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Alkali Metal Oligoether Carboxylates—A New Class of Ionic Liquids

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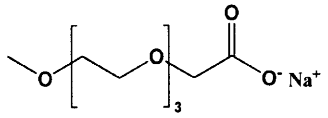
Ionic liquids (ILs) have attracted more and more attention in recent years because of their unique properties and the wide field of potential applications.[1,2] Generally, ionic liquids are defined as salts with melting points below 100 °C. Conventional ILs typically contain bulky organic cations with a low degree of symmetry such as imidazolium, pyrrolidinium, tetraalkylphosphonium, trialkylsulfonium, or quaternary ammonium. These cations hinder the regular packing in a crystal lattice. Consequently, the solid crystalline state becomes energetically less favorable, leading to low melting points.[3a,b] This effect can be enhanced further by using an anion with a delocalized charge, which results in decreased interionic interactions.[4] The electrochemical reactivity in ionic liquids[5] as well as their potential in biocatalysis,[6] catalysis in general,[7] and synthesis,[8a,b] have been reviewed recently.

To date, little attention has been paid to systems of ionic liquids involving small inorganic cations. Rees Jr. and Moreno investigated monomeric barium bisalkoxides of the general formula $Ba[O(CH_2CH_2O)_nCH_3]_2$ that were reported to be liquid at ambient temperature.[9] For these compounds, a solution structure with coordinative saturation at the central metal atom with oxygen atoms was proposed, which implied intramolecular complexation of the metal ions similar to the coordination prevailing in macrocyclic polyethers.[10] Other studies have described the synthesis and characterization of polyether carboxylates of heavy alkaline-earth metals,[11] which were found to be viscous oils that transform into hygroscopic solids upon reduction of the water content. Likewise, the yttrium(III) salt of 3,6,9-trioxadecanoic acid (TOD) was characterized as an extremely hygroscopic viscous oil that could only be isolated as a trihydrate.[12] Recently, Justus et al. reported novel ionic liquids consisting of trialkylammoniododecaborate anions and counter-ions including lithium and potassium.[13] Imidazolium cation-based ionic liquids with poly(ethyleneglycol) moieties[14] and fluorinated anions or ether and alcohol functional groups[15] with halide and fluorinated anions have also been discussed. Pernak et al. described dialkoxymethyl-substituted imidazolium cations combined with $[BF_4]$ and $[NTf_2]$ anions,[16] and ether-derivatized imidazolium halides were reported by Fei et al.[17]

In the present study, ionic liquids based on small inorganic cations and oligoether carboxylate anions were synthesized. We present for the first time a new family of ILs comprising alkali metal cations and 2,5,8,11-tetraoxatridecan-13-oate (TOTO) as anion, as shown exemplarily for the sodium salt in Scheme 1. Herein, we investigate the physicochemical properties of the salts, and propose possible reasons for the formation of ionic liquids with alkali metal ions.



Scheme 1. Sodium 2,5,8,11-tetraoxatridecan-13-oate [Na][TOTO].

2,5,8,11-Tetraoxatridecan-13-oic acid (TOTOA) was prepared in high purity (>99 %, GC) according to a modified procedure described by Matsushima et al.[18] Ionic liquids were easily obtained by neutralizing the acid with an equimolar amount of alkali metal hydroxide or hydrogencarbonate in aqueous solution. Water was first removed by lyophilization, followed by drying in vacuum. Both the lithium and the sodium salt were obtained as colorless or faint yellow liquids at room temperature, whereas the potassium carboxylate was a white solid.

The water content of the hygroscopic salts was determined by means of a Karl–Fischer titration and found to be below 300 ppm for the room-temperature liquid salts. All

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ionic liquids were characterized by ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. Melting and glass transition temperatures were measured by differential scanning calorimetry (DSC), decomposition temperatures by thermogravimetric analysis (TGA) (for more details see the Supporting Information). [Li]- and [Na][TOTO] show glass transitions, the temperature of which was determined from the intersection of the curve with the half-way line between the two baselines. The results are summarized in Table 1. Generally, the thermal stability of ILs is very sensitive to the type of both the cation and the anion. For instance, imidazolium cations tend to be thermally more stable than tetraalkylammonium species. Regarding the anions, a series of relative stability can be established ranking from PF_6 over BF_4 to halides.[20] All TOTOA alkali metal salts exhibit excellent thermal stability. The decomposition temperatures of the three substances are very similar, indicating that the nature of the cation plays a minor role in this context.

Table 1. Physical properties of the alkali metal salts of 2,5,8,11-tetraoxatri-decan-13-oic acid.

Cation	H_2O [ppm]	T_m[a] or T_g[b] [°C]	T_d[c] [°C]
Li^+	103	−53[b]	357
Na^+	211	−57[b]	384
K^+	1292	+60[a]	369

[a] T_m: melting point. [b] T_g: glass transition temperature. [c] T_d: decomposition temperature.

Exemplarily, we discuss in the following the conductivity, viscosity, and electrochemical stability for the sodium salt. Conductivity measurements were carried out in a temperature range between 25 °C and 145 °C. Viscosities were measured at defined temperatures between 25 °C and 65 °C, which revealed Newtonian behavior over the whole range. For the sodium salt, a characteristic increase in specific conductivity and decrease in viscosity with increasing temperature was detected. Both the conductivity and viscosity data were found to be well described by the empirical Vogel–Fulcher–Tammann equation (VFT). The three parameters were obtained by nonlinear fits. The corresponding plot and the fit results are given in Figure 1 and Table 2, respectively.

The electrochemical stability was studied by using cyclic voltammetry (CV) with Pt working and counter electrodes versus an Ag/Ag^+/Kryptofix reference, according to the method employed by Izutsu and co-workers.[19] Generally speaking, the electrochemical window of an ionic liquid is defined by the reduction of the cation and oxidation of the anion. The width of this window is quite high for many ILs, often exceeding 4 V.[20] The cyclic voltammogram of [Na][TOTO] was recorded first in the anodic direction with a scan rate of $10\,mV\,s^{-1}$. The cathodic and anodic limits are about −2.0 V and 2.7 V versus Ag/Ag^+, respectively, resulting in an electrochemical window of 4.7 V (more details are given in the Supporting Information, Figure S7). The CV data were recorded by using a 0.55 M solution of [Na][TOTO] in acetonitrile without added inert salt. These data gave rise to the appearance of traces of impurities such as the small peak seen in the anodic branch. All experiments were carried out in an inert gas atmosphere. For [Li][TOTO], an outstandingly wide electrochemical window of 6.7 V was found, with a cathodic limit of about −3.3 V and an anodic limit of about 3.4 V (for more details see the Supporting Information, Figure S8). These findings indicate an extraordinarily high electrochemical stability of the as-synthesized alkali metal oligoether carboxylates.

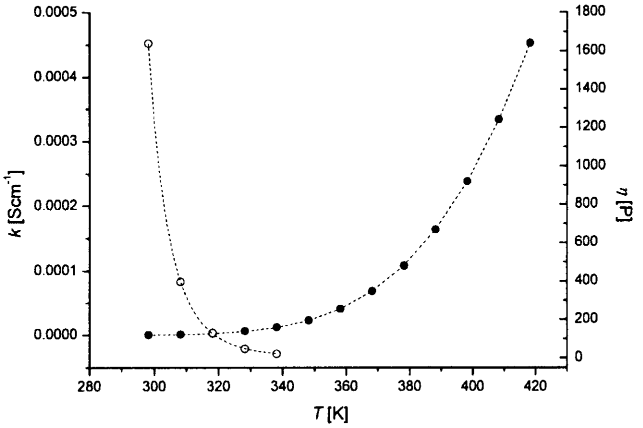

Figure 1. Specific conductivities κ (●) and viscosities η (○) of the sodium salt as a function of temperature, and the corresponding fit according to the VFT equation (line).

Table 2. VFT[a] equation parameters of conductivity and viscosity data for [Na][TOTO].

	κ_0 [Scm^{-1}]	B [K]	T_0 [K]
[Na][TOTO]	0.337	1485	193
	η_0 [P]	B [K]	T_0 [K]
[Na][TOTO]	0.0024	1140	213

[a] VFT equation for conductivity $\kappa = \kappa_0 \exp(-B/(T-T_0))$ and viscosity $\eta = \eta_0 \exp(B/(T-T_0))$, respectively.

The relationship between fluidity and conductance can be considered in terms of a Walden plot of the data, as described by Angell et al.[21a–c] The Walden rule relates the ion mobilities to the fluidity of the medium: if a liquid substantially consists of independent ions only, then the Walden plot will be close to an ideal line, which is typically represented by potassium chloride.[21b] Substances whose plot lies more than one order of magnitude below the ideal line can in this context be classified as “poor” ionic liquids. On that basis, MacFarlane et al. demonstrated recently that a number of phosphonium-based ILs appear to exhibit strong ion pairing.[22] The Walden plot obtained for the sodium salt over a temperature range of 25 to 65 °C is shown in Figure 2. It is obvious that the curve found for [Na][TOTO] lies significantly below the ideal KCl line. MacFarlane et al.[22] proposed to term systems exhibiting such behavior “liquid ion pairs”. The divergence of the single values obtained for [Na][TOTO] at different temperatures from the

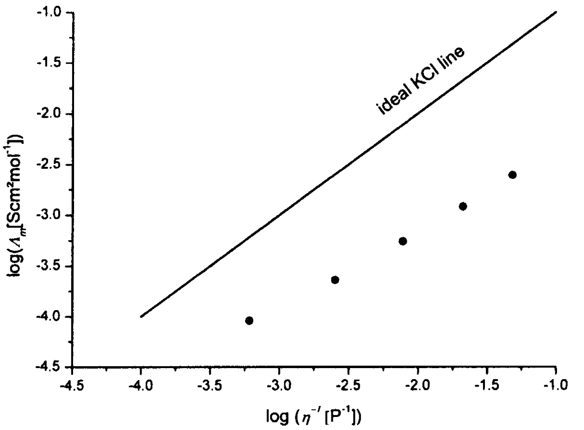

Figure 2. Walden plot for [Na][TOTO] over a temperature range between 25 and 65 °C in comparison to the ideal KCl line.

ideal line is summarized in Table 3, where ΔW is the vertical deviation. These findings clearly suggest the presence of strong ion pairing in the liquid sodium oligoether carboxylate.

Table 3. Deviation ΔW of [NA][TOTO] from the ideal KCl line in the Walden plot at different temperatures.

T [°C]	25	35	45	55	65
ΔW	0.8	1.0	1.1	1.2	1.3

It is evident that these new ionic liquids display interesting physicochemical properties, including remarkably high thermal and electrochemical stability. Noteworthy is that the lithium and sodium TOTO salts are liquids at room temperature. So far room-temperature ILs based on alkali metal cations have not been described in literature. Nonetheless, the reason for these substances being liquid at ambient temperature remains to be discussed.

The interactions of alkali and alkaline-earth metal ions with the CH_2CH_2O unit in solution have been studied extensively. The complexation of alkali metal ions by cyclic and acyclic polyether ligands has been reviewed.[23] It is furthermore well known that the so-called "glymes" (polyethylenglycol dimethyl ethers) with the general structure CH_3O-$(CH_2CH_2O)_nCH_3$ possess a high affinity to alkali metal cations. Interestingly, in particular the tetraglyme (TeG, $n=4$) is structurally very similar to the TOTO anion. Grobelny et al. conducted a comparative study on solutions of potassium ions in tetraglyme in the presence and absence of [18]crown-6.[24] It was claimed that tetraglyme is a strong complexing agent for K^+, the latter being surrounded by the tetraglyme molecules in a pseudo-crown ether fashion. Other studies reported significant interactions of glymes with Li^+ in solution.[25] Ab initio calculations for the tetra-, penta-, and hexaglyme complexes of lithium led to the conclusion that the coordination number for Li^+ with respect to the solvent oxygen atoms varies between 4 and 6.[26]

Based on this, we suggest that in the present case a complexation of the alkali metal cations by their combined oligoether–carboxylate counter-ion is sufficient to generate room-temperature liquid salts. Simultaneous "intramolecular" charge neutralization and complexation apparently diminishes the salt character of the substance, thereby shifting it to the state of a neutral "molecule" and correspondingly lowering the melting point. Such a hypothesis is supported by the recorded mass spectra, which indicate the presence of associated ion pairs in the gas phase (see the Supporting Information, Figures S8–S10), and by the Walden plot, which gives evidence for the formation of liquid ion pairs. Apart from that, there is experimental evidence suggesting that the net interactions between the alkali metal cations and the TOTO anion are stronger in the case of Li^+ than for Na^+. This becomes manifest in the extension of the electrochemical window both in cathodic and anodic direction when sodium is replaced by lithium. More thorough NMR and IR analyses further confirm the notion of a pronounced complexation in the present systems (data not shown). Detailed studies on the structure and properties of such complexes will be presented in a forthcoming publication.

To gain a better insight into potential applications, the cytotoxicity of the new ionic liquids was studied by using a MTT assay with Hela cells (for details see the Supporting Information). As a reference, several common ILs were tested, namely ethylammonium nitrate (EAN) as well as the imidazolium-based cations [emim] (1-ethyl-3-methylimidazolium) and [bmim] (1-butyl-3-methyl-imidazolium) with the anions tetrafluoroborate and ethyl sulfate. For each sample, the IC_{50} value was determined, which represents the concentration of the test substance that reduces cell viability by 50 % compared to the untreated control. Thus, the higher the IC_{50} value, the less toxic is the substance. All experiments were repeated four times; the resulting averaged IC_{50} values are plotted in Figure 3. From these data, two important conclusions can be drawn. First, the cytotoxicity of the alkali metal TOTO salts depends on the nature of the alkali metal cation, with [Na][TOTO] exhibiting the highest IC_{50} value and therefore being least toxic. Second, the IC_{50} values of the TOTO salts are significantly higher than those

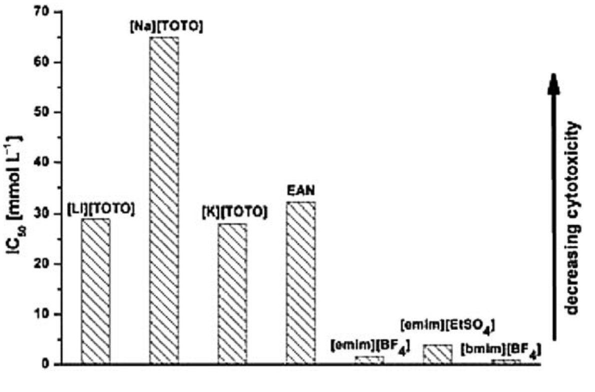

Figure 3. Cytotoxicity of the TOTO alkali metal salts as compared to common ILs.

of the widely studied imidazolium-based ILs. In this sense, [Na][TOTO] is, for example, fifty times less cytotoxic than [bmim][BF_4]. In fact, the cytotoxicity of the alkali metal TOTO salts was found to be comparable to that of EAN. This finding underlines the potential of these new ionic liquids for many applications.

In conclusion, a new family of ionic liquids was introduced based on the combination of simple alkali metal ions and oligoether carboxylates. The described substances are promising materials due to their pronounced electrochemical and thermal stability. The concept of the ionicity plot was successfully applied to the sodium salt for which strong ion pairing was observed. Furthermore, it was shown that the cytotoxicity of such "simple" alkali metal carboxylate ionic liquids is very low. The physicochemical properties and the design of additional new room-temperature liquid TOTOA derivatives are currently under investigation. In fact, the use of simple tri- and tetraalkylammonium instead of alkali metal ions has also yielded ionic liquids at ambient temperature that appear to display additional desirable properties, such as low viscosity. The combination of the TOTO anion with "biological" cations such as choline might pave the way to even "greener" ILs.

Experimental Section

Synthesis of 2,5,8,11-tetraoxatridecan-13-oic acid (TOTOA): Sodium (30.44 g, 1.32 mol) was added portionwise to triethylene glycol monomethyl ether (TEGME; 360 mL) under a nitrogen atmosphere. Dissolution of the sodium was achieved by vigorous stirring and gradual heating to 120 °C. The hydrogen that formed was removed by applying a slight N_2 flow. The clear yellowish solution was subsequently cooled to 100 °C, and chloroacetic acid (62.91 g, 0.67 mol) dissolved in TEGME (110 mL) was added dropwise within 20 min. Then, the reaction mixture was stirred at 100 °C for 12 h. Excess TEGME was removed by distillation in vacuo, leaving a brown suspension. Subsequent treatment with an aqueous solution of phosphoric acid (95.69 g, 0.98 mol) yielded a clear brown solution, to which dichloromethane (300 mL) was added. The organic phase was separated, and the aqueous phase was extracted repeatedly with dichloromethane (100 mL). The unified organic phases were dried over magnesium sulfate. Filtration and solvent evaporation resulted in a slightly yellow liquid. The crude 2,5,8,11-tetraoxatridecan-13-oic acid was purified by twofold distillation (b.p. 135–145 °C at 10^{-7} mbar) to give a clear colorless viscous liquid (120.91 g) in 81.2 % yield.

Synthesis of TOTOA alkali metal salts: Alkali metal salts of 2,5,8,11-tetraoxatridecan-13-oic acid were prepared by direct neutralization of the acid with alkali metal base. In the case of sodium and potassium, equimolar amounts of the corresponding hydrogen carbonate and the acid were dissolved in water and stirred for 1 h. Lyophilization and subsequent drying in vacuo gave the desired salts in quantitative yields. Na-TOTO was obtained as a faintly yellow viscous liquid, K-TOTO as white crystals. The synthesis of the Li salt was carried out in a 5:1 (v:v) mixture of ethanol and water using lithium hydroxide as base. After conversion, solvents were removed by lyophilization, and the product was vacuum-dried, resulting in a highly viscous colorless liquid.

Analytical methods: Spectral data (^{1}H NMR and ^{13}C NMR) of the as-prepared ionic liquids as well as results from ESI-MS and elemental analysis are given in the Supporting Information. The water content of all products was determined by Karl–Fischer titration, using an Abimed MCI analyser (Model CA-02). Conductivity measurements were carried out with an in- house built symmetrical Wheatstone bridge with Wagner earth, sine generator, and resistance decade. The electrolyte resistances were measured at frequencies between 10 kHz and 240 Hz and extrapolated to infinite frequency with cell constants in the range from 0.54 to 11.6 cm^{-1}. Viscosity measurements for the sodium salt were carried out on a Bohlin rheometer (type CVO 120 High Resolution) in an argon atmosphere at controlled temperature in the range 25–65 °C, working with a CP40/4° cone. Samples were studied at shear rates ranging from 0.25 to 200 s^{-1}, except for the measurement at 25 °C, which had to be stopped at 50 s^{-1} due to the high viscosity. Densities of [Na][TOTO], required for the calculation of the molar conductivities were measured by using a vibrating-tube densimeter (Anton Paar DMA60/601 HT) in a temperature range between 25 and 65 °C. The linear density equation for [Na][TOTO] was found to be $\rho_{[Na][TOTO]} = 1.26 \times 10^{-4}$ to $4.76 \times 10^{-4}\,t$ [gcm^{-3}] (t in °C). Differential scanning calorimetry (DSC) data were recorded on a Mettler DSC 30 in a nitrogen atmosphere using Al crucibles. The Li and Na salts were investigated within a temperature range of −150 to 20 °C, whereas the K salt was measured from −100 to 100 °C. The heating rate in all cases was 10 K min^{-1}. Transition temperatures were generally obtained from heating curves. Glass points were determined from the thermograms using the half-step temperature of the transition. Thermal stability was studied by using a thermogravimetric analyser from Perkin–Elmer (model TGA 7). Samples were measured at a heating rate of 10 K min^{-1}, applying a continuous nitrogen flow. Decomposition temperatures were determined using onset points of mass loss, being defined as the intersection of the baseline before decomposition and the tangent to the mass loss versus temperature plot in the following. The electrochemical stability of the salts was investigated by cyclic voltammetry (CV) measurements, employing platinum working and counter electrodes, and Ag/Ag^+ (BAS) with Kryptofix 22 (Merck, for synthesis) as reference electrode. For measurement, samples were dissolved in dry acetonitrile (Merck, for DNA synthesis, $\leq$ 10 ppm H_2O). Scans were recorded first in the anodic direction, with a rate of 10 mV s^{-1}. Cytotoxicity tests were performed by using Hela cells obtained from the American Type Culture Collection (ATCC). MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assays were conducted following a procedure proposed by Mosmann.[27]

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Keywords: green chemistry · ionic liquids · oligoether carboxylate · toxicity · Walden plot

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