

New generation ionic liquids: cations derived from amino acids†

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Two families of a new generation of ionic liquids, in which the chiral cations are directly derived from naturally occurring α -amino acids and α -amino acid ester salts, have been obtained *via* very simple preparations.

The rapidly growing research interest in ionic liquids (ILs) is undoubtedly stimulated by the development of green chemistry.^{1–4} ILs have been widely considered as greener alternatives to volatile organic solvents.^{5,6} Commonly used ILs, however, are synthetic chemicals and are therefore not as green as desired. Development of bio-renewable ILs to take the place of the synthetic quaternary nitrogen cations such as alkylammonium, dialkylimidazolium, and pyridinium usually used in ILs, is thus of great importance. Amino acids and their derivatives are the most abundant natural source of quaternary nitrogen precursors, however they have rarely been directly used to prepare the cations in ILs. In this paper, we report two families of a new generation of ILs, in which the cations involved are derived directly from natural α -amino acids and α -amino acid ester salts. More than one hundred ILs have been obtained *via* very simple preparations. The chiral centers present in the original α -amino acids have been successfully retained in the final ILs.

ILs are composed entirely of ions. Use of bio-renewable natural compounds as starting materials for the preparation of the ions in ILs is a promising ongoing approach.⁷ Successful procedures for the preparation of ions, some of which contain chiral centers, have been reported for a variety of precursors including lactates,^{8,9} sugars,¹⁰ sugar substitutes¹¹ and amino acids.¹² Chirality continues to receive significant attention from chemists and biologists.¹³ Preparation of chiral cations from natural materials has resulted in several publications,^{14–18} however these studies surprisingly tend to use the natural materials merely as precursors for multi-step syntheses of more complex materials: for example, use of amino acids to prepare imidazolium-based cations.^{17,18}

Our strategy using amino acids to prepare ILs is shown in Fig. 1. Some representative materials obtained by the one-step acidification of amino acids, which results in the formation of the amino acid salts [AA]X (X = Cl⁻, NO₃⁻, BF₄⁻, PF₆⁻, 1/2SO₄²⁻, CF₃COO⁻), is illustrated in Table 1. The products are named using the general three-letter symbols for amino acids and the chemical formula of the anion: for example, AlaNO₃ represents alanine nitrate (Table 1).

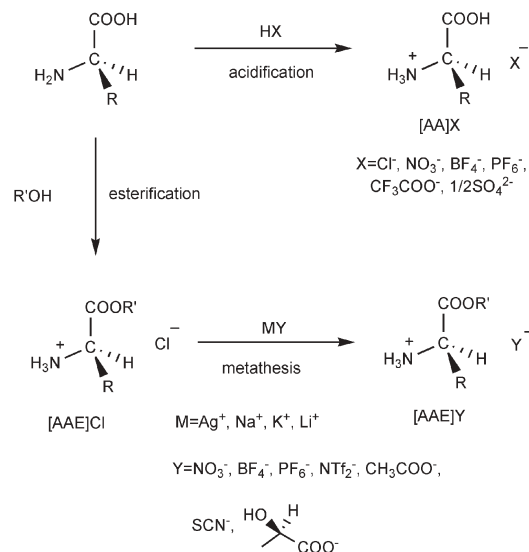


Fig. 1 Schematic strategy for the synthesis of amino acid-based ionic liquids.

The formation of [AA]X is a simple protonation reaction carried out by mixing the correct molar ratio of amino acid and relevant strong acid in water, followed by evaporation of the water in air and finally under vacuum. This one-step procedure is a typical atom-economic reaction without any poisonous

Table 1 The properties of amino acid salts ([AA]X)

No.	Product	$T_m/^\circ\text{C}^a$	$T_{dec}/^\circ\text{C}^c$	$d_4^{20}/\text{g}\cdot\text{cm}^{-3}(\pm 5\%)$	$[\alpha]_D^{20d}$
1	GlyCl	186	195	1.40	—
2	GlyNO ₃	111	192	1.22	—
3	GlyBF ₄	116	220	1.51	—
4	GlyPF ₆	101	157	1.37	—
5	AlaNO ₃	159	168	1.26	+15.9°
6	AlaBF ₄	78	241	1.44	+11.6°
7	AlaPF ₆	^b	176	1.33	+8.4°
8	AlaCF ₃ COO	82	119	1.02	+8.6°
9	Ala ₂ SO ₄	141	193	1.55	+9.1°
10	ValNO ₃	134	169	1.06	+27.2°
11	IleNO ₃	105	167	1.05	+40.3°
12	ThrNO ₃	^b	147	1.86	-10.8°
13	ProNO ₃	^b	138	1.38	-29.7°
14	ProBF ₄	76	236	1.63	-26.8°
15	ProPF ₆	^b	168	1.56	-24.0°
16	Pro ₂ SO ₄	92	206	1.58	-38.7°
17	ProCF ₃ COO	78	192	1.48	-36.1°

^a Melting points (T_m) were determined by DTA, heating at 5 °C min⁻¹ under nitrogen. ^b No melting transition observed. ^c Decomposition temperatures (T_{dec}) were determined by TGA, heating at 5 °C min⁻¹ under nitrogen. ^d Solution in CH₃OH and $c = 2$.

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by-product.¹⁹ It can be seen from Table 1 that half of the products (8 out of 17) are white solids, of which several have been used to prepare amino acid crystals.^{20–23} The other 9 samples are ILs having melting points lower than 100 °C. Of these, AlaPF₆ and ThrNO₃ are both viscous liquids at room temperature while ProNO₃ and ProPF₆ are genuine room temperature ILs.

It is reasonable to assume that the high melting points of some of the [AA]X salts result mainly from strong hydrogen bonds involving the carboxylic acid group. Esterification is an appropriate way to minimize such hydrogen bonding. A general synthetic strategy based on the family of amino acid ester salts, [AAE]Y (Y = NO₃⁻, BF₄⁻, PF₆⁻, NTf₂⁻, SCN⁻, CH₃COO⁻, CH₃CH(OH)COO⁻), has therefore been proposed in order to prepare a greater variety of room temperature ILs, as shown in Fig. 1. In principle, such a strategy makes an extensive family of more than one hundred ILs immediately available. Esterification reduces the amount of hydrogen bonding, resulting in a significant decrease in the melting points of the salts whilst having little influence on the quaternary nitrogen cations, and a series of lower melting point salts or ILs have been successfully obtained. Some representative examples are summarised in Table 2. We again use the general symbols to represent the amino acids, and use the number of carbon atoms to represent the alkyl groups: for example, alanine methyl ester nitrate is denoted AlaC₁NO₃. Since amino acid ester hydrochlorides, [AAE]Cl, are available commercially, the preparation of [AAE]Y ILs is as straightforward as that of the [AA]X salts. Furthermore, it should be noted that esterification provides the possibility of adjusting the properties of the resulting ILs, and the “designer solvent” character of ILs is therefore potentially enhanced.

It is clear from Table 2 that half of the products (12 out of 22) are room temperature ILs and almost all of the products are ILs below 100 °C. It is interesting to note that although the [AAE]Cl salts used as precursors in this work usually have melting points

near 200 °C and decompose at that temperature, they can be completely transformed into ideal ILs by anion replacement. The ILs obtained are thermally stable up to 150 to 200 °C, a little lower than those of imidazolium ILs, but much higher than the minimum 100 °C criterion described by Wasserscheid for chiral ILs.¹⁶ All the [AAE]Y ILs have the same glassy state character as that of commonly used ILs. The glass transition temperatures were determined by differential scanning calorimetry (DSC) from the first heating cycle, after initially cooling samples to -70 ~ -100 °C. All of them had a glass transition temperature (*T*_g) in the range -10 to -40 °C. Then, as the temperature increased, the solid samples showed clear melting peaks on the DSC curves. For example, AlaC₁NO₃ showed a *T*_g at -34 °C with m.p. at 61 °C (Fig. 2). The room temperature liquid samples have different characteristics however, showing solid–solid transitions at lower temperatures and solid–liquid transitions at higher temperatures. A typical DSC curve, for IleC₁NO₃, is illustrated in Fig. 2. After cooling in a dry ice/acetone bath to -70 °C, IleC₁NO₃ became a

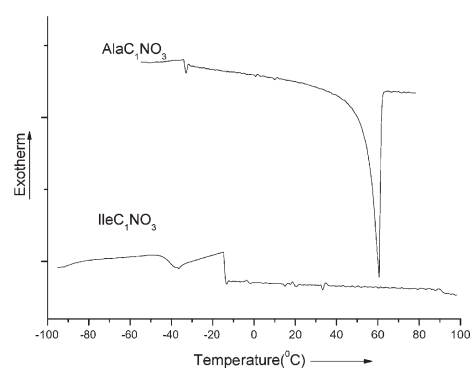


Fig. 2 Differential scanning calorimetry (DSC) trace of [AAE]Y-based ionic liquids (AlaC₁NO₃ and IleC₁NO₃).

Table 2 The properties of amino acid ester salts ([AAE]Y)

No.	IL	<i>T</i> _m /°C ^a	<i>T</i> _g /°C ^a	<i>T</i> _{dec} /°C ^b	<i>d</i> ₄ ²⁰ /g·cm ⁻¹ (±5%)	[<i>α</i>] _D ^{20c}	[AAE]Cl [<i>α</i>] _D ^{20c}	Viscosity/cP (±5%)
1	GlyC ₁ NO ₃	44	-26	178	1.50	—	—	92(70 °C)
2	GlyC ₂ NO ₃	49	-10	182	1.67	—	—	
3	AlaC ₁ NO ₃	61	-34	186	1.26	+6.2°	+6.2°	
4	AlaC ₁ BF ₄	-18 ^d	-48 ^e	230	1.53	+5.6°	+6.2°	96(30 °C)
5	AlaC ₁ PF ₆	^d	-35	209	1.36	+5.8°	+6.2°	
6	AlaC ₁ NTf ₂	-17 ^d	-61 ^e	150	1.55	+5.8°	+6.2°	
7	AlaC ₁ SCN	62	-38	139	1.27	+5.2°	+6.2°	103(80 °C)
8	AlaC ₁ Ace	^d	-23	172			+6.2°	
9	AlaC ₁ Lac	38	-24	77	1.20	-4.5°	+6.2°	
10	AlaC ₂ NO ₃	-17 ^d	-45 ^e	187	1.29	+4.7°	+2.9°	2030(30 °C)
11	AlaC ₂ Lac	75	-29	82	1.19	-5.7°	+2.9°	
12	ValC ₁ NO ₃	74	-33	195	1.31	+22.5°	+22.3°	
13	LeuC ₁ NO ₃	75	-31	210	1.15	+15.4°	+17.6°	1550(80 °C)
14	IleC ₁ NO ₃	-14 ^d	-36 ^e	172	1.35	+32.7°	+37.8°	
15	PheC ₁ NO ₃	92	-32	224	1.16	+21.1°	+18.1°	
16	ThrC ₁ NO ₃	-12 ^d	-32 ^e	156	1.72	-9.5°	-9.4°	
17	SerC ₁ NO ₃	105	-30	179	1.44	+7.3°	+3.7°	
18	ProC ₁ NO ₃	-16 ^d	-67 ^e	159	1.53	-36.4°	-34.5°	186(30 °C)
19	ProC ₁ BF ₄	^d	-20	234	1.45	-20.7°	-34.5°	
20	ProC ₁ PF ₆	^d	-22	221	1.47	-32.2°	-34.5°	
21	ProC ₁ Lac	^d	-20	140	1.22	-23.8°	-34.5°	
22	ProC ₂ NO ₃	-17 ^d	-50 ^e	183	1.57	-30.9°	-36.4°	

^a Glass transition temperatures (*T*_g) and melting points (*T*_m) from the onset position were determined by DSC from the first heating cycle, after initially cooling samples to -70 ~ -100 °C. ^b Decomposition temperatures (*T*_{dec}) were determined by TGA, heating at 5 °C min⁻¹ under nitrogen. ^c Solution in CH₃OH and *c* = 2. ^d No melting transition observed or solid–liquid transition temperature. ^e Solid–solid transition temperature.

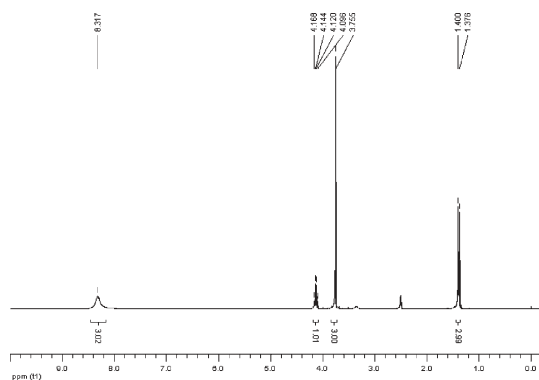


Fig. 3 ^1H NMR spectrum of AlaC_1NO_3 in d_6 -DMSO.

hard transparent solid. On heating, this became a very viscous opaque material near $-35\text{ }^\circ\text{C}$ and subsequently a transparent liquid near $-15\text{ }^\circ\text{C}$.

The ^1H NMR spectrum of AlaC_1NO_3 , as an example of [AAE]Y, is shown in Fig. 3. The broad peak at 8.32 ppm that can be assigned to the RNH_3^+ hydrogen, is similar to that of the 2-H of imidazolium cations, indicating a certain acidity for the [AAE]Y ILs. The pH value of AlaC_1NO_3 , measured in a 1 mol L^{-1} aqueous solution, was 3.5, showing weak Brønsted acidity. Since only a single positive ion ($\text{C}_4\text{H}_{10}\text{NO}_2^+$, $m/z = 104.0706$) was found for AlaC_1NO_3 by secondary ion mass spectrometry (SIMS), the acidity is believed to come from the hydrogen of the quaternary nitrogen.

It is very important to this work that the chiral centers in the synthetic precursors, whether amino acids or amino acid esters, are retained in the resulting ILs. Some asymmetric carbon atoms in chiral ILs have been reported to undergo racemization after a certain time.²⁴ In Table 2, the specific rotations in degrees of the ILs are compared with those of the corresponding synthetic precursors, [L-AAE]Cl. It can be seen that most of the ILs almost have the same specific rotation values as those of the precursors. When L-lactate is the anion (items 9, 11 and 21 in Table 2) however, the specific rotation values are altered significantly, indicating that two independent chiral centers exist in solution. Furthermore, regular monitoring indicated that the chirality of all the samples shown in Table 2 showed no change even after one month or longer, demonstrating that [AAE]-type ILs offer a new family of easily-prepared chiral ILs.

Table 2 also gives viscosity data for some [AAE]Y ILs when they are in the liquid state. From these data it can be concluded that [AAE]Y ILs display qualitatively similar viscosity behaviour to common imidazolium ILs.²⁵

Development of [AA]- and [AAE]-type cations provides a great opportunity to prepare novel green ILs, which are promising alternatives to commonly used ILs. Combination of [AAE] cations with suitable natural anions in order to prepare fully natural ILs is

being carried out in our laboratory. In evaluating any such work concerning the preparation of ILs from natural materials, we want to emphasize that (1) the natural properties of the materials, *i.e.*, the bio-renewable/bio-degradable properties should be retained; (2) the chiral centers in the synthetic precursors should be unchanged; and (3) the “designer solvent” properties of ILs, *i.e.*, the fact that the physical/chemical properties of the ILs can be adjusted by changing a side-chain connected to the core, should be maintained. The work described here completely satisfies these criteria. Furthermore, the simple preparation involved encourages the commercialization of processes based on [AA] and [AAE]-type ILs.

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