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Choline Saccharinate and Choline Acesulfamate: Ionic Liquids with Low Toxicities

Peter Nockemann,[†] Ben Thijs,[†] Kris Driesen,[†] Colin R. Janssen,[‡] Kristof Van Hecke,[§] Luc Van Meervelt,[§] Simone Kossmann,[||] Barbara Kirchner,[||] and Koen Binnemans*,[†]

Laboratory of Coordination Chemistry and Biomolecular Architecture, Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium, Laboratory of Environmental Toxicology and Aquatic Ecology, Department of Applied Ecology and Environmental Biology, Ghent University, Plateaustraat 22, B-9000 Gent, Belgium, and Institut für Physikalische und Theoretische Chemie, Universität Bonn, Wegelerstrasse 12, D-53115 Bonn, Germany

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Choline saccharinate and choline acesulfamate are two examples of hydrophilic ionic liquids, which can be prepared from easily available starting materials (choline chloride and a non-nutritive sweetener). The (eco)-toxicity of these ionic liquids in aqueous solution is very low in comparison to other types of ionic liquids. A general method for the synthesis and purification of hydrophilic ionic liquids is presented. The method consists of a silver-free metathesis reaction, followed by purification of the ionic liquid by ion-exchange chromatography. The crystal structures show a marked difference in hydrogen bonding between the two ionic liquids, although the saccharinate and the acesulfamate anions show structural similarities. The optimized structures, the energetics, and the charge distribution of cation−anion pairs in the ionic liquids were studied by density functional theory (DFT) and second-order (Møller−Plesset) perturbation theory calculations. The occupation of the non-Lewis orbitals was considered to obtain a qualitative picture of the Lewis structures. The calculated interaction energies and the dipole moments for the ion pairs in the gas phase were discussed.

Introduction

There is a strong interest in ionic liquids as alternatives for volatile organic solvents.[1−11] They can act as solvents for chemical reactions, including catalytic reactions.[12−17] Ionic liquids are an interesting reaction medium for the synthesis of unusual inorganic compounds.[18−21] They find use in electrochemical applications,[22] for example, as electrolytes in batteries,[23,24] in photovoltaic devices,[25−27] and also as a medium for electrodeposition of metals.[28] Ionic liquids can also find applications in separation sciences as solvents for extraction processes,[29,30] as a stationary phase for gas chromatography,[31−35] as well as in mass spectrometry.[36,37] Most studies on ionic liquids are about imidazolium salts, although pyridinium, phosphonium, quaternary ammonium, and other organic salts are thoroughly being investigated as well. The widespread use of ionic liquids implies their availability at a reasonable price. Choline chloride (also known as 2-hydroxyethyltrimethyl ammonium chloride or vitamin B4) is a cheap organic salt, which is used, for instance, as a chicken feed additive. Unfortunately, choline chloride has a high melting point (298−304 °C). Therefore, it is itself not useful as an ionic liquid. Abbott and co-workers obtained ionic liquids by mixing choline chloride with hydrated transition metal salts,[38] or with anhydrous zinc(II) chloride or tin(II) chloride.[39,40] They found that choline chloride forms so-called "deep eutectic solvents" with hydrogen-bond donors; a mixture of urea and choline chloride in a 2:1 molar ratio is a liquid at room temperature.[41] These ion-liquid-like solvents were applied for the synthesis of zeolite analogues[42] and for the functionalization of cellulose.[43] Mixtures of choline chloride and malonic acid were used for the synthesis of iron(III) oxalatophosphates.[44] Because the melting points of ionic liquids strongly depend on the nature of the anion and because it is known that imidazolium halides have higher melting points than imidazolium salts with hexafluorophosphate, tetrafluoroborate, or with other fluorinated anions, one can imagine that it is possible to obtain room-temperature ionic liquids by replacing the chloride anions in choline chloride by other counterions.

In this paper, we describe the synthesis and properties of two hydrophilic ionic liquids: choline saccharinate ($[Chol]^+[Sac]^-$) and choline acesulfamate ($[Chol]^+[Ace]^-$) (Figure 1). These two ionic liquids have low toxicities. A general method for the purification of hydrophilic ionic liquids is presented. Although the two anions have a similar chemical structure, the hydrogen bonding between the cation and the anion is markedly different in the crystal structures of the two components. Quantum chemical calculations of the cation−anion interactions can offer an explanation for these differences in bonding behavior.

Experimental Section

General Techniques. Elemental analyses (carbon, hydrogen, and nitrogen) were made on a CE Instruments EA-1110 elemental analyzer. Fourier transform FTIR spectra were recorded on a Bruker IFS-66 spectrometer. The samples were measured using the KBr pellet method or as a thin film between KBr windows. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 spectrometer (operating at 400 MHz for ^{1}H

* Author to whom correspondence should be addressed. E-mail: Koen.Binnemans@chem.kuleuven.be.
[†] Laboratory of Coordination Chemistry, Department of Chemistry, Katholieke Universiteit Leuven.
[‡] Ghent University.
[§] Biomolecular Architecture, Department of Chemistry, Katholieke Universiteit Leuven.
[||] Universität Bonn.

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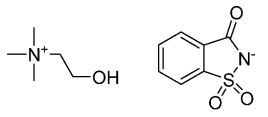
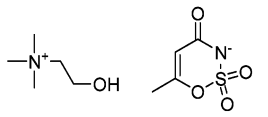


[Chol]$^+$[Sac]$^-$



[Chol]$^+$[Ace]$^-$

Figure 1. Structures of choline saccharinate ([Chol]$^+$[Sac]$^-$) and choline acesulfamate ([Chol]$^+$[Ace]$^-$).

and 100.61 MHz for ^{13}C). The water content of the ionic liquids was determined by a Coulometric Karl Fischer titrator (Mettler Toledo Coulometric Karl Fischer Titrator, model DL39). The viscosity of the ionic liquids was measured by the falling ball method (Gilmont Instruments). The density was measured by pyknometry. Differential scanning calorimetry (DSC) measurements were made on a Mettler-Toledo DSC822e module (scan rate of 10 °C min^{-1} under helium flow). Thermogravimetric analyses were made with a Polymer Laboratories STA 1000H TG-DTA apparatus. Atomic absorption spectrometry (AAS) measurements were performed with a Shimadzu AA-660 apparatus. Choline chloride, sodium saccharinate, and potassium acesulfamate were purchased from Acros Organics or Fluka. All chemicals were used as received without any additional purification step.

Quantum Chemical Methodology. Density functional theory (DFT) calculations with the density functional BP and B3LYP[45,46] were performed for isolated complexes using Turbomole.[47] The TZVP basis set from the Turbomole library was employed throughout.[48] All interaction energies were calculated with the supermolecular Ansatz. These interaction energies were then counterpoise-corrected (CP) using the procedure of Boys and Bernardi.[49,50] However, counterpoise corrections were not included during the structure optimization. Moreover, second-order Møller−Plesset (MP2) perturbation theory, in combination with the resolution of the identity technique (RI), was applied.[51,52] For the MP2 calculations, the slightly larger basis set TZVPP was used. Atomic charges with multicenter corrections from the shared electron population analysis were also considered.[53] The shared electron number (SEN) analysis was performed as developed by Davidson and Roby (Davidson−Roby population analysis).[53,54] Furthermore Weinhold's natural population analysis (NPA)[55,56,57] in the ORCA implementation was carried out for comparative purposes.[58] Structures were visualized with Molden and VMD.[59] The calculation of the electron localization function was carried out with the CPMD code.[60]

X-ray Crystallography. X-ray intensity data were collected on a SMART 6000 diffractometer equipped with CCD detector using Cu Kα radiation (λ = 1.54178 Å). The images were interpreted and integrated with the program SAINT from Bruker.[61] The structures were solved by direct methods and refined by full-matrix least squares on F^2 using the SHELXTL program package.[62] Non-hydrogen atoms were anisotropically refined, and the hydrogen atoms in the riding mode with isotropic temperature factors were fixed at 1.2 times U(eq) of the parent atoms (1.5 times for methyl groups). CCDC-285408 and CCDC-285409 contain the crystallographic data for this paper and can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

Crystal Data for Choline Acesulfamate. Single crystals were obtained by slowly cooling a molten sample. $C_9H_{18}N_2O_5S$, M = 266.32 Da, monoclinic, space group $P2_1/n$ (no. 14), a = 7.1338(4) Å, b = 14.2416(8) Å, c = 12.8338(6) Å, β = 104.758(3)°, V = 1260.86(12) Å^3, T = 100(2) K, Z = 4, D_c = 1.403 g cm^{-3}, μ(Cu Kα) = 2.426 mm^{-1}, F(000) = 568, crystal size = 0.35 × 0.15 × 0.1 × mm^3, 2416 independent reflections (R_{int} = 0.1078). Final R = 0.0579 for 2130 reflections with $I > 2\sigma(I)$ and ωR_2 = 0.1533 for all data.

Crystal Data for Choline Saccharinate. Single crystals were obtained by slowly cooling a molten sample. $C_{12}H_{18}N_2O_4S$, M = 286.35 Da, orthorhombic, space group *Pbca* (no. 61), a = 25.654(3) Å, b = 10.4439(10) Å, c = 10.2801(12) Å, V = 2754.3(5) Å^3, T = 100(2) K, Z = 8, D_c = 1.381 g cm^{-3}, μ(Cu Kα) = 2.214 mm^{-1}, F(000) = 1216, crystal size 0.45 × 0.3 × 0.1 × mm^3, 2662 independent reflections (R_{int} = 0.0764). Final R = 0.0535 for 2001 reflections with $I > 2\sigma(I)$ and ωR_2 = 0.1530 for all data.

Ecotoxicological Evaluation. The ecotoxicity of the two ionic liquids considered in this study was assessed using the acute immobilization assay with the crustacean *Daphnia magna*. The origin and culturing conditions of the test organisms have been described elsewhere.[63] The actual toxicity tests were performed according to the Organization for Economic Cooperation and Development Guideline 202.[64] After preliminary range-finding tests, definitive tests were performed in which five replicates of five juveniles (<24 h old) were exposed to choline saccharinate and choline acesulfamate concentrations ranging from 180 to 1800 mg L^{-1}. These concentrations were prepared using the chemically defined M4 medium for dilution.[65] Each test vessel contained 50 mL of test medium. After 48 h, the number of immobilized organisms was recorded, and the medium effective concentration (EC50) values were calculated using the trimmed Spearman−Karber method.[66]

Synthesis of Choline Saccharinate and Choline Acesulfamate. First, a metathesis reaction to synthesize the crude products was performed. Equivalent amounts (0.2 mol each) of choline chloride and sodium saccharinate (or potassium acesulfamate) were dissolved in absolute ethanol, mixed, and stirred for 1 h at room temperature. A white precipitate of sodium chloride (or potassium chloride) was formed and removed by filtration. Ethanol was evaporated on a rotary evaporator. A cation-exchange resin (DOWEX 50 W, total exchange capacity 1.9 equiv/L) was washed with ethanol and water and regenerated using an aqueous HCl solution. The resin was loaded with choline cations by pouring an aqueous solution of choline chloride through the column until the pH of the effluent was neutral. The anion-exchange resin (DOWEX 1 × 2−400, total exchange capacity 1.3 equiv/L) was treated in a similar way and regenerated with an aqueous sodium chloride solution. This column was loaded with an aqueous solution of sodium saccharinate or potassium acesulfamate, until no chloride was detected in the effluent by the silver nitrate test. The crude product of the metathesis reaction was dissolved in water and poured over the cation- and anion-exchange columns, respectively. After this step, no alkaline or halide impurities could be detected in the effluent by atomic absorption spectrometry (AAS) or by the silver nitrate test. The products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. For choline saccharinate, ^{1}H NMR (400 MHz, [D$_6$]DMSO, ppm): 7.62 (m, 4 H) 5.44 (s, 1 H), 3.47 (m, 2 H), 3.45 (q, 2H), 3.13 (s, 9H). ^{13}C NMR (100 MHz, [D$_6$]DMSO, ppm): 168.17 (C═O), 145.17, 134.64 (C), 131.78, 131.23, 122.61, 119.20 (CH), 67.05 (N−CH$_2$), 55.23 (CH$_2$), 53.28, 53.25, 53.21 (3 × CH$_3$). IR (KBr pellet): 3261 (ν(OH), s,br; choline), 1626 (ν(C═O), vs), 1336 (ν_s(CNS), m), 1257 (ν_{as}(SO$_2$), vs), 1150 (ν_s(SO$_2$), vs), 954 (ν_{as}-

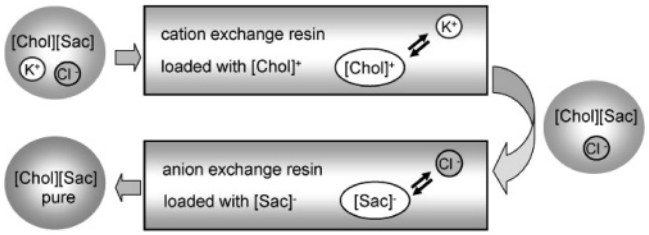


Figure 2. Schematic illustration of the purification of ionic liquids after the metathesis reaction by ion-exchange chromatography. The given example is for the purification of choline saccharinate.

(CNS), m). For choline acesulfamate, ^{1}H NMR (400 MHz, [D_6]-DMSO, ppm): 5.36 (s, 1 H), 3.84 (m, 2 H), 3.42 (m, 2 H), 3.12 (s, 9 H), 1.92 (s, 3 H). ^{13}C NMR (100.61 MHz, [D_6]DMSO, ppm): 168.45 (C═O), 160.44, 101.86 (CH), 67.03 (N−CH_2), 55.20 (CH_2), 53.26, 53.22, 53.18 (3 × CH_3), 19.29 (CH_3). IR (KBr pellet): 3262 (ν(OH), s, br; choline), 1658 (ν(C═O), vs), 1371 (ν_s(CNS), m), 1296 (ν_{as}(SO_2), vs), 1178 (ν_s(SO_2), vs), 947 (ν_{as}(CNS), m). The water content of the products, which were dried for 2 h on a rotary evaporator with the flask heated in an oil bath at 120 °C, was determined by a Coulometric Karl Fischer titrator and found to be 0.07 wt % for choline saccharinate and 0.06 wt % for choline acesulfamate. The density of choline saccharinate is 1.383 g cm^{-3}, and that of choline acesulfamate is 1.284 g cm^{-3} (both at 25 °C). The viscosity is 328 cP (at 70 °C) for choline saccharinate and 1072 cP (at 25 °C) for choline acesulfamate. The ionic conductivity of the ionic liquids ranges from 2.1 × 10^{-4} S cm^{-1} for supercooled choline saccharinate to 4.5 × 10^{-4} S cm^{-1} at 25 °C for choline acesulfamate.

Results

Synthesis of the Ionic Liquids. Choline saccharinate and choline acesulfamate were prepared in a two-step procedure. The first stage was the metathesis reaction between choline chloride and sodium saccharinate or between choline chloride and potassium acesulfamate in absolute ethanol. A precipitate of sodium chloride or potassium chloride was formed. Even if the precipitated alkaline salts were carefully removed by filtration, the crude products of this metathesis step always contained alkaline ion impurities as well as chloride impurities. This was confirmed by atomic absorption spectrometric analysis and by the silver nitrate test. The chloride content of the ionic liquids was determined gravimetrically from the mass of precipitated AgCl (about 1% w/w for typical batches). The second stage of the synthesis was a purification step by an ion-exchange process (Figure 2). Just as in the case of the deionization of water, a cation-exchange resin (loaded with choline cations) with an anion-exchange resin (loaded with saccharinate or acesulfamate anions) was combined. Aqueous solutions of the crude products were passed through the two columns and were found to be free of impurities. Choline saccharinate and choline acesulfamate are supercooled liquids at ambient temperature, but they tend to crystallize spontaneously after leaving the samples at room temperature for several days. After crystallization, the melting points of the ionic liquids were determined, 69 °C for choline saccharinate and 25 °C for choline acesulfamate. By cooling the samples down to −60 °C, we were not able to detect any glass transition or crystallization peak by differential scanning calorimetry. Thermogravimetric analysis showed that these ionic liquids are stable to at least 230 °C. The remaining chloride impurities, which were present before the ion exchange, change the properties of the ionic liquids drastically; both chloride-contaminated compounds were solids with melting points around 65 °C and became supercooled liquids at room temperature after the purification step. A study of the efficiency of the purification process showed that the ion-exchange efficiency for saturation of the anion-exchange column (loaded with chloride) with saccharinate or acesulfamate, respectively, was rather high (85%). The reexchange efficiency was significantly lower (15%), but this emphasizes the applicability of ion-exchange resins for purification rather than for synthesis. The efficiency of purification by an ion-exchange column depends on different factors, such as the type and capacity of the resin, the length and diameter of the column, the flow rate, the pH, the nature of the ion groups, the solution concentrations, and the solvent.

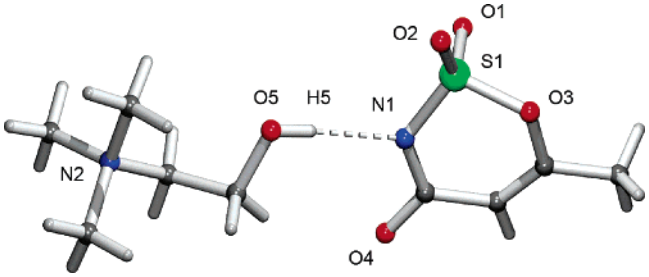


Figure 3. Molecular structure of choline acesulfamate, showing the OH···N hydrogen bonding between cation and anion. This pair is abbreviated [Chol]$^+$[Ace]$^-$ in the quantum chemical section.

No differences in solvent miscibility were observed for [Chol]$^+$[Ace]$^-$ and [Chol]$^+$[Sac]$^-$. Both ionic liquids are fully miscible with polar organic solvents such as ethanol, dimethylsulfoxide, acetonitrile, acetone, and dimethylformamide. Both compounds are immiscible with less polar organic solvents such as toluene, hexane, dichloromethane, chloroform, ethylacetate, diethylether, and dioxane.

Crystal Structures of Choline Acesulfamate and Choline Saccharinate. The crystal structures of choline acesulfamate and choline saccharinate were determined. Crystals suitable for X-ray diffraction were obtained by slowly cooling a melt of the ionic liquid. The structure of choline acesulfamate, [Chol]$^+$[Ace]$^-$, exhibits a strong hydrogen bond between the OH group of the choline cation and the nitrogen of the acesulfamate anion (N1···(H)O5 distance is 281.5(3) pm) (Figure 3). The hydrogen-bonded cation−anion pairs in [Chol]$^+$[Ace]$^-$ are packed along the *a*-axis and exhibit only weak interactions to neighboring pairs (Figure 4). The structure of the choline saccharinate ionic liquid, [Chol]$^+$[Sac]$^-$, shows a disorder of the CH_2OH group of the choline cation, one part (population 0.49) with a O(H)···N hydrogen bond (O4A(H)···N1 = 285.2(5) pm) and one part (population 0.51) with a O(H)···O hydrogen bond (O4B(H)···O3 = 266.4(5) pm), respectively (Figure 5). This disorder might be interpreted as due to a stronger delocalization of the charge in the latter compound. The hydrogen-bonded cation−anion pairs in [Chol]$^+$[Sac]$^-$ are packed along the *a*-axis and exhibit only weak interactions with neighboring pairs. The phenyl rings of the saccarinate anion are directed toward each other in a crossed manner along the *a*-axis without showing any $\pi-\pi$ interactions (Figure 6).

Quantum Chemical Investigations. The structural properties of isolated clusters consisting of [Chol]$^+$[Sac]$^-$ and [Chol]$^+$[Ace]$^-$ were obtained by DFT calculations. The calculations were done to learn more about the hydrogen bonding in the system, to determine the strength of the cation−anion interaction, and to find out which geometry is more favorable. (The most stable conformation in a crystal structure is not necessarily the most

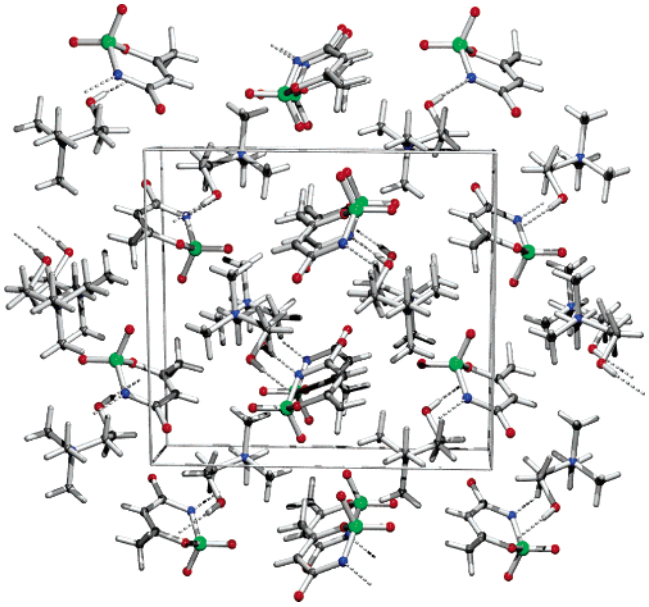


Figure 4. Packing diagram of the structure of $[Chol]^+[Ace]^-$ viewed down the *a*-axis.

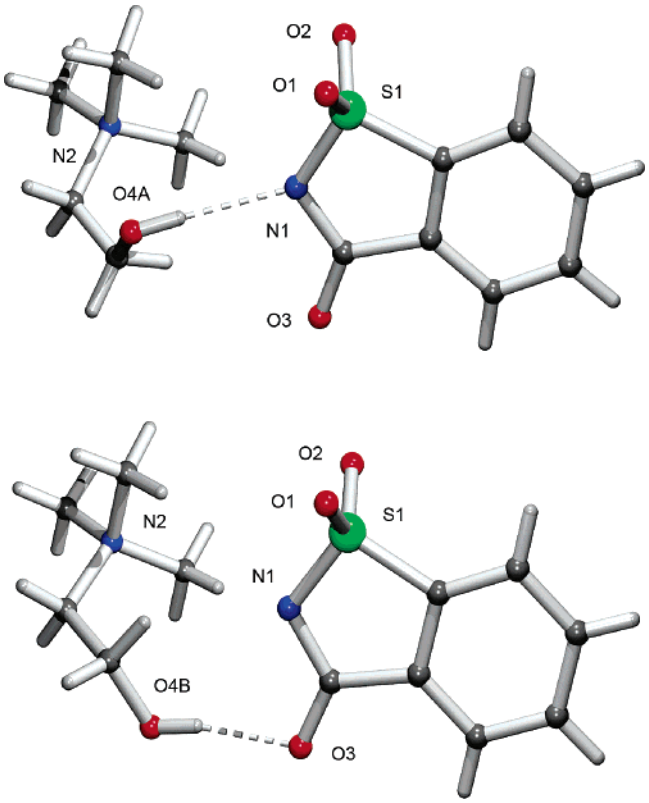


Figure 5. Molecular structure of choline saccharinate, showing both residues of the disordered choline moiety with the OH···N hydrogen bonding (abbreviated to $[Chol]^+[Sac]^-_A$ in the quantum chemical section, upper figure) and with the OH···(O) hydrogen bonding (abbreviated to $[Chol]^+[Sac]^-_B$ in the quantum chemical section, lower figure) between cation and anion.

stable in an isolated cluster.) Finally, the locations of the negative charges on the anion and the positive charge on the cation are determined to obtain an idea where preferred hydrogen bonding and ionic interactions can occur. The crystal structures were used as starting points for the quantum mechanical optimizations.

In Table 1, the calculated interaction energies E_I (in kJ/mol) and dipole moments (in debye) are given for two ion pairs of

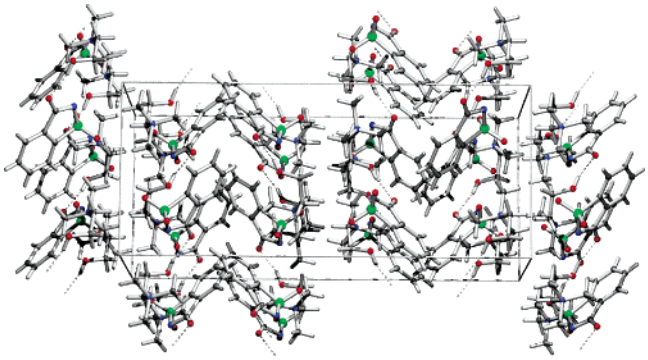


Figure 6. Packing diagram of $[Chol]^+[Sac]^-$ viewed down the *a*-axis.

TABLE 1: Calculated Interaction Energies E_I (in kJ mol^{-1}) and Dipole Moments (in debye) for the Experimental (Expt.) and Optimized (Opt.) Cation−Anion Pairs of Choline Saccharinate and Choline Acesulfamate

ion pair	method	E_I (kJ mol^{-1})	dipole moment (D)
$[Chol]^+[Sac]^-_A$ (expt.)	BP/TZVP	−346.2	14.9
	B3LYP/TZVP	−350.8	14.8
	MP2/TZVPP	−334.2	14.7
$[Chol]^+[Sac]^-_A$ (opt.)	BP/TZVP	−392.2	10.9
	B3LYP/TZVP	−392.8	10.9
	MP2/TZVPP	−390.3	10.9
$[Chol]^+[Sac]^-_B$ (expt.)	BP/TZVP	−345.7	14.0
	B3LYP/TZVP	−350.2	13.8
	MP2/TZVPP	−334.6	13.6
$[Chol]^+[Sac]^-_B$ (opt.)	BP/TZVP	−396.3	8.6
	B3LYP/TZVP	−396.5	8.4
	MP2/TZVPP	−390.3	8.1
$[Chol]^+[Ace]^-$ (expt.)	BP/TZVP	−285.5	22.6
	B3LYP/TZVP	−287.1	22.7
	MP2/TZVPP	−267.9	22.7
$[Chol]^+[Ace]^-$ (opt.)	BP/TZVP	−372.1	11.6
	B3LYP/TZVP	−371.3	11.6
	MP2/TZVPP	−373.9	11.5

choline saccharinate and for one ion pair of choline acesulfamate. The reason why two ion pairs are considered for choline saccharinate is that experimentally two different types of hydrogen bonding are observed in the crystal structure of this compound, whereas only one type of hydrogen bonding is observed for choline acesulfamate (see above). The ion pair with OH···N hydrogen bonding is abbreviated as $[Chol]^+[Sac]^-_A$ and the ion pair with OH···(O) hydrogen bonding is abbreviated as $[Chol]^+[Sac]^-_B$. The geometries of the cation and anion are taken from the experimental crystal structures (expt.) and from subsequently optimized structures with BP/TZVP (opt.). Upon these structures we performed single-point calculations with BP/TZVP, B3LYP/TZVP, and MP2/TZVPP. Additionally, an alternative structure of $[Chol]^+[Ace]^-$ was investigated, which represents OH···(O) hydrogen bonding, analogous to $[Chol]^+[Sac]^-_B$. This ion pair is referred to as $[Chol]^+[Ace]^-_B$. The alternative structure is ∼12.6 kJ mol^{-1} more stable in the gas phase compared to $[Chol]^+[Ace]^-_A$ (i.e., the structure taken from the crystal structure and in which no hydrogen bonding between cation and anion is present). The fact that the favored geometry in the crystal structure is not necessarily the energetically advantageous one in the gas phase is thereby again confirmed. The crystal structure of $[Chol]^+[Ace]^-_A$ is stabilized through neighbor effects, which cannot be described by gas-phase calculations. Independently of the methodology, all trends for the interaction energies are similar. The interaction energies are

TABLE 2: Charges Obtained from the Davidson−Roby Population Analysis (DRPA) Method and from Weinhold's Natural Population Analysis (NPA) Method for the BP/TZVP Optimized Structures of the Isolated Ions[a]

ion	method	q(N)	q(X)[b]	q(Y)[c]
choline	DRPA	0.255	0.175	0.034
	NPA	−0.080	0.437	−0.099
saccharinate	DRPA	−0.040	1.120	−0.255
	NPA	−0.805	2.165	−0.612
acesulfamate	DRPA	−0.169	0.887	−0.252
	NPA	−0.872	2.338	−0.606

[a] q(C) is the charge (in a.u.) on the carbon atom that binds the hydroxyl group in the case of the choline cation. q(O) is the charge (in a.u.) on the oxygen atom that forms a hydrogen bond in the case of $[Chol]^+[Sac]^-_B$. [b] $q(X) = q(H)$ for the choline cation and $q(X) = q(S)$ for the saccharinate and acesulfamate anions. [c] $q(Y) = q(C)$ for the choline cation and $q(Y) = q(O)$ for the saccharinate and acesulfamate anions.

in the same range for all methods for the optimized structures with a deviation of less than 4 kJ mol^{-1}. However, for the experimental structures the different methods give a variation of approximately 20 kJ mol^{-1}. $[Chol]^+[Sac]^-_B$ shows the strongest interactions, followed by $[Chol]^+[Sac]^-_A$, but the difference between the two ion pairs is less than 4 kJ mol^{-1}. $[Chol]^+[Ace]^-$ is by 60 kJ mol^{-1} (expt.) and 20 kJ mol^{-1} (opt.) less strongly bound. With the help of the shared electron number method, the individual hydrogen-bond energies could be estimated via the parametrization described by Thar and Kirchner.[67] The hydrogen-bond energies determined by BP/TZVP are: −46.2 kJ mol^{-1} for $[Chol]^+[Sac]^-_A$, −53.1 kJ mol^{-1} for $[Chol]^+[Sac]^-_B$, and −36.5 kJ mol^{-1} for $[Chol]^+[Ace]^-$. The trends for the individual hydrogen bonds between the cation and the anion are the same as the trends in the total binding energy. Not surprisingly, the total interaction energy is much stronger than the hydrogen-bond energy, because Coloumbic interactions between the two charges of the different species contribute to the total energy. The dipole moments vary between 8 and 23 debye. The largest dipole moment was observed for choline acesulfamate.

For the partial charges on the atoms, we can restrict the discussion to the BP/TZVP values since similar trends are observed for all chosen computational methods. Tables 2 (isolated ions), 3 (cation in the pair), and 4 (anion in the pair) contain the charges as obtained from the Davidson−Roby population analysis (DRPA) method and from Weinhold's natural population analysis (NPA) method. Standard population analyses are strongly basis-set-dependent, and different methods can yield very different results. However, one advantage of the NPA method is that it is almost not basis-set-dependent and usually leads to a chemically intuitive picture. The Davidson−Roby population analysis shows that the nitrogen atom is the most positively charged atom in the choline cation. Therefore, the nitrogen atom is directed toward the negative charge of the anion. However, the natural population analysis shows that the nitrogen atom and the carbon atom provide small or negligible charges but that the hydrogen atom contains a 0.5e charge. Because a hydrogen bond between the cation and the anion can only be formed with the hydroxyl group, the hydroxyl group is close to the anion (see also Table 6). The Davidson−Roby population analysis shows that both isolated anions are more negatively charged at the oxygen atom (which accepts in one pair the hydrogen bond) than the central nitrogen atom. However, the natural population analysis shows that the nitrogen atoms bear a larger negative charge than the oxygen atoms. For the acesulfamate anion, both calculation methods show that the charges for the nitrogen atom as well as for the oxygen atom are close to each other.

TABLE 3: Charges Obtained from the Davidson−Roby Population Analysis (DRPA) Method and from Weinhold's Natural Population Analysis (NPA) Method for the Choline Cation in the Different Ion Pairs[a]

ion pair	method	q(N)	q(H)	q(C)
$[Chol]^+[Sac]^-_A$ (expt.)	DRPA	0.315	0.170	0.086
	NPA	−0.078	0.468	−0.103
$[Chol]^+[Sac]^-_A$ (opt.)	DRPA	0.278	0.203	0.061
	NPA	−0.158	0.501	−0.132
$[Chol]^+[Sac]^-_B$ (expt.)	DRPA	0.339	0.185	−0.270
	NPA	−0.076	0.464	−0.113
$[Chol]^+[Sac]^-_B$ (opt.)	DRPA	0.281	0.211	0.053
	NPA	−0.158	0.495	−0.129
$[Chol]^+[Ace]^-$ (expt.)	DRPA	0.269	0.155	0.051
	NPA	−0.080	0.481	−0.112
$[Chol]^+[Ace]^-$ (Opt.)	DRPA	0.273	0.184	0.037
	NPA	−0.157	0.503	−0.140

[a] Geometries of the isolated cation in the pair are taken from the crystal structure (expt.) and from optimization with BP/TZVP (opt.). A charge analysis upon these structures was performed. The charges are given in a.u. and are chosen on the same atoms as described in Table 2.

TABLE 4: Charges Obtained from the Davidson−Roby Population Analysis (DRPA) Method and from Weinhold's Natural Population Analysis (NPA) Method for the Anions in the Different Ion Pairs[a]

ion pair	method	q(N)	q(S)	q(O)
$[Chol]^+[Sac]^-_A$ (expt.)	DRPA	−0.050	0.902	−0.073
	NPA	−0.919	2.177	−0.612
$[Chol]^+[Sac]^-_A$ (opt.)	DRPA	−0.269	1.266	−0.081
	NPA	−0.895	2.077	−0.586
$[Chol]^+[Sac]^-_B$ (expt.)	DRPA	−0.020	0.908	−0.079
	NPA	−0.892	2.174	−0.627
$[Chol]^+[Sac]^-_B$ (opt.)	DRPA	−0.150	1.270	−0.117
	NPA	−0.850	2.066	−0.627
$[Chol]^+[Ace]^-$ (expt.)	DRPA	−0.445	0.908	−0.079
	NPA	−0.892	2.345	−0.623
$[Chol]^+[Ace]^-$ (opt.)	DRPA	−0.436	0.886	−0.406
	NPA	−0.922	2.219	−0.596

[a] Geometries were taken from the crystal structure (expt.) and from optimization with BP/TZVP (opt.). Upon these structures a charge analysis was performed. The charges are given in a.u. The nitrogen and the oxygen atoms are those atoms that accept hydrogen bonding.

TABLE 5: Hydrogen-Bond Parameters for the Different Ion Pairs Taken from the Crystal Structure (Expt.) and from Optimization with BP/TZVP (Opt.)

ion pair	r(H-acceptor)[a] (pm)	angle[b] (deg)
$[Chol]^+[Sac]^-_A$ (expt.)	204.4	168.6
$[Chol]^+[Sac]^-_A$ (opt.)	172.2	164.3
$[Chol]^+[Sac]^-_B$ (expt.)	186.8	163.3
$[Chol]^+[Sac]^-_B$ (opt.)	164.4	174.5
$[Chol]^+[Ace]^-$ (expt.)	199.5	177.5
$[Chol]^+[Ace]^-$ (opt.)	179.6	160.4

[a] The distances r(H-acceptor) are the hydrogen-bond lengths [b] The angle is the angle between the three atoms acceptor−hydrogen−oxygen. The hydrogen-bond acceptor is a nitrogen atom in $[Chol]^+[Sac]^-_A$ and in $[Chol]^+[Ace]^-$ but an oxygen atom in $[Chol]^+[Sac]^-_B$.

Table 3 contains the charges of the choline cation in the ion pair. Comparing the charges of the isolated choline with the charges of the optimized choline as found in the pair, a sizable

TABLE 6: Geometry Parameters of the Ion Pairs Taken from Experiment (Expt.) and from Optimization with BP/TZVP (Opt.)

ion pair	*r*(NO) (pm)	*r*(NN) (pm)	*r*(CO) (pm)	*r*(CN) (pm)
$[Chol]^+[Sac]^-_A$ (expt.)	505.7	418.0	353.3	344.9
$[Chol]^+[Sac]^-_A$ (opt.)	487.5	383.2	356.2	322.2
$[Chol]^+[Sac]^-_B$ (expt.)	505.7	418.0	361.9	332.8
$[Chol]^+[Sac]^-_B$ (opt.)	483.5	365.8	333.4	327.8
$[Chol]^+[Ace]^-$ (expt.)	608.9	587.7	360.9	351.8
$[Chol]^+[Ace]^-$ (opt.)	494.0	419.9	320.0	319.5

[a] The first atom X in *r*(XY) is from the cation; the second atom Y is from the anion.

polarization of the three atoms for the Davidson−Roby population analysis as well as for the natural population analysis can be observed. The nitrogen and the hydrogen atoms of the choline cation are most polarized in the $[Chol]^+[Sac]^-_B$ pair for charges derived from Davidson−Roby population analysis. Comparing the experimental and optimized structures, only minor changes can be observed. For both methods, the hydrogen atom is polarized in the optimized structure, because the geometrical arrangement can adjust better to the hydrogen-bonding situation. The charges on the anions in the ion pairs are given in Table 4. In comparison to the isolated anions, the polarizations on the nitrogen and the oxygen atoms are less pronounced in the natural population analysis (Table 2). The charge on the sulfur atom is always positive, and the differences to the isolated optimized anions are negligible for both methods. The experimental observation that the hydrogen bond in $[Chol]^+[Sac]^-_B$ is directed to the oxygen atom instead of to the nitrogen atom is reflected in the *q*(O) values obtained by both calculation methods. The two calculation methods result in decreased *q*(O) values and increased *q*(N) values. The differences between the nitrogen atom and the oxygen atom are more pronounced in $[Chol]^+[Sac]^-_A$ than in $[Chol]^+[Sac]^-_B$ due to the hydrogen bonding to the nitrogen atom.

As described above, the experimental and optimized structures result in different values for the calculated dipole moments. These differences can be traced back to the geometrical parameters (Table 5). Please note that in $[Chol]^+[Sac]^-_B$ the hydrogen bond is formed to the oxygen atom instead of to the nitrogen atom. Experimentally, the longest hydrogen bond is formed by the $[Chol]^+[Sac]^-_A$ ion pair. The $[Chol]^+[Ace]^-$ ion pair exhibits a slightly smaller hydrogen-bond bridge. Comparison of the experimental and optimized structures shows reduced hydrogen-bond lengths and smaller angles for the optimized structures. This is due to the fact that neighbor effects were neglected in the isolated pair optimizations and that the two ions arrange in such a way that they can interact ideally with each other, i.e., bringing the opposite charges as close as possible to each other, which does not necessarily result in the best hydrogen-bond parameters. However, in the experimental structure, the ions are solvated such that the bond lengths are in accordance with the trends calculated for the single hydrogen-bond energies of the shared electron number. Other geometrical parameters are given in Table 6. The quaternary ammonium group of the cation approaches the nitrogen atom and the oxygen atom of the anion due to the absence of environmental effects, which leads to smaller dipole moments, because the charge centers are now less separated. The hydrogen-bonding patterns can be recognized in the distances of the carbon atom from to the anion if one compares the experimental and optimized structures. In $[Chol]^+[Sac]^-_A$, there is no reduction of the C−O distance but a slight reduction of the C−N distance due to hydrogen bonding at the nitrogen atom. The opposite trend for the *r*(CO) distance is found for $[Chol]^+[Sac]^-_B$ due to hydrogen bonding at the oxygen atom of the anion. Both distances are reduced in $[Chol]^+[Ace]^-$, so the carbon atom holds similar distances to both atoms of the anion.

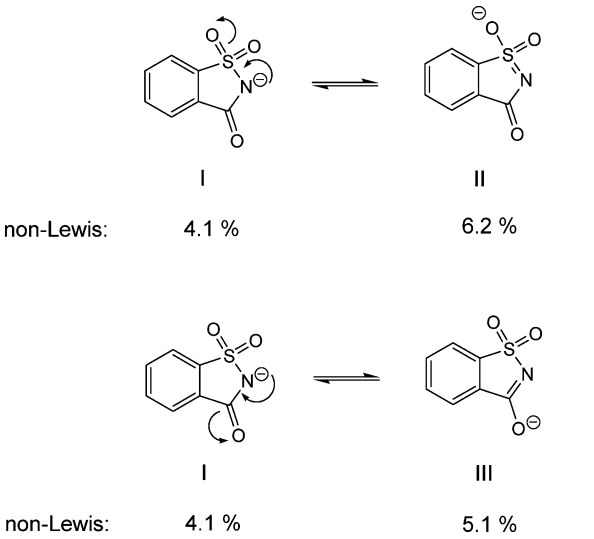


Figure 7. Lewis structures for the saccharinate anion. The percent values give the percentage of the occupation of the non-Lewis orbitals. A small non-Lewis occupancy indicates a more localized charge in the molecule.

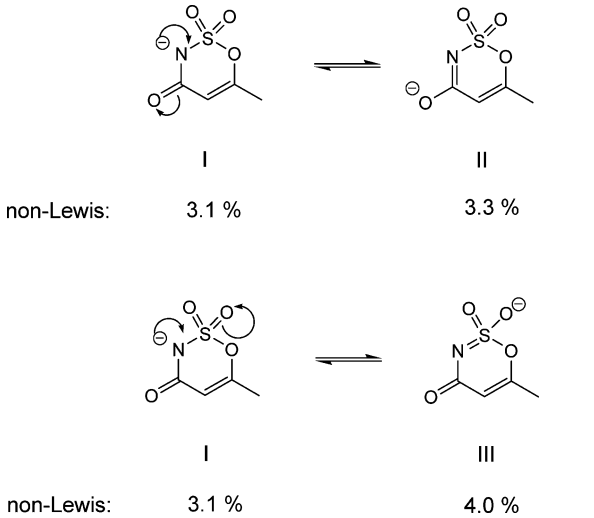


Figure 8. Lewis structures for the acesulfamate anion. The percent values give the percentage of the occupation of the non-Lewis orbitals. A small non-Lewis occupancy indicates a more localized charge in the molecule.

We also determined three alternative Lewis structures per anion to assess the quality of these structures (Figures 7 and 8). We restricted ourselves to examining only these structures for reference, but we realize that not all possible resonance structures are regarded. The percent value listed under each Lewis structure gives the percentage of the occupation of the non-Lewis orbitals, i.e., the unoccupied orbitals in the traditional Lewis picture. The quality of a given Lewis structure can be estimated in terms of the non-Lewis density. A smaller non-Lewis occupancy indicates that the charges are more localized in the molecule. In this case, the molecule can be described sufficiently by the traditional Lewis representation. Applied to the saccharinate and the acesulfamate anions, this means that Lewis structure I is in both cases the best fitting structure with the negative charge on the nitrogen. This fact is confirmed by the charges of the anions determined by the natural population

analysis (Table 2), which show that the most negative charge is located on the nitrogen. This is not a surprise, because both results are descended from Weinhold's natural population analysis. The structures of the saccharinate anion are more delocalized in comparison to the structures of the acesulfamate anion due to the additional benzyl group. Furthermore, interaction of the choline cation with the oxygen of structure III of the acesulfamate as well as with the saccharinate anion is less probable.

Ecotoxicological Study. Choline saccharinate and choline acesulfamate are expected to have a low toxicity to higher organisms, because choline chloride is an animal feed additive and because saccharinate and acesulfamate salts are being used as artificial sweeteners. We could demonstrate that the choline ionic liquids exhibit a low toxicity to the freshwater crustacean *Daphnia magna*. The test consisted of a standard acute immobilization test.[60] The tested concentrations of the ionic liquids had different degrees of effects on the mobility (swimming activity) of *Daphnia magna*. Animals that were not able to swim within 15 s after gentle agitation of the test container were considered to be immobile. The ecotoxicity of a compound is given by its 48 h EC50 value, which is the concentration estimated to immobilize 50% of the *Daphnia magna* after 48 h of exposure. The calculated 48 h EC50s (and 95% confidence limits) were 1219 (1109−1340) mg L^{-1} for choline saccharinate and 1378 (1288−1480) mg L^{-1} for choline acesulfamate.

Discussion

Most ionic liquids are being prepared from precursors with halide counterions (chloride or bromide) because the haloalkanes are the starting products for the quaternization reaction leading to the formation of the organic cation. The halide counterions can be replaced via a metathesis reaction by anions such as $[BF_4]^-$, $[PF_6]^-$, $[Tf_2N]^-$, and $[CF_3SO_3]^-$. This metathesis reaction is easy to perform, provided that the starting products are soluble in water and that the resulting ionic liquid separates as a hydrophobic phase from the aqueous phase as in the case of ionic liquids with hexafluorophosphate anions. In contrast, the synthesis of hydrophilic ionic liquids via a metathesis reaction is considerably more difficult, because the resulting water-miscible ionic liquid will remain in the aqueous phase and no phase separation takes place. The classical way to synthesize hydrophilic ionic liquids is to perform a metathesis reaction using the silver salt of the anion, which results in the precipitation of a silver halide.[68−70] The disadvantages of this method are the high price of silver salts and the risk of contamination of the ionic liquid by silver ions. Silver halides might be soluble in ionic liquids, and the silver salts exhibit slow kinetics in the presence of organic salts. An example of an alternative method for the synthesis is the use of alkylating reagents to synthesize intrinsically halide-free ionic liquids.[71,72] Only a few authors have reported the use of ion-exchange resins for the synthesis of hydrophilic ionic liquids, although the potential of this method for the synthesis of very pure ionic liquids has been recognized.[16,73,74] However, this method is hardly suitable for upscaling due to the relatively low exchange capacity of the ion-exchange resins.[75] In the methodology presented in this paper, the ion-exchange resin is used as a purification method rather than as a synthetic method. In the first step, a metathesis reaction was performed. Anhydrous lower alcohols (such as methanol or ethanol) are used as the solvents for the metathesis reaction. This method is based on the low solubility of alkali metal halides in these solvents, resulting in their precipitation. The precipitate can be removed by filtration. Acetone is also a good solvent for this kind of metathesis reaction, because alkaline halides are hardly soluble and precipitate in the solvent. However, acetone is not appropriate as a solvent for choline chloride as reactant due to the low solubility of choline chloride in acetone. Ion-exchange resins are applied in a second stage to remove impurities of alkali cations and halide anions that remain in the ionic liquid after the metathesis reaction. Halide impurities have a pronounced effect on the physicochemical properties of ionic liquids. This method was applied in this paper to the synthesis of choline saccharinate and choline acesulfamate, but this method is also useful for the preparation of other hydrophilic ionic liquids as well (e.g., with acetate, benzoate, or nitrate anions). Once loaded for a specific ionic liquid, the ion-exchange resins can be recycled several times and simply recovered with small amounts of aqueous reactant solutions. The method is not restricted to aqueous solutions since the ion exchange can also be done in alcohols or other polar organic solvents as well as in solvent mixtures.

It has been recognized that hydrogen bonding can play an important role in the behavior of ionic liquids.[76−81] The crystal structures of choline saccharinate and choline acesulfamate show that the hydrogen-bonding interaction between the anion and the cation are different in the two cases, although the two anions have structural similarities. Choline acesulfamate exhibits only one type of hydrogen bonding, i.e., hydrogen bonding between the hydroxyl group of choline and the nitrogen atom of acesulfamate. However, two types of hydrogen bonding are observed for choline saccharinate. In one type of ion pairs, the hydroxyl group of the choline cation is hydrogen-bonded with the nitrogen atom of the saccharinate anion (similarly as in the case of the acesulfamate anion), but in another type of ion pairs, the hydroxyl group is hydrogen-bonded with the carbonyl oxygen of the saccharinate anion. The experimental results are supported by the quantum chemical analyses of the different Lewis structures of the anions. The percentage of the occupation of the non-Lewis orbitals in saccharinate and acesulfamate (Figure 7) indicates that the negative charges are more delocalized in the saccharinate anion than in the acesulfamate anion due to the presence of the phenyl ring in the saccharinate anion. In the acesulfamate anion, the negative charge is largely localized on the nitrogen atom. Therefore, preferential hydrogen bonding occurs between the hydroxyl group of choline and the nitrogen atom of acesulfamate. In the saccharinate anion, both the nitrogen atom and the carbonyl oxygen atom bear a considerable partial negative charge, so the hydroxyl group of the choline cation form hydrogen bonds to both the nitrogen atom and the carbonyl oxygen of the saccharinate anion. Although the quantum chemical analyses of different Lewis structures for the anions give hints on the nature of the preferential acceptor atom for the hydrogen bond, the interpretation of the occupancies of the non-Lewis orbitals must carefully be carried out. The percentages indicate that the molecule cannot be fully described by the traditional Lewis picture but that charge delocalization takes place. For the saccharinate and acesulfamate anions, the best fitting Lewis structure is the one in which the negative charge is localized on the nitrogen atom. However, one should keep in mind that this structure is not completely localized. Furthermore, the differences in the non-Lewis occupancies are in both cases rather small. The NPA charges of the isolated anions (Table 2) confirm that preferred Lewis structure I (with the most negative charge on the nitrogen atom) is the preferred structure but also reflects

the delocalization by a somewhat minor negative charge on the oxygen atom.

The calculated dipole moments for the choline saccharinate and choline acesulfamate ion pairs are very large, ranging from 8 to 23 debye. These high values are not unexpected, because of the strong charge separation in the ion pairs. The calculated interaction energies are much larger for the choline saccharinate than those for the choline acesulfamate ion pairs; hence the choline saccharinate ion pairs are more strongly bound than the acesulfamate ion pairs. One should realize that these interaction energies were calculated for ion pairs in the gas phase and that the interaction energies in the liquid phase and in the solid phase are different from those in the gas phase. The differences in interaction energies calculated for the experimental molecular geometries (as obtained from the crystal structures) and for the gas-phase optimized structures indicate that solvent effects are playing an important role. There are for the same reasons considerable differences between the dipole moments calculated for the experimental and optimized ion-pair structures. Many theoretical studies on ionic liquids consider ion pairs only to understand the basic intermolecular interactions.[82−86] Calculation of the behavior of ionic liquids in the condensed phase is still a challenge,[87−92] not only because calculations on many particle systems are expensive in computer time, but also because the intermolecular forces that govern the dynamics are not easy to describe.

Most of the crystal structures reported for ionic liquids are structures of imidazolium salts, which form in the solid state an extended network of cations and anions linked by hydrogen bonds.[93,94] They are mainly determined by the presence of $\pi-\pi$ stacking interactions and relatively weak C−H···π hydrogen bonds or C−H···halogen hydrogen bonds.[95] In some cases, only weak electrostatic anion−cation interactions are present, e.g., in 1-ethyl-2-methyl-3-benzyl imidazolium bis(trifluoromethylsulfonyl)imide.[96] However, quaternary ammonium ions are lacking a π-electron system that can interact with other π electrons or with CH groups. In the crystal structure of a chiral ammonium ionic liquid reported by Pernak, the cations create channels, which are filled by chains, made up of anions and water molecules.[97] However, these anion−cation pairs are not involved in further hydrogen-bonding networks, as reported for several imidazolium or non-imidazolium ionic liquids.[95,98,99] The crystal structures of choline salts reported in the literature are mainly dominated by anion−cation hydrogen-bonding interactions.[100−102] In the structure of $[Chol]^+[Sac]^-$, no $\pi-\pi$ interactions occur, as the shortest phenyl ring−ring interactions found are between phenyl rings C2−C7 and the same ring of symmetry equivalent $^1/_2 - x, 1 - y, -^1/_2 + z$ (distance between the centroids is 5.618(2) Å and the angle between the planes through the rings is 75.82°) and between the phenyl rings C2−C7 and the symmetry equivalent $^1/_2 - x, -^1/_2 + y, z$ (distance between the centroids is 5.6916(19) Å and the angle between the planes through the rings is 76.59°). This is in contrast to most of the imidazolium ionic liquids, which are often stacked along the short crystallographic axis.[95] Only one π-interaction is observed between C1−O3 and the ring C2−C7 (distance between O3 and the ring centroid is 3.941(2) Å and an angle of 167.34(19)°). Although the crystal structures of ionic liquids can tell us something about the cation−anion interactions in the solid and the liquid states, one should be aware that the liquid-phase structure cannot simply be obtained by extrapolation from the solid-state structure and taking randomization of the molecular positions into account. The ionic liquid cations with flexible alkyl chains can occur in different conformers that are energetically nearly equivalent. This is also evident from studies where different crystal structures could be obtained from one and the same ionic liquid.[86,103] However, also distinct conformers can occur within the asymmetric unit of an ionic liquid crystal, as shown by Armstrong and co-workers for a dicationic pyrrolidinium ionic liquid.[95]

Recent reports on the (eco)toxicity of ionic liquids questioned the "green" aspects of some ionic liquids and put them in a bad light.[104−106] Therefore, there is definitely the need for an approach toward "greener" ionic liquids. Ionic liquids with counterions such as saccharinate or acesulfamate have been described.[107,108] Advantages are their well-established toxicological properties, easy availability, and low price (these are salts of artificial sweeteners). Thus by combining these anions with a choline cation, which is derived from choline chloride (an essential vitamin-like nutrient used as a chicken feed additive), these ionic liquids are expected to have a very low toxicity. As such these environmentally friendly compounds might approach the ideal of "food grade" ionic liquids. They are complementary to ionic liquids with amino-acid-based anions.[109−111] The acesulfamate and saccharinate ionic liquids described in the present study are hydrophilic, but their miscibility with organic solvents depends very much on the type of cation. Pernak and co-workers found that phosphonium acesulfamate ionic liquids are hydrophobic, although they are hygroscopic.[108]

The very low ecotoxicity of choline saccharinate and choline acesulfamate was demonstrated using an internationally accepted standard assay with the invertebrate *Daphnia magna*. Bernot and co-workers used the same assay to evaluate the ecotoxicity of imidazolium-based ionic liquids and found 48 h EC50 values ranging from 8.03 to 19.19 mg L^{-1}, depending on the anion.[112] They also demonstrated that this toxicity is mainly related to the imidazolium cation and not to the various anions (Cl^-, Br^-, $[PF_6]^-$, and $[BF_4]^-$) tested. The same authors also reported on the effects of imidazolium- and pyridinium-based ionic liquids (with Br^- and $[PF_6]^-$ as anions) on the freshwater snail *Physa acuta*.[113] The 96 h LC50's (lethal concentration for 50% of the test organisms) ranged from 1 to 325 mg L^{-1} with the highest toxicity being observed with an eight-carbon alkyl chain attached to both pyridinium and imidazolium rings (96 h LC50s = 1 and 8.2 mg L^{-1}, respectively). Toxicity decreased as a function of alkyl chain length. Garcia and co-workers used the acute *Daphnia magna* assay and the rapid microbial test with *Vibrio fisheri* (Microtox) to asses the ecotoxicity of 1-alkyl-3-methylimidazolium ionic liquids.[114] With the former test organism they obtained similar toxicity values to those reported by Bernot et al., with the 24 h EC50s in the low mg L^{-1} range.[112] For these ionic liquids, *Vibrio fisheri* was approximately 1−2 orders of magnitude less sensitive than *Daphnia magna*. On the basis of the above comparison, it can be concluded that choline saccharinate and choline acesulfamate described in this paper were at least 2 orders of magnitude less toxic (to *Daphnia magna*) than other ionic liquids such as imidazolium and pyridinium compounds and approximately 4 orders of magnitude less toxic than cationic surfactants possessing an imidazolium core.

Conclusions

Although choline chloride has a high melting point, this salt is a useful and cheap precursor for the preparation of ionic liquids based on the choline cation. New ionic liquids can simply be made by metathesis reactions. We illustrate this by preparing the hydrophilic ionic liquids choline saccharinate and choline

acesulfamate. For the synthesis of hydrophilic ionic liquids, a convenient method has been developed, which is essentially a silver-free metathesis reaction, followed by purification of the ionic liquid by ion-exchange chromatography. Choline saccharinate and choline acesulfamate are ionic liquids with a low toxicity, since these ionic liquids are composed of animal feed additives and of additives for human nutrition. The low environmental hazard of these compounds is confirmed by the ecotoxicity evaluations performed in this study. Quantum chemical analyses of different Lewis structures for the anions have been used to rationalize the distinct differences in hydrogen bonding in the cation−anion pairs of choline saccharinate and choline acesulfamate.

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Supporting Information Available: CIF files of the crystal structures, ^{1}H and ^{13}C NMR spectra of choline acesulfamate and choline saccharinate, and a picture of a three-phase system consisting of chloroform, choline acesulfamate, and toluene. This material is available free of charge via the Internet at http://pubs.acs.org.

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