Chiral Stability of Phosphonium-type Amino Acid Ionic Liquids

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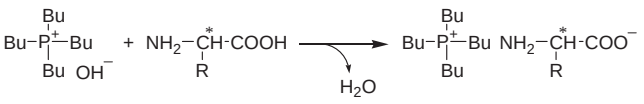
Tetrabutylphosphonium salts having amino acid-derived chiral anion exhibited melting point below 100 °C and retained their chirality at least 10 h at 100 °C.

Ionic liquids (ILs)[1] have been studied well as alternative solvents of conventional volatile organic compounds because of their characteristic features such as negligibly small volatility and less flammability. Various reactions have already been studied in ILs, and some advantages have been found in ILs.[2] Additionally, functionalized ILs, called "task-specific ILs (TSILs)[3]" have also been studied. The TSILs are symbolic development of designable organic ions. Among TSILs, chiral ILs[4] having chiral center in the component ion were expected to be valuable for asymmetric synthesis[2a,5] without chiral catalysis, enantiometric recognition,[6] and chiral separation. Although chiral stability was very important for their applications to prevent racemization of chiral compounds, there is no effective study on the chiral stability of chiral ILs. Difficulty of preparing pure and a large quantity of chiral ILs by general multi-step process is one of serious reasons of this slow progress.

We have already reported amino acid ILs prepared by the neutralization of native amino acids with suitable cations.[7] Especially, amino acids combined with tetrabutylphosphonium [P_{4444}] provided higher thermal decomposition temperature and less viscosity than imidazolium-based amino acid ILs.[7b] These amino acid ILs were chiral ILs having various side chain structure prepared easily and quantitatively compared to conventional chiral ILs. We have already confirmed that [P_{4444}][L-Glu], which was solid at room temperature, is enantio-pure by X-ray diffraction analysis. In this study, thermal stability on the chirality of amino acid ILs has been investigated, and the effect of component ion structure was discussed.

Amino acid ILs[7] were prepared by the similar procedure to that we have reported. Slightly excess amount of amino acid was added to [P_{4444}][OH] aqueous solution, and then water was removed by freeze drying (Scheme 1). The [P_{4444}][OH], a gift from Hokko Chem. Ind. Co. Ltd., was used without further purification. Then, the reaction mixture was added into methanol/acetonitrile solution, and filtrated to remove excess amino acid. Filtrate was evaporated to remove solvents. The product was dried in vacuo for at least 3 days at 50 °C until water content of ILs checked less than 0.5 wt % determined by Karl–Fischer Coulombic titrator (Kyoto Electronics. MKC-510N). The sample was sealed off in a vessel under N_2 atmosphere, and then stored in an oven at a given temperature. Although, there are some methods currently available for the determination of chirality, some methods have disadvantages for the detection of chiral stability. For example, HPLC using chiral column needs strict setting for each compounds, and CD spectroscopy cannot be used for compounds having no UV–vis absorption. An NMR spectroscopy with chiral recognition reagent such as Mosher's reagent is not suitable for the dynamic measurement. Based on these, optical rotation of the ILs was measured with JASCO DIP-1000 digital polarimeter in this study. The heat-treated ILs were diluted with methanol for constant concentration ($c = 2.0\,g/100\,mL$ MeOH), and the degree of optical rotation was measured at 25 °C using digital polarimeter with sodium D line.



Scheme 1. Preparation of phosphonium-based amino acid ILs [P_{4444}][amino acid]. R is a side group.

Since optical rotation value of amino acid is the function of the side chain structure, diluent solvent, and pH, amino acid ILs were carefully dried by freeze dryer without heat treatment, and they were analyzed by the digital polarimeter. Optical rotation value of amino acid ILs was also affected by the side chain structure (Table 1), similar to unmodified amino acids.

Among [P_{4444}][amino acid], chiral stability of [P_{4444}][L-Val] was studied because of large optical rotation value and no functional group on the side group. Small amount of samples were periodically drew from [P_{4444}][L-Val] maintained at 100, 120, or 150 °C. Then, the optical rotation value was divided by that for not heat-treated sample ($t = 0$), and their ratio ($[\alpha]_{d,t}/[\alpha]_{d,0}$) was used to evaluate the chiral stability. Although significant loss of optical rotation value for [P_{4444}][L-Val] treated at 100 °C for 10 h was not observed, heat treatment at 120 °C induced gradual decrease of chirality. Furthermore, chirality of samples decreased rapidly at 150 °C (Figure 1).

Then, ^{1}H NMR spectra of [P_{4444}][L-Val], which was heat-treated at 120 °C for 10 h, was measured (Figure 2). The optical rotation value of the sample treated at 120 °C decreased to about 20% of the sample without heat-treatment. Thermal decomposition temperature of [P_{4444}][L-Val], determined by successive heating of the thermal gravimetric analysis (Seiko Instrument Inc. TG/DTA 220, heating rate 10 °C min^{-1}, N_2 atmosphere)

Table 1. Optical rotation values of amino acid ILs

Ionic Liquid	R	$[\alpha]_D^{25}$
[P_{4444}][L-Ala]	CH_3	-1.1 ± 0.2
[P_{4444}][L-Leu]	$CH_2CH(CH_3)_2$	-1.3 ± 0.2
[P_{4444}][L-Val]	$CH(CH_3)_2$	$+5.0 \pm 0.3$
[P_{4444}][L-Thr]	CH_2OH	-1.3
[P_{4444}][L-Phe]	$CH_2C_6H_5$	-7.1 ± 0.2
[P_{4444}][L-Met]	$CH_2CH_2SCH_3$	-2.8
[P_{4444}][L-Lys]	$(CH_2)_4NH_2$	$+2.3$
[P_{4444}][L-Asp]	CH_2COOH	-29.4 ± 0.2
[P_{4444}][L-Glu]	CH_2CH_2COOH	-5.0 ± 0.5
[P_{4444}][D-Val]	$CH(CH_3)_2$	-5.1

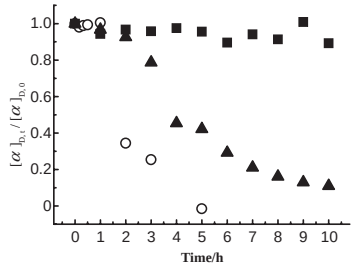


Figure 1. Thermal stability of chirality for $[P_{4444}][$L-Val] at different temperatures (■: 100 °C, ▲: 120 °C, ○: 150 °C).

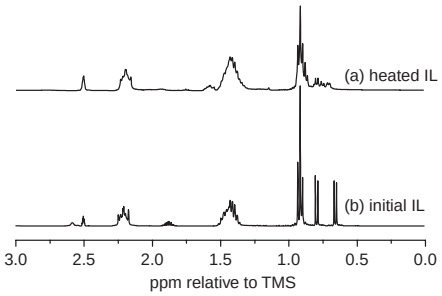


Figure 2. ^{1}H NMR spectra of $[P_{4444}][$L-Val] (a) heated at 120 °C for 10 h, (b) and not heat-treated one.

was 286 °C. Though significant weight loss was not observed at 150 °C, ^{1}H NMR spectra of $[P_{4444}][$L-Val] heat-treated at 120 °C for 10 h was changed. The peaks at 0.66 (3H), 0.80 (3H), and 1.89 ppm (1H) of $[P_{4444}][$L-Val] were assigned to isopropyl group of side chain. The peak at 2.59 ppm was assigned to the proton on the α-carbon of amino acid anion (Figure 2b). The heating of $[P_{4444}][$L-Val] induced the decrease of the peak assigned to side chain of amino acid anion in comparison with the peak of P_{4444} cation, and especially the peak for the proton on the α-carbon disappeared. Although partial racemization might also occur, these suggested that the decrease of optical rotation value of amino acid ILs was attributable to thermolysis of amino acid anions. However, both carboxylic acid group and amino group were detected by FT-IR spectroscopy even after heating at 120 °C for 10 h. The decrease in the optical rotation value still cannot be explained.

The effect of water content of ionic liquid was studied. When 12 wt % water (73 mol % to the ILs) was added to $[P_{4444}][$L-Val], there was no significant difference of chiral stability after heat treatment at 120 °C for 3 h. The decrease of the optical rotation values was attributable to the thermolysis of amino acid anions, rather than simple racemization. Stability of pure amino acids was comprehensible to the effect of the formation of zwitterionic structure. Actually, unmodified amino acids in acidic or alkaline aqueous solution were racemized easier than those in neutral aqueous solution. After neutralization of amino acids with phosphonium cations, free amino groups cannot contribute to form the zwitterionic structure. This free amino group should lower the chiral stability of the salts.

Additionally, chiral stability of both $[P_{4444}][$L-Phe] and $[P_{4444}][$L-Asp] was also studied (Figure 3). The chirality was maintained under heating as the following sequence: $[P_{4444}][$L-Asp] < $[P_{4444}][$L-Phe] < $[P_{4444}][$L-Val]. Although a particular

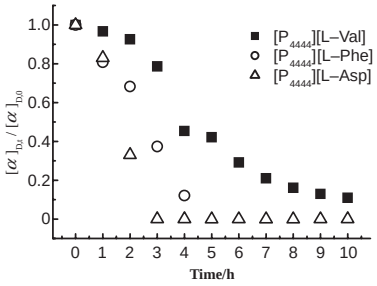


Figure 3. Side chain effects on chiral stability of ILs at 120 °C.

mechanism is still not clear, side chain structure should affect the stability of α-hydrogen or other site.

In conclusion, chiral stability of amino acid ILs as a model of ILs having chiral center was investigated. For example, $[P_{4444}][$L-Val] was stable over 10 h at 100 °C. Though significant weight loss was not found by TG/DTA measurement, the decrease in the optical rotation value of heat-treated amino acid ILs at 120 °C might be attributed to a slow thermolysis of amino acid anions.

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