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ORIGINAL PAPER

# Mass spectrometric study of amino acid–triethylborane chelates

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**Abstract** Synthesis of chelates from selected L-amino acids and triethylborane, and the mass spectra of the chelates, are described. Conditions for forming dimers between the chelates and the sodium ion are discussed, and structures are proposed for the dimers.

**Keywords** Amino acids · Boron · Chelates · Mass spectrometry

## Introduction

In recent years, boron compounds have been exploited not only for reduction [1–5] and functionalization of double bonds [6–9] but also as groups enabling the synthesis of excellent catalysts for asymmetric reactions [10–15]. Boron compounds react with amino alcohols or amino acids to give heterocompounds by formation of strong intramolecular coordinate bonds between the nitrogen and boron atoms. Use of reagents containing electrophilic atoms usually leads to formation of amino acid complexes with five-membered heterocyclic structures [16, 17].

Amino acids are fundamental components of living organisms. Their capability to form chelates, e.g. with boron compounds, and intermolecular interactions are current interests in modern chemistry. Conversion of amino acids into boron chelates has some advantages:

1 it is a convenient method for simultaneously blocking both functional groups (amino and carboxyl) in a one-pot reaction;
2 the chelates are useful reagents for further structural modifications of the side chain;
3 in contrast with the starting amino acids, the chelates are soluble in a variety of solvents; and
4 mild conditions are used for hydrolysis of the chelates.

9-Borabicyclo[3.3.1]nonane (9-BBN) is a remarkably useful reagent for making amino acid boron chelates [18].

During our research on the synthesis of amino acids chelates from triethylborane, we found that the ESI-MS spectra of all the chelates contained very intense peaks corresponding to dimeric chelates with the sodium ion. In order to explain this observation, we present below a mass spectrometric study of selected chelates.

## Results and discussion

Heating an amino acid with excess $BEt_3$ in THF as solvent leads to dissolution of the starting amino acid. Spectroscopically pure amino acid chelates precipitate as white crystals on addition of toluene or acetonitrile to the oily residue remaining after removal of the THF. Synthesis of the chelates was performed according to Scheme 1.

The structures of the boron chelates thus obtained were confirmed by $^{1}H$ and $^{13}C$ NMR, and by EI and ESI-mass spectrometry. As mentioned above, all ESI-MS spectra reveal the formation of the ion $[2M + Na]^+$ between the chelate dimers and the sodium ion. In order to establish the effect of the presence of chelates on the chemical shift of sodium, we recorded the $^{23}Na$ NMR spectrum for a mixture of phenylalanine chelate **4** and $NaClO_4$ in the molar ratio 2

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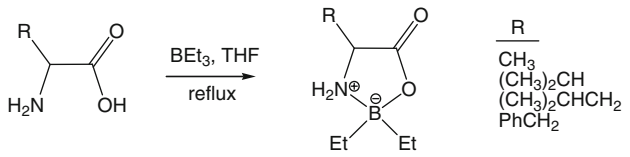



**Scheme 1**

to 1. The experiment indicated that addition of the chelate **4** caused a small shift of the sodium signal. The sodium signal for $NaClO_4$ was observed at $\delta = -4{,}830$ ppm which, in the presence of 2 equivalents of chelate **4**, was shifted to $\delta = -4{,}726$ ppm. It is also evident that the sodium ion has a small effect on electrostatic stabilization of the dimer being formed. Similarly, a small difference in chemical shift of the amine protons ($NH_2$) was observed in the $^1$H NMR spectrum. In the absence of $Na^+$, these protons resonated at $\delta = 5{,}036$ ppm. Addition of sodium ions ($NaClO_4$) moved the signal downfield. When the molar ratio of phenylalanine chelate **4** to sodium ions was 2 to 1, the amine protons were observed at $\delta = 5{,}071$ ppm. To determine the stability of the dimers, we performed more accurate measurements of the mass spectra using EI and ESI methods.

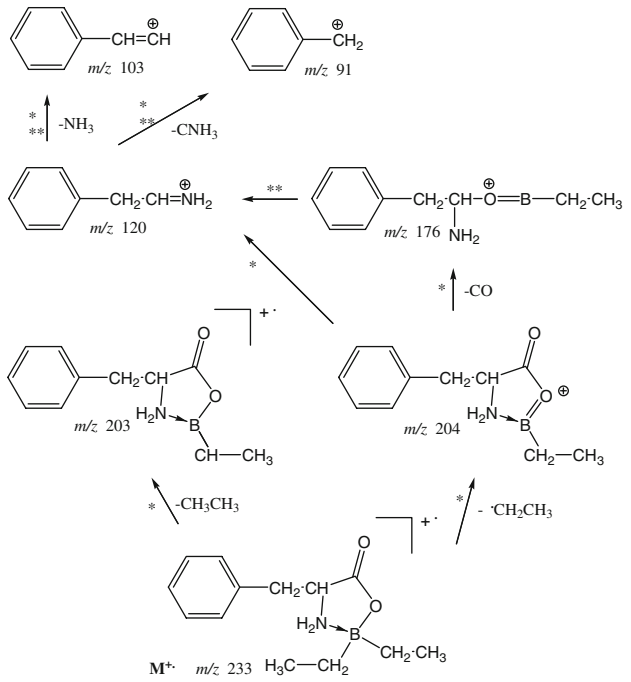
The EI mass spectra of α-amino acids and chelates of α-amino acids contain characteristic peaks arising from fragmentation of either of the two carbon–carbon bonds to which the amino group is attached, and to fragmentation of the group R if it contains any one of the structural features leading to the preferred fragmentation. Because of the presence of a number of easily cleaved bonds in these molecules, the molecular ion is very unstable and has a high tendency to decompose. Examination of the EI mass spectra of the compounds revealed very low-abundance signals of their molecular ions (0.1–0.6% r.a.). The EI-MS data of the chelates of the amino acids are listed in Table 1. These compounds show very similar behaviour upon electron impact. As an example, the fragmentation pathway proposed for phenylalanine chelate **4** is shown in Scheme 2 and its fragmentation behaviour could be extended to the other chelates.

The EI-MS spectra of all the compounds studied contain a peak corresponding to loss of mass 29 ($\cdot C_2H_5$ radical) from the molecular ion **a**. It follows from B/E linked-scan mass spectra that decomposition of this fragment ion **c** involves elimination of masses 28 and 84. The eleven-electron ion **c** loses a CO molecule to form ion **g**. Further fragmentation of ion **g** proceeds with elimination of the $BOCH_2CH_3$ molecule (ion **b** is obtained). Ion **b** may also be obtained directly from ion **c** by elimination of $CO_2BCH_2CH_3$ (mass 84). The "amine fragment" [R–CH–$NH_2$]$^+$ obtained gives the most intense peak in the mass spectra of all compounds studied. The B/E mass spectra of metastable ions recorded for ion **b** have shown the abundant product ions formed by loss of mass 17 ($NH_3$ molecule), and mass 29 (:CH–$NH_2$ molecule). In these fragmentation pathways formation of ions **e** and **f** is observed. For phenylalanine chelate **4** the relative abundance of ion **f** is high, because of a number of resonance structures which can be proposed for this ion. The next abundant odd-electron fragment ion **d** derived from the molecular ion **a** is that formed by loss of mass 30 ($C_2H_6$ molecule). This loss involves hydrogen rearrangement to the ethyl group of the diethylborone moiety.

For MS analysis, positive and negative-ion mode electrospray ionization (ESI) were applied in this study, as they

**Table 1** EI-MS data obtained for compounds studied

| Ion | Observed ions, *m/z* (relative abundance/%) | | | |
|---|---|---|---|---|
| | **1** | **2** | **3** | **4** |
| $M^{+\cdot}$ | $C_7H_{16}BNO_2$ | $C_9H_{20}BNO_2$ | $C_{10}H_{22}BNO_2$ | $C_{13}H_{20}BNO_2$ |
| | 157 (0.2) | 185 (0.1) | 199 (0.6) | 233 (0.4) |
| **b** | $C_2H_6$ N | $C_4H_{10}$ N | $C_5H_{12}$ N | $C_8H_{10}$ N |
| | 44 (100) | 72 (100) | 86 (100) | 120 (100) |
| $[M - C_2H_5]^+$ **c** | $C_2H_{11}BNO_2$ | $C_7H_{15}BNO_2$ | $C_8H_{17}BNO_2$ | $C_{11}H_{15}BNO_2$ |
| | 128 (22.3) | 156 (20.3) | 170 (44.5) | 204 (71.2) |
| $[M - C_2H_6]^{+\cdot}$ **d** | $C_2H_{10}BNO_2$ | $C_7H_{14}BNO_2$ | $C_8H_{16}BNO_2$ | $C_{11}H_{14}BNO_2$ |
| | 127 (5.9) | 155 (5.1) | 169 (11.4) | 203 (18.4) |
| $[b - NH_3]^+$ **e** | – | $C_4H_7$ | $C_5H_9$ | $C_8H_7$ |
| | | 55 (20.6) | 69 (5.9) | 103 (15.6) |
| $[b - CH–NH_2]^+$ **f** | – | $C_3H_7$ | $C_4H_9$ | $C_7H_7$ |
| | | 43 (3.4) | 57 (7.0) | 91 (34.8) |
| $[c - CO]^+$ **g** | $C_4H_{11}BNO$ | $C_6H_{15}BNO$ | $C_7H_{17}BNO$ | $C_{10}H_{15}BNO$ |
| | 100 (1.8) | 128 (1.0) | 142 (1.0) | 176 (10.1) |




* Transition checked by B/E spectra. ** Transition checked by $B^2$/E spectra.

**Scheme 2**

easily provided information about the molecular mass of the compounds analysed (Table 2). In the negative-ion mode the spectra show the abundant $[M - H]^-$ ion (100% r.a.), and the peak of the ion corresponding to $[M + Cl]^-$ is of low intensity (6–12%). At cone voltage $V_c = 30$ V for all compounds studied mild fragmentation occurs. The $[M - H - 68]^-$ ion can be assigned to the anion formed from the $[M - H]^-$ ion by the loss of the $BC_4H_9$ molecule.

In the positive-ion ESI mass spectra of chelates of the amino acids recorded at a $V_c$ of 30 V the peaks of sodium and potassium adduct ions $[M + Na]^+$ and $[M + K]^+$ are much more intense than the peaks of protonated ion $[M + H]^+$. The abundance ratio of the $[M + Na]^+$ and $[M + K]^+$ ions, is 10:1 for alanine, 10:5 for valine, 10:7 for lysine, and 10:8 for phenylalanine derivatives, which means that the compounds studied are more prone to form adducts with sodium than with potassium. In addition to these ions, the peaks corresponding to the $[2M + Na]^+$ ion are also observed (15–60% r.a.).

**Table 2** ESI-MS data obtained for compounds studied

| Ion | Observed ions, *m/z* (relative abundance/%) | | | |
|---|---|---|---|---|
| | **1** | **2** | **3** | **4** |
| $[M + H]^+$ | 158 (13) | 186 (4) | 200 (7) | 234 (7) |
| $[M + Na]^+$ | 180 (100) | 208 (100) | 222 (100) | 256 (100) |
| $[M + K]^+$ | 196 (8) | 224 (50) | 238 (70) | 272 (80) |
| $[2M + Na]^+$ | 337 (15) | 393 (28) | 421 (60) | 489 (47) |
| $[M + H - 68]^+$ | – | 118 (9) | 132 (10) | 166 (13) |
| $[M - H]^-$ | 156 (100) | 184 (100) | 198 (100) | 232 (100) |
| $[M + Cl]^-$ | 192 (6) | 220 (7) | 234 (12) | 268 (8) |
| $[M - H - 68]^-$ | – | 116 (7) | 130 (18) | 164 (5) |

The intensity of the dimer signal strongly depends on cone voltage ($V_c$) as shown for phenylalanine chelate **4** in Fig. 1. The most intense peak of the ion $[2M + Na]^+$ is observed at a cone voltage of 10 V whereas at $V_c = 50$ V practically only a trace of this ion is present.

The main conclusion we can draw from these observations is that the dimers possess a weakly bonded structure, probably stabilized by electrostatic interaction between the boron and oxygen atoms of each of chelate molecules and with a sodium ion. Molecular mechanics calculations by the MM+ method [19] which were performed for the complex of phenylalanine chelate **4** with sodium ion in the ratio (2:1) also support the dimer structure proposed (Fig. 2).

The calculations suggest that the sodium ion forms a complex with two molecules of phenylalanine chelate by ion–dipole interaction. In this case we also observe interactions of the type sodium cation–$\pi$ electrons of phenylalanine, and we obtained a symmetrical structure.

## Experimental

All $^1$H and $^{13}$C NMR spectra were measured at 500 and 125 MHz, respectively, with a Bruker DRX 500 spectrometer. Melting points were recorded with a Boetius melting-point instrument. Optical rotation was measured with an Optical Perkin–Elmer model 341 polarimeter that was operated at $\lambda = 589$ nm, which corresponds to the sodium D line, at 25 °C. Reactions were monitored by thin-layer chromatography (TLC) on plastic sheets coated with Merck silica gel 60 $F_{254}$. TLC plates were visualized by UV irradiation at a wavelength of 254 nm. Reagents and solvents were obtained from Fluka and Merck and were used without purification.

MS measurements: for the EI-MS measurements an AMD 402 two-sector mass spectrometer (AMD Intectra, Germany) was used. The compounds were introduced into the mass spectrometer by use of a direct insertion probe in the EI mode with an acceleration voltage of 8 kV, electron energy 70 eV, a source temperature of 200 °C, and an inlet temperature of 70–150 °C. Metastable ions were recorded on the same instrument using linked scans (B/E, $B^2$/E).

Accurate mass measurements were confirmed by high-resolution mass spectrometry performed by the peak-matching technique. Elemental compositions of the ions were determined with an error of less than 5 ppm relative

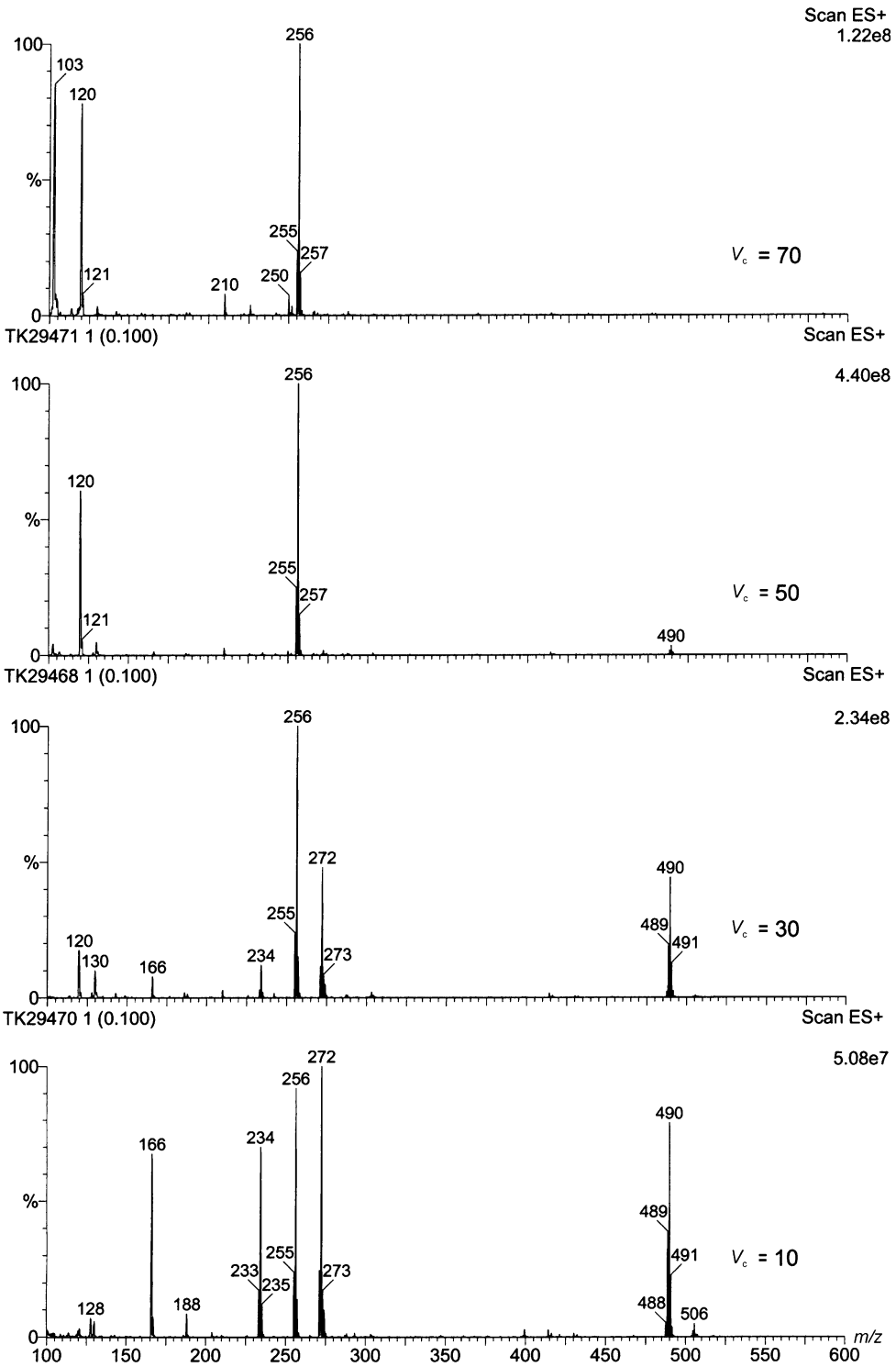



**Fig. 1** Dependence on cone voltage ($V_c$) of the signal intensity of the ion $[2M + Na]^+$ of phenylalanine chelate **4**

to perfluorokerosene (Fluka, Switzerland) at a resolving power of 10,000.

ESI-MS measurements were performed with a Waters/Micromass (Manchester, UK) ZQ mass spectrometer, equipped with an ESI source and operated in the positive and negative-ion mode, in accordance with the manufacturer's specifications for tuning, resolution adjustment, and calibration. The sample solutions were prepared in methanol at a concentration $5 \times 10^{-5}$ M, with the same concentration of $Na^+$ and $K^+$ ions. The sample solutions were infused into the ESI source using a Harvard syringe pump, at a rate of 40 $mm^3$/min. The ESI source potentials

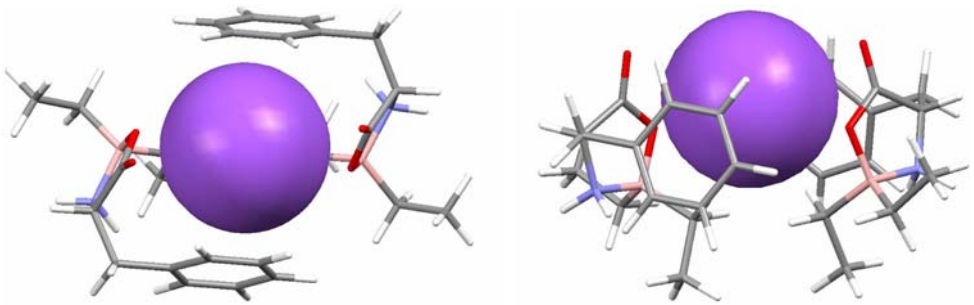


**Fig. 2** The structure of the complex of the phenylalanine chelate **4** with the sodium ion, calculated by the MM+ method. *Left* view from the top, *right* view from the side

were: capillary 3 kV, lens 0.5 kV, extractor 4 V, and cone voltage 30 V, unless indicated otherwise. The source and desolvation temperatures were 120 and 300 °C. Nitrogen was used as the nebulizing and desolvating gas at flow rates of 100 and 300 $dm^3$/h, respectively.

General procedure for the synthesis of boron chelates from selected amino acids and triethylborane: to a suspension of 10 mmol finely ground amino acid in 5 $cm^3$ THF, a 1 M solution of $BEt_3$ in THF (12 mmol) was added and the reaction mixture was gently heated until the amino acid had dissolved (several hours). The solution was then filtered and concentrated to dryness. The spectroscopically pure boron chelates were obtained as colourless solids after addition of toluene or acetonitrile, depending on the amino acids used.

*2,2′-Diethyl-4-methyl-1,3,2-oxazaborolidin-5-one*
(**1**, $C_7H_{16}BNO_2$)
Yield 67%; m.p.: 130°C; $^1$H NMR (500 MHz, methanol-$d_4$): $\delta = 0.30$–$0.40$ (m, 4H, $BCH_2CH_3$), 0.77 (t, $J = 7.55$ Hz, $BCH_2CH_3$), 1.44 (d, $J = 7.55$ Hz, $CH_3$), 3.70 (q, $J = 7.50$ Hz, $CH_3CH(N)CO_2$), 4.87 (s, $NH_2$) ppm; $^{13}$C NMR (125 MHz, methanol-$d_4$): $\delta = 8.94$, 8.98, 16.69, 51.87, 51.97, 178.44 ppm; $[\alpha]_D^{25} = -1.0$ $dm^{-1}$ $g^{-1}$ $cm^3$ ($c = 0.268$, $CH_3OH$).

*2,2′-Diethyl-4-isopropyl-1,3,2-oxazaborolidin-5-one*
(**2**, $C_9H_{20}BNO_2$)
Yield 42%; m.p.: 80 °C; $^1$H NMR (500 MHz, methanol-$d_4$): $\delta = 0.28$–$0.43$ (m, 4H, $BCH_2CH_3$), 0.76 (t, $J = 7.55$ Hz, $BCH_2CH_3$), 0.79 (t, $J = 7.55$ Hz, $BCH_2CH_3$), 0.99 (d, $J = 6.9$ Hz, 3H, $(CH_3)_2CH$–), 1.09 (d, $J = 6.9$ Hz, 3H, $(CH_3)_2CH$–), 2.29– 2.31 (m, $(CH_3)_2CH$–), 3.59 (d, $J = 2.5$ Hz, $(CH_3)_2CH$–$CH(N)CO_2$), 4.86 (s, $NH_2$) ppm; $^{13}$C NMR (125 MHz, methanol-$d_4$) $\delta = 8.96$, 9.08, 17.11, 19.18, 30.20, 61.76, 68.13, 177.01 ppm; $[\alpha]_D^{25} = -34.0$ $dm^{-1}$ $g^{-1}$ $cm^3$ ($c = 0.292$, $CH_3OH$).

*2,2′-Diethyl-4-isobutyl-1,3,2-oxazaborolidin-5-one*
(**3**, $C_{10}H_{22}BNO_2$)
Yield 65%; m.p.: 117 °C; $^1$H NMR (500 MHz, methanol-$d_4$): $\delta = 0.32$–$0.39$ (m, 4H, $BCH_2CH_3$), 0.77 (dt, $J = 7.55$ Hz, $J = 3.15$ Hz, 6H, $BCH_2CH_3$), 0.96 (d, $J = 6.3$ Hz, 3H, $(CH_3)_2CHCH_2$–), 0.99 (d, $J = 3.25$ Hz, 3H, $(CH_3)_2CHCH_2$–), 1.55–1.62 (m, $(CH_3)_2CHCH_2$–), 3.61 (dd, $J_1 = 14.45$ Hz, $J_2 = 3.8$ Hz, CH–$CH(N)CO_2$), 4.87(s, $NH_2$) ppm; $^{13}$C NMR (125 MHz, methanol-$d_4$): $\delta = 7.97$, 9.04, 18.38, 21.20, 23.51, 25.90, 41.46, 41.75, 54.53, 178.21 ppm; $[\alpha]_D^{25} = -32$ $dm^{-1}$ $g^{-1}$ $cm^3$ ($c = 0.186$, $CH_3OH$).

*4-Benzyl-2,2′-diethyl-1,3,2-oxazaborolidin-5-one*
(**4**, $C_{13}H_{22}BNO_2$)
Yield 58%; m.p.: 170 °C; $^1$H NMR (500 MHz, methanol-$d_4$): $\delta = 0.22$–$0.36$ (m, 4H, $BCH_2CH_3$), 0.61 (t, $J = 8.15$ Hz, $BCH_2CH_3$), 0.74 (t, $J = 7.55$ Hz, $BCH_2CH_3$), 3.05 (dd, $J_1 = 14.45$ Hz, $J_2 = 8.15$ Hz, Ph–$CH_aH_b$–), 3.28 (dd, $J_1 = 14.45$ Hz, $J_2 = 4.4$ Hz, Ph–$CH_aH_b$–), 3.96 (q, $J = 4.4$ Hz, $PhCH_2CH(N)CO_2$), 4.88 (s, $NH_2$), 7.33 (m, 5H, Ar*H*) ppm; $^{13}$C NMR (125 MHz, methanol-$d_4$): $\delta = 8.72$, 9.03, 37.26, 57.55, 128.37, 129.97, 130.03, 130.39, 137.53, 176.53 ppm; $[\alpha]_D^{25} = -61.0$ $dm^{-1}$ $g^{-1}$ $cm^3$ ($c = 0.278$, $CH_3OH$).

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