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A simple preparation of D-alloisoleucine from L-isoleucine via acetylation and separation of the ammonium salts

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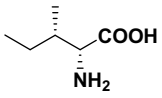
ABSTRACT

D-Alloisoleucine was obtained from L-isoleucine by acetylation and epimerization by acetic anhydride followed by separation of the diastereoisomeric ammonium salts using the solubility difference. The structure–solubility relationship of diastereoisomeric salts was explained by X-ray crystal structure analysis.

1. Introduction

D-Alloisoleucine ((2*R*,3*S*)-2-amino-3-methylpentanoic acid; D-alle) is a diastereoisomer of L-isoleucine ((2*S*,3*S*)-2-amino-3-methylpentanoic acid; L-Ile) and is known to be contained in biologically active peptides such as theonellapeptolides.[1–3] It is a starting material for the synthesis of isostatine,[4] which is a component of potent antitumor peptides, tamandarins, and didemnins.[5,6] Considering that compounds containing nonprotein amino acids such as D-alle could be less biodegradable, D-alle may be expected to be important for potential medical use.



(2*R*,3*S*)-2-Amino-3-methylpentanoic acid
D-Alloisoleucine (D-aIle)

D-Alle has been prepared by various methods: a total synthesis from (*S*)-2-methyl-1-butanol by the Strecker method,[7] a chemoenzymatic method using alcalase,[8] and some resolution methods using resolving reagents.[9,10] Noda et al. prepared D-alle via an insoluble salt with a chiral tartaric acid derivative.[11] These methods are rather complicated and expensive, and there is a strong demand for a facile and low-cost method of preparation of D-alle. We report herein a simple method for preparation of D-alle from L-Ile in several steps via acetylation and recrystallization of the ammonium salts.

2. Results and discussion

2.1. Epimerization of L-Ile

Among several methods of racemization (or epimerization) at α-position of α-amino acids, we examined two methods to epimerize L-Ile: one using acetic anhydride,[12] which causes N-acetylation, and one using a catalytic amount of salicylaldehyde[13] in glacial acetic acid. By the latter method about 50% of L-Ile was converted to D-alle at 80 °C within 1 h, and an additional reaction time made little change to the ratio of epimers. Acetic anhydride in glacial acetic acid reacted with L-Ile to acetylate and epimerized it simultaneously at 80 °C, giving a mixture of approximately equal amounts of *N*-acetyl-L-isoleucine (Ac-L-Ile) and *N*-acetyl-D-alloisoleucine (Ac-D-alle) within 15 min. Although these two types of epimerizations take place through different reaction mechanisms, the ratios of the acetylated epimers, Ac-L-Ile: Ac-D-alle, were very similar (ca. 1:1). However, Ac-D-alle and Ac-L-Ile have similar solubilities in various solvents, so that it is difficult to separate Ac-D-alle from the mixture by recrystallization.

2.2. Solubilities of the ammonium salts of N-acetylated derivatives

An approximately 1:1 mixture of Ac-L-Ile·NH_3 and Ac-D-alle·NH_3, obtained by treating the N-acetylated mixture with 1 mol/dm^3 aq NH_3, gave Ac-D-alle·NH_4 by recrystallization from C_2H_5OH in 94% yield. We found that the solubilities in C_2H_5OH of these N-acetylated derivatives are drastically reduced by conversion to ammonium salts: while the solubilities of Ac-D-alle and Ac-L-Ile in 100 cm^3 of 95% C_2H_5OH at 20 °C are 85.9 and 89.6 g, respectively, those of the corresponding ammonium salts, Ac-D-alle·NH_4 **1** and Ac-L-Ile·NH_4 **2**, are 0.25 and 2.29 g, respectively,

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which indicates that compound **2** is about 9 times more soluble than **1**. Compound **1** could be isolated from the mixture of the ammonium salts and converted to D-alle in 89.0% yield,[14] which exhibited $[\alpha]_D = -38.3$ (*c* 2, 5 mol/dm^3 HCl) {lit.[15] $[\alpha]_D = -38.4$ (*c* 4, 6 mol/dm^3 HCl)}.

2.3. Relationship between solubilities and structures in crystals

In order to reveal the observed large solubility difference between the ammonium salts **1** and **2**, we determined their structures by X-ray crystal structure analysis.[16] The molecular structures of **1** and **2** are shown in Figures 1 and 2, respectively, and the distances of the hydrogen bonds in these structures are summarized in Tables 1 and 2, respectively. Because Ac-D-alle and Ac-L-Ile are epimers regarding the C_α carbon, they have different conformations at the C_α–C_β bond. Considering that the C(2)–C(3)–C(5)–N(1) torsion angles for **1** and **2** are 56.88(11)° and −167.14(16)°, respectively, the conformations of the acetylamino group on C_α (C(5)) and the ethyl group on C_β (C(3)) in the Ac-L-alle anion are gauche in order to make the molecule compact, while those for the Ac-L-Ile anion are equatorial to make the molecule linear. The difference of the molecular shapes might have influences on molecular packing (Fig. 3). The ethyl group of **1** is stretched in a direction perpendicular to the *ab* plane, which is parallel to the layer formed by hydrogen bonds between the ammonium ions and carboxylates or amides, giving a more densely packed crystal structure. The ethyl group of **2** gives rise to a steric hindrance for packing the Ac-L-Ile anions, and thus vacant sites in hydrophobic layers. The interactions between the side chains of the anions have strong effects on crystal packing and the other interactions in crystals. The crystal of **1** belongs to the orthorhombic system, which is of higher symmetry than the monoclinic system, to which the crystal of **2** belongs. The ammonium ion interacts with the oxygens of three carboxylate groups and one oxygen of the amide group. The Ac-D-alle anion forms four similar hydrogen bonds with the ammonium ion with the H···O distances of 1.85–1.88 Å (Table 1). On the other hand, because of the steric hindrance between the side chains, the Ac-L-Ile anion interacts with the ammonium ions with two strong hydrogen bonds (d(H···O) = 1.81 and 1.82 Å) and two weak hydrogen bonds (d(H···O) = 1.91 and 1.97 Å) (Table 2), differences between the bond distances being over 0.1 Å. Since the stability of the crystal structure is considered to largely depend on the strength of the intermolecular interactions, the difference in the hydrogen bonding modes between **1** and **2** may explain the difference in the solubility.

Table 1
Hydrogen bond distances around an ammonium ion of **1**

Atoms	Distance (Å)
O(1)···H(15)	1.88(1)
O(1′)···H(16)	1.85(2)
O(2″)···H(17)	1.87(2)
O(3‴)···H(18)	1.88(1)

Table 2
Hydrogen bond distances around an ammonium ion of **2**

Atoms	Distance (Å)
O(1)···H(15)	1.81(3)
O(1′)···H(16)	1.91(2)
O(2″)···H(17)	1.82(2)
O(3‴)···H(18)	1.97(2)

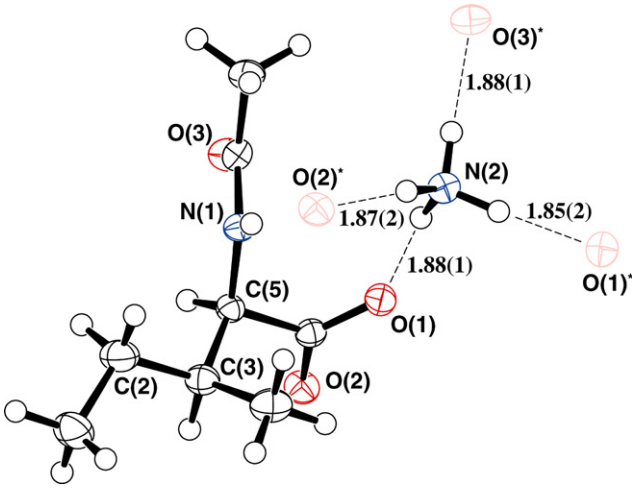

Figure 1. Structure of Ac-D-alle·NH_4 (**1**).

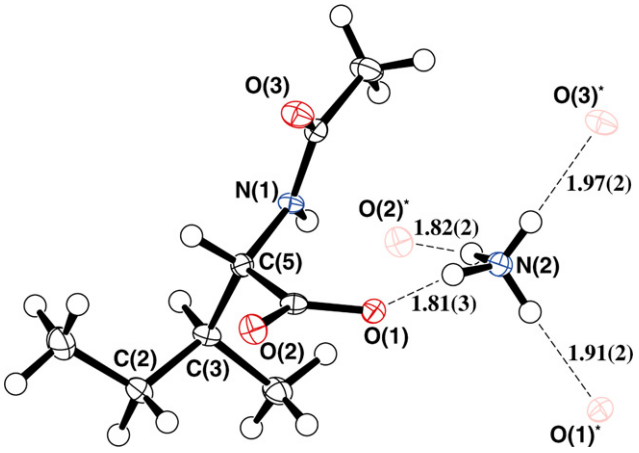

Figure 2. Structure of Ac-L-Ile·NH_4 (**2**).

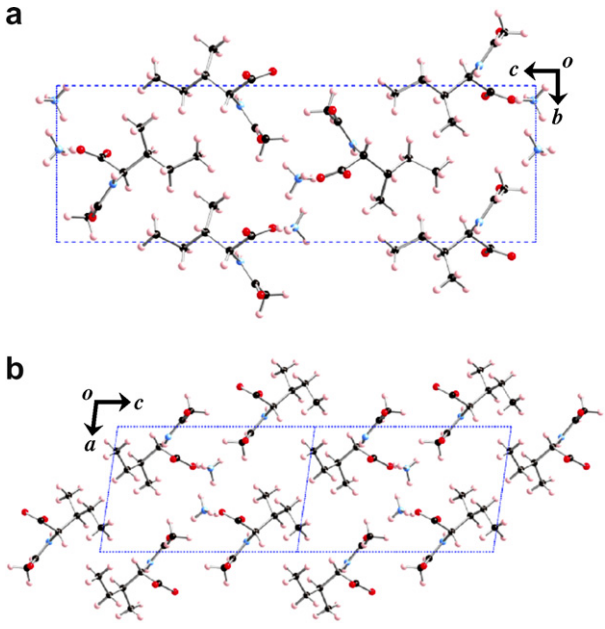

Figure 3. Schematic views of packing in **1** and **2**: (a) Ac-D-alle·NH_4; (b) Ac-L-Ile·NH_4.

3. Conclusion

In conclusion, we established a facile method of preparation of D-alle via acetylation and separation of Ac-D-alle in the form of the ammonium salt. We revealed that the ammonium salts of (*RS*)-*N*-acetyl-aminobutanoic acid, *N*-acetyl-DL-norvaline, *N*-acetyl-DL-norleucine,[17] and *N*-benzoyl-DL-alanine[18] are conglomerates, which are optically resolved by preferential or replacing crystallization. The procedure which makes use of the hydrogen bonds involving the ammonium ion will be applicable to similar systems.

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14. Ac-D-alle·NH_4 1.24 g (6.52 mmol) was dissolved in water (10 cm^3), and 5 mol/dm^3 aq HCl was added until pH < 1. Ac-D-alle was collected by filtration as a white precipitate and dried. Yield 1.08 g (95.7%). $[\alpha]_D = -21.5$ (*c* 2, C_2H_5OH) (lit. $[\alpha]_D = -21.5$ (*c* 2, C_2H_5OH)). ^1H NMR(400 MHz, 0.1 mol/dm^3 DCl, DSS) δ_H: 4.44 (1H, d, 2-C*H*), 2.06 (3H, s, –NHCOCH_3), 2.00 (1H, sep, 3-C*H*), 1.33 (2H, quin, 4-CH_2), 0.92 (3H, d, 3-CHCH_3), 0.89 (2H, t, 5-CH_3).
Ac-D-alle 3.01 g (17.4 mmol) dissolved in 2 mol/dm^3 aq HCl (20 cm^3) was refluxed for 2 h at 80 °C, and the resulting solution was evaporated to dryness. The residue was dissolved in C_2H_5OH (20 cm^3) and neutralized by triethylamine. D-Alle was obtained by filtration as a white powder and recrystallized from hot water. Yield 2.12 g (93.0%). ^1H NMR(400 MHz, 0.1 mol/dm^3 DCl, DSS) δ_H: 4.11 (1H, d, 2-C*H*), 2.17 (1H, sep, 3-C*H*), 1.40 (2H, quin, 4-CH_2), 1.00 (3H, d, 3-CHCH_3), 0.96 (2H, t, 5-CH_3).
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16. Crystals for X-ray crystal structure analysis were obtained by recrystallization from 95% C_2H_5OH. The X-ray experiments for **1** were carried out on a Rigaku Saturn CCD system with graphite-monochromated Mo Kα radiation (λ = 0.71070 Å). The crystal was mounted on a nylon loop at −100 °C. For determination of the cell constant and orientation matrix, six oscillation photographs were taken for each frame with the oscillation angle of 0.5° and the exposure time of 5 s. The X-ray experiments for **2** were carried out on a Rigaku RAXIS imaging plate area detector with graphite-monochromated Mo Kα radiation. The crystal was mounted on a nylon loop at −100 °C. For determination of the cell constant and orientation matrix, three oscillation photographs were taken for each frame with the oscillation angle of 3° and the exposure time of 3 s. Intensity data were collected by taking oscillation photographs, and the reflection data were corrected Lorentz and polarization effects. The structures were solved by the direct method and expanded by Fourier techniques. The non-hydrogen atoms were refined anisotropically by full-matrix least-squares calculation. Crystallographic data for **1**: $C_8H_{18}O_3N_2$, M = 190.24, orthorhombic, $P2_12_12_1$, a = 5.7896(15) Å, b = 7.754(3) Å, c = 23.961(6) Å, V = 1057.7(6) $Å^3$, Z = 4, D_{calc} = 1.175 g cm^{-3}, 2455 unique reflections. Refinement with all 17,776 reflection converged at final R = 0.0673 and wR_2 = 0.1799. **2**: $C_8H_{18}O_3N_2$, M = 190.24, monoclinic, $P2_1$, a = 7.743(4) Å, b = 5.849(3) Å, c = 12.195(6) Å, b = 98.229(9)°, V = 546.7(5) $Å^3$, Z = 2, D_{calc} = 1.156 g cm^{-3}, 2429 unique reflections. Refinement with all 2429 reflection converged at final R = 0.0662 and wR_2 = 0.0783. Crystallographic data (excluding structure factors) for **1** and **2** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication numbers CCDC 659189 and 659190, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-003; e-mail: deposit@ccdc.cam.ac.uk).
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