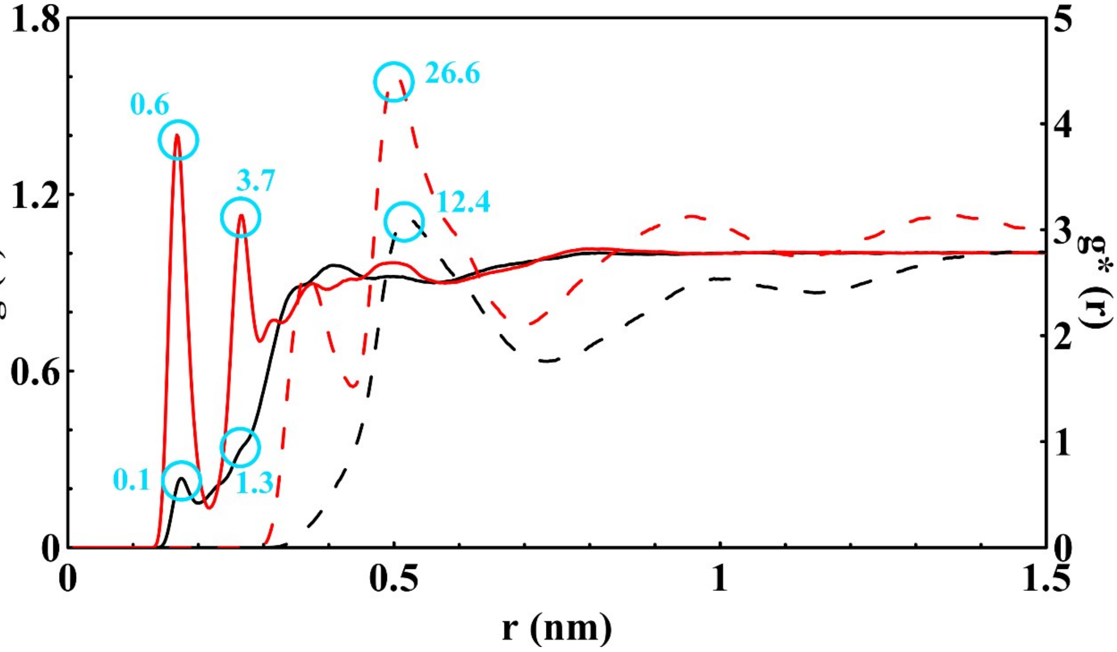

Figure S4. The RDF profiles between the carboxylic acid group and water were obtained for the AA (solid lines) and CG (dashed lines) GA models. The *y*-axis in the left is associated to the AA model while the right one shows the values for the CG version. Prot. GA is depicted in black while Deprot. GA (-1) is presented in red. Cyan circles show the water coordination numbers (CN). The AA main peaks arise at r ≈ 0.17 nm and 0.26 nm for Prot. GA and Deprot. GA (-1) respectively, whereas r ≈ 0.51 nm was obtained in both GA-CG versions.

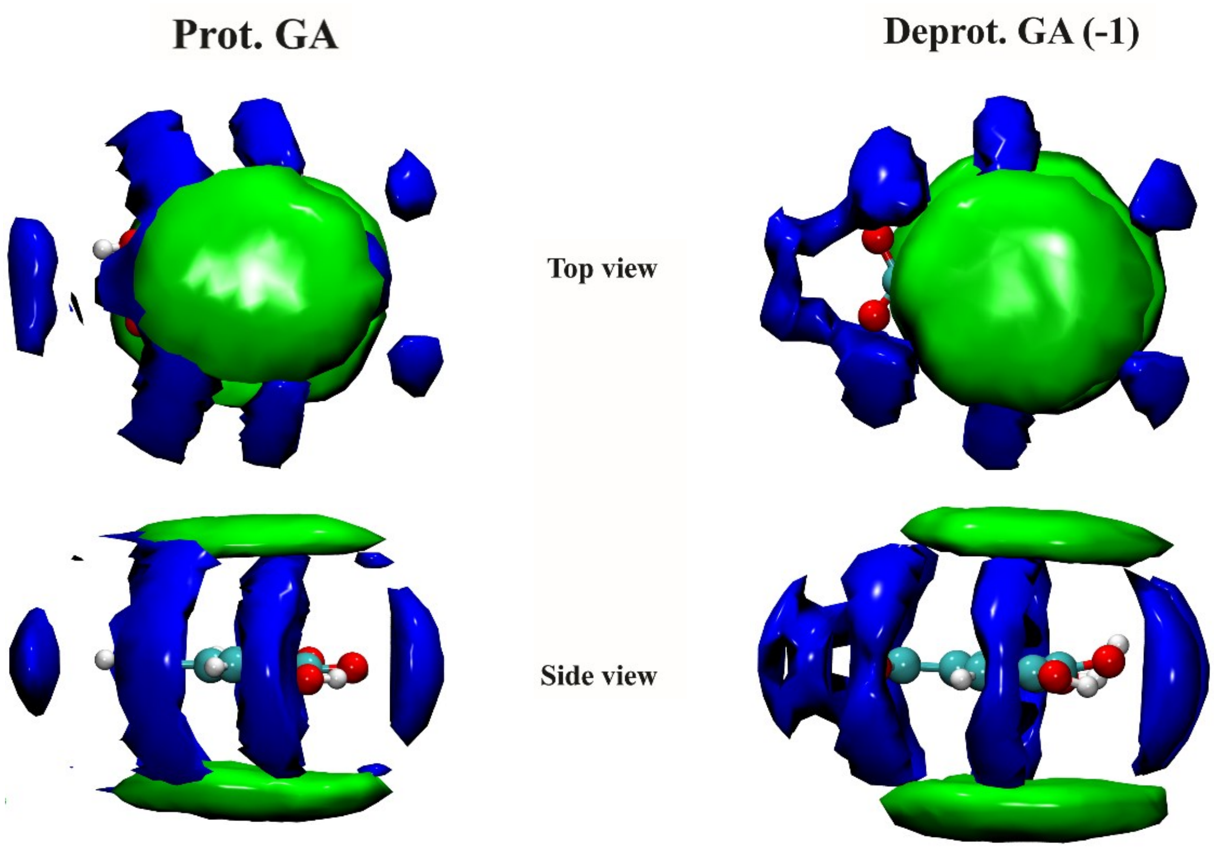

Figure S5. The SDF of water and neighbour GA molecules are plotted surrounding the reference Prot. or Deprot. (-1) GA molecules in the left and right, respectively. Water is shown in blue while other GA molecules are presented in green. Isovalues are 47.9 and 0.4655, respectively.

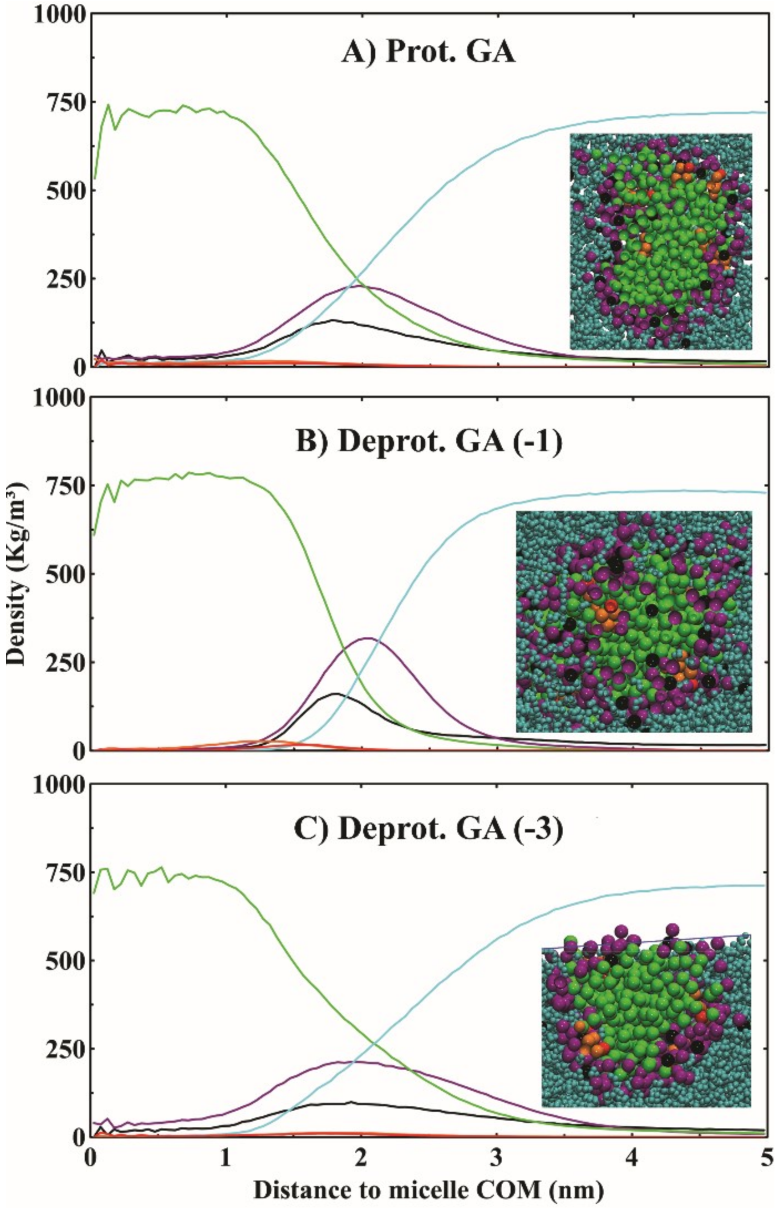

Figure S6. Density profiles for the aqueous systems (**Table S1**: systems 9-11) of $[N_{4,4,4,14}]^+$ and GA. The references were the micelle center of mass (COM) with a micelle simulation snapshot as an inset. QAILS cation polar heads are shown in purple, tail atoms in green. GA was divided in a carboxylic group coloured in red and the rest of the molecule in orange. Chloride ions were represented in black and water in cyan.

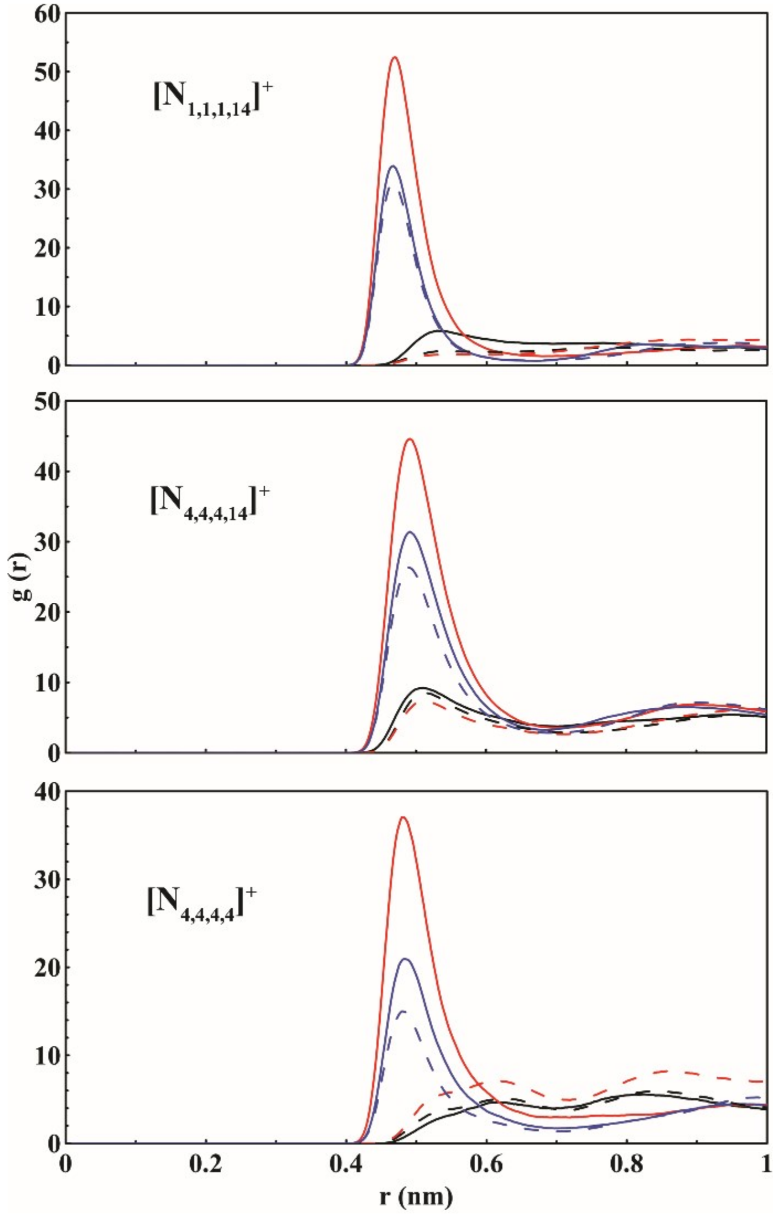

Figure S7. RDF profiles for the QAS + GA aqueous systems (**Table S1**: systems 5-7, 12-14, 19-21). The carboxylic (solid lines) and hydroxylic (dashed lines) moieties were used as a reference and the QAILS cation polar heads as the selection. Systems containing Prot. GA are depicted in black, Deprot. GA (-1) in red and Deprot. GA (-3) in blue.

B. Ion-exchange hypothesis

The RDFs profiles between the QAILS charged moieties and the chlorides are presented in **Figure S8** for low and high GA concentrations. In the micellar $[N_{1,1,1,14}]^+$ system, the presence of chloride anions at the micelle surface was reduced with the addition of GA. This effect was increased with the deprotonation degree of GA. Although this was observed for the system with Prot. GA, an ion exchange would only occur with the deprotonation of the carboxylic acid and further hasted by the ionization of the hydroxylic group. This was noticed by the difference between the CNs and intensity of the RDF main peaks of the two deprotonated versions of GA shown in **Figure S8 – high [GA]**. This can be corroborated by a brief comparison of these profiles with those presented in **Figure S7**. The GA partition in $[N_{1,1,1,14}]^+$ micelles reflects the presence of these moieties at the micelle surface. The Deprot. GA (-3) molecules were completely arranged at this interface, representing a large extent of ion exchange.

The ion exchange was not observed in the $[N_{4,4,4,14}]^+$ at low or high GA concentration (**Figure S8**) for the Prot. GA system as a consequence of its neutral net charge. When deprotonated, GA exchanges with chloride as observed for the $[N_{1,1,1,14}]^+$ systems. Finally, the $[N_{4,4,4,4}]^+$ profiles suggest a different scenario. Only the Deprot. GA (-3) induced a decrease of chloride surrounding the $[N_{4,4,4,4}]^+$ aggregates. This was a consequence of a complete salting-out induced by the higher density of charge exhibited by the Deprot. GA (-3). Structurally, this is expected since there would be a larger ionic density by fully deprotonating the hydroxylic moiety rather than the carboxylic acid.

Overall, ion exchange was possibly observed in QAILS with surfactant behaviour. This can originate novel QAILS formed by the quaternary ammonium cation and the deprotonated GA as the anion. The formation of a QA-GA compound was reported before using ion-exchange mechanisms.[87] This work paves the way for the formation of QAILS-gallate surfactants, with the advantage of being a simple one-pot process relying on the pH effect.

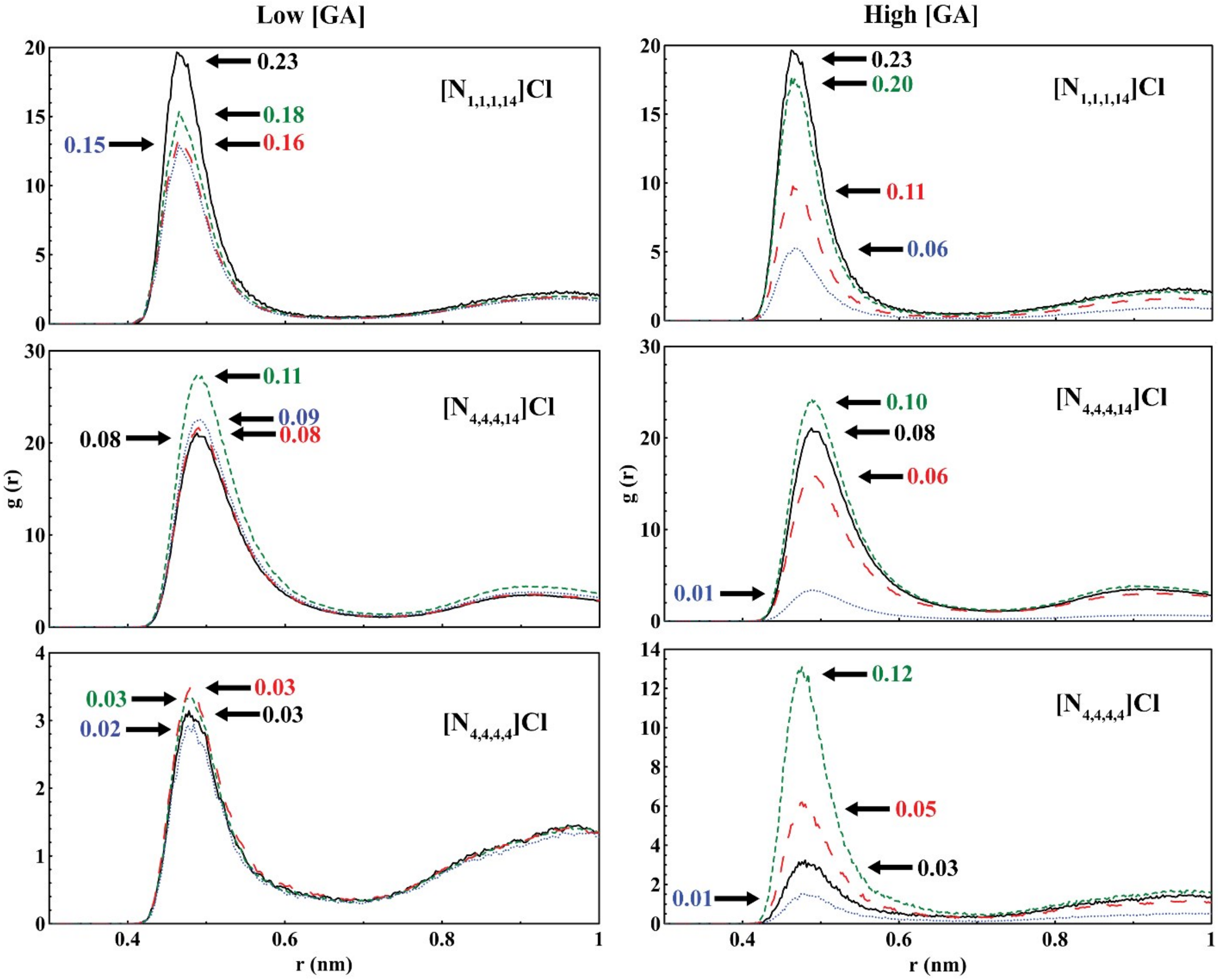

Figure S8. RDF profiles for (Table S1: systems 1-21) all QAILS aqueous solutions with GA. The QAILS polar heads cations were used as a reference and chloride ions as the selection. Systems containing Prot. GA are depicted in green, Deprot. GA (-1) in red and Deprot. GA (-3) in blue. A control system without GA was used on each case, showed in black. The coordinates used for the described CNs were 0.47 nm.