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α-Hydroxymethylaspartic acid: Synthesis and absolute configuration by X-ray analysis of its derivative (+)-4-benzoylamino-4-carboxy-γ-butyrolactone

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(+)-4-Benzoylamino-4-carboxy-γ-butyrolactone was synthesized, and its structure solved by direct methods and refined to $R = 0.033$. The molecule adopts a skew conformation with a C7—N1—C8—C12 torsion angle of 59.6(2)°. The lactone ring has an envelope conformation, with the $C^{\alpha}(8)$ atom deflected from the ring plane. The absolute configuration of (+)-benzylamino-4-carboxy-γ-butyrolactone **5** was assigned as *R* by the application of Hamilton's test to the unique diffraction data, and confirmed by the estimation of the Bijvoet coefficient *B* from *hkl* and $\overline{hkl}$ diffraction data. This result proves the *R* configuration for (+) enantiomer of the parent α-hydroxymethylaspartic acid.

Introduction

α-Hydroxymethylaspartic acids belong to the family of nonproteinogenic α, α-disubstituted amino acids, and offers a useful addition to the arsenal of the peptide chemist, whether his or her major concern is stereochemistry of the peptide chain, enzymatic resistance, or other interesting biological effects. Interest in the research on α, α-disubstituted amino acid is stimulated by the usefulness of these residues to produce restraints on conformational freedom of peptide chain, and by their potential to furnish highly specific enzyme inhibitors. The crystal structure of racemic α-hydroxymethylaspartic acid and the preliminary evaluation of its interaction with cytosolic aspartate aminotransferase from pig heart have been published (Walsh and Metzler, 1980). Although several variations of the Strecker synthesis were attempted, as was synthesis via hydantoin, the authors were able to prepare the compound only in 3% yield.

In this paper we describe the practical synthesis of α-hydroxymethylaspartic acid in 55% overall yield, enantiomeric separation, and absolute configuration determined via X-ray analysis of its derivative (+)-4-benzoylamino-4-carboxy-γ-butyrolactone **5**.

Experimental procedures

Synthetic scheme

α-Hydroxmethylaspartic acid was prepared by our general procedure for the transformation of protein amino acids into α-hydroxymethylated analogs via selective α-hydroxymethylation (Kamiński *et al.*, 1973). *N*-Benzoyl-α-hydroxymethylaspartic acid β-methyl ester (**4**), obtained as an intermediate product after acidic degradation of 4-oxo-1,3-dioxane 3, cyclized in solution spontaneously giving the corresponding 4-benzoylamino-4-carboxy-γ-butyrolactone **5**. This

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racemic lactone was resolved by crystallization of its salt with (−)-cinchonidine and the (+)-enantiomer was used for the measurements.

N-Benzoylaspartic acid β-methyl ester (1). This starting material was prepared according to general procedure for a Schotten–Bauman reaction. From 26 g of aspartic acid β-methyl ester hydrochloride and 17.8 ml of benzoyl chloride, 28.2 g (81%) of **1** was obtained. Mp 118–119°. ^{1}H-nmr (CD_3COCD_3), δ_H: 3.05(d,2H,J = 2 Hz), 3.7(s,3H), 4.98 (t,1H,J = 6 Hz), 7.38,7.57(m,3H), 7.62, 7.86(m,2H). Elemental analysis for $C_{12}H_{13}NO_5$ (251.25) required C,57.4; H,5.2; N,5.6%. Found C,57.6; H,5.2; N,5.4%.

5-Benzoylamino-5-methoxycarbonylmethylene-4-oxo-1,3-dioxane (3). To a cooled (−5°C), vigorously stirred solution of **1** (15.07 g, 60 mmol) and ethyl chloroformate (7.2 g, 66 mmol) in tetrahydrofuran (240 ml), triethylamine (6.66 g, 66 mmol) was added. The mixture was stirred at 0° for 0.5 h, then filtered, and the solvent evaporated. IR spectrum of the oily residue showed a strong absorption band at 1820 cm^{-1}, characteristic for 5-oxo-4,5-dihydro-1,3-oxazoles. The resultant 2-phenyl-4-methoxycarbonylmethyl-5-oxo-4,5-dihydro-1,3-oxazole (**2**) was dissolved in pyridine (7.6 ml), and aqueous (35%) formaldehyde (40 ml) was added. The mixture was stirred for 3 h at room temperature, diluted with water, and extracted with ethyl acetate. The extract was washed successively with cold 1 *N* HCl, sodium bicarbonate solution, water, and then dried over anhydrous $MgSO_4$. After evaporation of ethyl acetate, the crude product was recrystallized from ethyl acetate–light petroleum. Yield 13.7g (78%), Mp 82–83°C. ^{1}H-nmr ($CDCl_3$), δ_H: 3.04(s,1H), 3.06(s,1H), 3.72(s,3H), 4.15,4.35 (2H,AB system, J = 8 Hz), 5.43,5.64 (2H,AB system, J = 5.4 Hz), 7.41,760(m,3H), 7.80,7.96(m,2H), 8.39(broad s,1H). Elemental analysis for $C_{14}H_{15}O_6N$ (293.26) required C,57.3; H,5.2; N,4.8%. Found C,57.7; H,5.3; N,4.7%.

N-Benzoyl-α-hydroxymethylaspartic acid β-methyl ester (4). A solution of **3** (3.78 g, 13.4 mmol) in methanol (15 ml) and 1 *N* hydrochloric acid (26.8 ml) was heated for 10 min. Methanol was evaporated, and the aqueous layer was extracted with ethyl acetate. Evaporation of the dried extract yielded 3.25 g (88%) of crystalline **4**. Analytical sample mp 215–216°C was recrystallized from ethyl acetate. ^{1}H-nmr (CD_3COCD_3), δ_H: 3.16,3.18(AB system, 2H, J = 17 Hz), 4.52,4.88 (AB system, 2H, J= 9.6 Hz), 5.02 (s,3H), 7.24,7.62 (m,3H), 7.83,8.05 (m,2H). Elemental analysis for $C_{13}H_{15}NO_6$ (281.25) required C,55.5; H,5.4; N,5.0%. Found C,55.4; H,5.5; N,4.9%.

4-Benzoylamino-4-carboxy-γ-butyrolactone (5). Ester **4**, when kept in solution cyclizes to γ-lactone **5**. Mp 216–218°C, after recrystallization from ethanol–light petroleum. ^{1}H-nmr (CD_3COCD_3) δ_H: 3.17 (s,1H), 4.63,4.88 (AB system, 2H, J = 10.6 Hz), 7.36,7.56 (m,3H), 7.81,7.99 (m,2H), 8.51 (broad s,1H). Elemental analysis for $C_{12}H_{11}O_5N$ (249.21) required C,57.8; H,4.5; N,5.7%. Found C,57.9; H,4.5; N,5.7%. The same γ-lactone was obtained after hydrolysis of **4** by means of 1N sodium hydroxide.

Resolution of racemic 4-benzoylamino-4-carboxy-γ-butyrolactone. A salt formed from equimolar amounts of racemic γ-lactone **5** and (−)-cinchonidine was separated by fractional crystallization first from ethyl acetate and then from ethyl acetate–hexane into diastereoisomeric salts *A* and *B*. The less soluble salt *A* had a constant Mp of 196–198°C, and a constant $[\alpha]_D^{20}$ = 341.7° (c = 1, MeOH). The more soluble salt *B* had a constant mp of 178–179°C and a constant $[\alpha]_D^{20}$ = −84.7° (c = 1, MeOH). The salt *A* was suspended in 2 *N* HCl, shaken, and extracted with ethyl acetate (5 × 25 ml). Evaporation of the dried extract furnished crystalline (+)γ-lactone [(+)5], mp. 240–242°C, $[\alpha]_D^{20}$ = +58.3° (c = 1; MeOH). The same procedure applied to more soluble salt *B* yielded (−)γ-lactone [(−)5]. Mp = 240–242°C; $[\alpha]_D^{20}$ = −49.2° (c = 1; MeOH).

(+)- and (−)-α-Hydroxymethylaspartic acid. A suspension of (+)-γ-lactone **4** (2.5 g, 10 mmol) in 5 *N* hydrochloric acid (12.5 ml) was refluxed for 5 h. The resulting insoluble benzoic acid was filtered off, and the solution was evaporated to give crude solid α-hydroxymethylaspartic acid hydrochloride. This was dissolved in water and passed through an ion exchange column. The column was washed with water until the eluate became neutral, and then eluted with 2 *N* ammonia. The eluates which gave a positive ninhydrin test were combined and evaporated to dryness. Crystallization of the solid residue from water–ethanol yielded (+)-α-hydroxymethylaspartic acid as amorphous solid (1.4 g, 86%), $[\alpha]_D^{20}$ = +28.8° (c = 1, 2 *N* HCl). The enantiomeric purity was 91.7%, as determined with HPLC using Marfey reagent. ^{1}H-nmr ($NaOD/D_2O$) δ_H: 2.46,2.88 (AB system, 2H, J = 15.5 Hz), 3.65,3.88 (AB system, 2H, J = 12.0 Hz). The same procedure applied to the (−)-γ-lactone **5** gave (−)-α-hydroxymethylaspartic acid, $[\alpha]_D^{20}$ = −25.8° (c = 1, 2 *N* HCl). The enantiomeric purity was 74% (determined with Marfey reagent).

Crystal and intensity data

A crystal with approximate dimensions 0.3,0.2,0.2 mm, obtained by slow evaporation of an ethanol-water solution was used for data collection. Crystal data are given in Table 1.

The intensity data were collected on an Enraf-Nonius CAD-4-diffractometer, within the θ range of 1-75°. X-ray intensity data of 1255 unique reflections and 951 $\overline{hkl}$ reflections were measured in a ω-2θ scan mode; 1186 unique reflections with $I \geq 1.96\sigma(I)$ were used for the structure determination and 930 $\overline{hkl}$ reflections with $I \geq 1.96\sigma(I)$ for the selection of Bijvoet's pairs. Accurate cell parameters and the orientation matrix were determined from a least-squares fit of the angular settings of 25 high-order reflections. The intensities were corrected for Lorentz and polarization factors, but not for absorption.

Structure determination, refinement, and absolute configuration determination

The structure was solved by direct methods, using the SHELXS-86 programs (Sheldrick, 1986), and refined by full-matrix least-squares method, using the program SHELX-76 (Sheldrick, 1876). The function $\Sigma w(F_o - F_c)^2$ was minimized. Initially, each reflection was given unit weight, but in the final cycles $w = 1/\sigma^2(F_0)$ was used for the observed reflections and $w = 0$ for the unobserved reflections. After isotropic refinement a difference map yielded approximate positions of the hydrogen atoms. Only hydrogen atoms of hydroxyl and N-H groups were refined. The other hydrogen atoms were placed in geometrically calculated positions and refined in the riding model. An empirical isotropic extinction correction was introduced in the form: $F_c' = F_c\,(1 - xF_c^2/\sin\theta)$, and the parameter x was refined to the value of 0.032(4). Refinement was continued with anisotropic thermal parameters for all nonhydrogen atoms and terminated when the maximum shift of any parameter was $<0.02\sigma$. The final value for R was 0.033 and for R_w was 0.043. A final difference map showed no electron density >0.3 e Å^{-3}.

Table 1. Crystal data

Formula	$C_{12}H_{11}NO_5$
M_r	249.22
a/Å	6.0506(7)
b/Å	10.3338(6)
c/Å	18.106(1)
V_c/Å^3	1132.2(2)
Z	4
F(000)	520
μ(Cu $K\alpha$)/mm^{-1}	0.936
λ(Cu $K\alpha$)/Å	1.54178
Space group	$P2_12_12_1$
D_x/mg m^{-3}	1.462(3)
D_m/mg m^{-3}	1.46(2)

The absolute configuration of **5** was determined by Hamilton's method (Hamilton, 1965; Rogers, 1981) and confirmed by the comparison of the Bijvoet's pairs. The model of the structure with the reversed signs of all the positional atomic parameters was refined as described above. The resulting R^- and R_w^- values of 0.033 and 0.043 showed that the model with inverse configuration had to be rejected with very high probability. The R_w ratio $= R_w^-/R_w^+ = 0.0432/0.0429 = 1.007$ for $N = 1186 - 181 = 1005$. According to the Pearson and Hartley tables of R-ratio values as the function of the significance level α, and number of independent parameters N, for a one-dimensional hypothesis, the significance level $\alpha = 3 \times 10^{-4}$ (Pearson and Hartley, 1966). Although Hamilton's method safely established the absolute configuration of **5**, we decided to confirm this assignment by a direct comparison of Bijvoet pairs and estimation of the Bijvoet coefficient B (Beurskens *et al.*, 1980). The differences $\Delta F_o = F_o(h) - F_o(\bar{h})$ and $\Delta F_c = F_c(h) - F_c(\bar{h})$ were calculated. The 48 Bijvoet pairs

Table 2. Positional parameters ($\times 10^4$) for the nonhydrogen atoms

	x	y	z
O(1)	11490(2)	3974(1)	855(1)
O(2)	7981(2)	1156(1)	2148(1)
O(3)	4484(3)	899(1)	2497(1)
O(4)	6947(3)	3606(1)	182(1)
O(5)	6954(3)	1560(1)	571(1)
N(1)	8498(2)	4460(1)	1523(1)
C(1)	10875(3)	6210(1)	1093(1)
C(2)	9404(3)	7191(2)	1270(1)
C(3)	9977(4)	8480(2)	1169(1)
C(4)	12087(5)	8794(2)	911(1)
C(5)	13534(4)	7828(2)	730(1)
C(6)	12964(3)	6530(2)	818(1)
C(7)	10317(3)	4816(1)	1147(1)
C(8)	7715(2)	3137(1)	1470(1)
C(9)	5650(3)	2922(2)	1942(1)
C(10)	5901(3)	1570(2)	2226(1)
C(11)	9339(3)	2143(2)	1800(1)
C(12)	7179(3)	2816(1)	661(1)

Table 3. Anisotropic thermal parameters ($\times 10^4$) for the nonhydrogen atoms

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	489(6)	355(5)	382(5)	−42(4)	128(5)	36(5)
O(2)	597(7)	342(5)	388(6)	85(4)	17(5)	13(6)
O(3)	818(11)	483(8)	589(7)	113(6)	241(8)	−185(7)
O(4)	874(10)	408(6)	413(6)	115(5)	−136(7)	−80(7)
O(5)	892(10)	348(6)	361(6)	−15(4)	−126(7)	−149(7)
N(1)	434(6)	241(5)	378(6)	−51(5)	124(6)	−29(5)
C(1)	430(7)	323(7)	258(6)	16(5)	2(6)	−40(6)
C(2)	571(9)	318(7)	397(7)	−2(6)	73(7)	5(7)
C(3)	814(14)	315(8)	576(11)	7(7)	57(10)	25(9)
C(4)	852(14)	375(8)	534(10)	75(7)	3(11)	−172(10)
C(5)	607(10)	523(11)	554(10)	155(8)	17(9)	−178(9)
C(6)	457(8)	421(8)	447(8)	94(6)	21(7)	−65(7)
C(7)	389(6)	307(6)	254(6)	−20(5)	26(6)	0(6)
C(8)	361(6)	251(6)	315(6)	−12(4)	57(6)	0(5)
C(9)	434(8)	315(7)	488(7)	16(6)	161(7)	−21(6)
C(10)	570(9)	354(7)	306(6)	8(6)	94(7)	−52(7)
C(11)	431(7)	317(7)	359(7)	29(5)	−35(6)	17(6)
C(12)	415(7)	310(7)	336(7)	27(5)	−9(6)	−44(6)

for which $|\Delta F_o| > 3\sigma(\Delta F_o)$ and $|\Delta F_c| > 0.0015\,[F_c(h) + F_c(\bar{h})]$ were selected and Bijvoet's coefficient $B = \Sigma(\Delta F_c \Delta F_o)/\Sigma|\Delta F_o \Delta F_c| = 0.30$ was computed. The positive value of this coefficient confirms the configuration determined by Hamilton test.

The final atomic parameters are given in Tables 2, 3, and 4. Plots were made with PLUTO program (Mortherwell, 1976), while geometrical calculations were performed using the program PARST (Nardelli, 1983). All calculations were performed on AMSTRAD 1512 microcomputer.

Table 4. Positional parameters ($\times 10^3$) and U_{iso} ($\times 10^3$) for hydrogen atoms

	x	y	z	U
H(1)	773(5)	500(2)	−824(1)	58(7)
H(5)	666(5)	129(3)	15(2)	67(8)
H(21)	781	695	148	53(6)
H(31)	881	922	129	171(16)
H(41)	1257	979	85	90(10)
H(51)	1513	807	52	85(9)
H(61)	1412	578	68	119(11)
H(91)	419	300	161	76(8)
H(92)	557	360	239	73(8)
H(111)	1038	260	220	63(7)
H(112)	1034	173	137	45(5)

Results and discussion

Figure 1 shows a perspective view of (+)-*N*-benzoyl-α-hydroxmethylaspartic acid lactone. The configuration at the $C^{\alpha}(8)$ atom is *R*, according to the Cahn-Ingold-Prelog conventions (1965). Selected bond lengths and angles are listed in Table 5. The backbone conformation is different from the other α,α-disubstituted aminoacids (Wieczorek *et al.*, 1989). Intramolecular hydrogen bonds are not observed, and the backbone chain is not extended. The torsion angle Φ(C7—N1—C8—C12) of 59.6(2)° corresponds to a skew conformation of the N1—C′(7) and $C^{\alpha}(8)$—C12 bonds. The out-of-plane deformation of the amide group can be described in terms of two out-of-plane bending

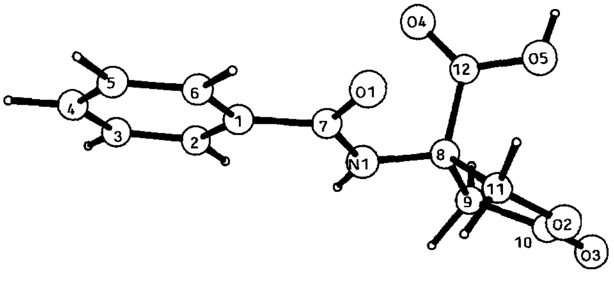

Fig. 1 Molecular structure of 5 with the atom labeling scheme.

Table 5. Bond lengths (Å) and angles (deg)

C(7)—O(1)	1.242(2)	C(10)—O(2)	1.337(2)
C(11)—O(2)	1.453(2)	C(10)—O(3)	1.207(2)
C(12)—O(4)	1.199(2)	C(12)—O(5)	1.320(2)
C(7)—N(1)	1.345(2)	C(8)—N(1)	1.449(2)
C(2)—C(1)	1.387(2)	C(6)—C(1)	1.398(3)
C(7)—C(1)	1.483(2)	C(3)—C(2)	1.388(2)
C(4)—C(3)	1.398(4)	C(5)—C(4)	1.368(3)
C(6)—C(5)	1.395(3)	C(9)—C(8)	1.530(2)
C(11)—C(8)	1.542(2)	C(12)—C(8)	1.536(2)
C(10)—C(9)	1.496(3)		
C(11)—O(2)—C(10)	110.7(1)	C(8)—N(1)—C(7)	119.5(1)
C(6)—C(1)—C(2)	119.4(1)	C(7)—C(1)—C(2)	123.3(2)
C(7)—C(1)—C(6)	117.3(1)	C(3)—C(2)—C(1)	120.7(2)
C(4)—C(3)—C(2)	119.7(2)	C(5)—C(4)—C(3)	119.7(2)
C(6)—C(5)—C(4)	121.1(2)	C(5)—C(6)—C(1)	119.4(2)
N(1)—C(7)—O(1)	119.4(1)	C(1)—C(7)—O(1)	121.5(1)
C(1)—C(7)—N(1)	119.1(1)	C(9)—C(8)—N(1)	111.6(1)
C(11)—C(8)—N(1)	113.2(1)	C(11)—C(8)—C(9)	102.0(1)
C(12)—C(8)—N(1)	109.6(1)	C(12)—C(8)—C(9)	109.2(1)
C(12)—C(8)—C(11)	111.1(1)	C(10)—C(9)—C(8)	104.2(1)
O(3)—C(10)—O(2)	121.9(2)	C(9)—C(10)—O(2)	111.0(1)
C(9)—C(10)—O(3)	127.1(2)	C(8)—C(11)—O(2)	106.0(1)
O(5)—C(12)—O(4)	124.8(2)	C(8)—C(12)—O(4)	124.6(1)
C(8)—C(12)—O(5)	110.7(1)		

coordinates χ_N and χ_C, and a twisting coordinate τ (Winkler and Dunitz, 1971). The four torsion angles on the C7—N1 bond [ω_1(C1—C7—N1—C8) = 169.0(1), ω_2(O1—C7—N1—H1) = 174(2), ω_3(O1—C7—N1—C8) = −11.1(2), ω_4(C1—C7—N1—H1) = −6(2)°] indicate that the deviations form planarity of the six atoms C1, C7, N1, C8, O1, H1 are caused mainly by twist around the C7—N1 bond [τ(C7—N1) = 171.5°] and an out-of-plane bending at the N atom (χ_N = 5.1°). The out-of-plane bending at C7 is only 0.1°. It confirms a much greater resistance to out-of-plane bending of the carboxyl end of the amide group than at the nitrogen end (Dunitz and Winkler, 1975; Ealick and Helm, 1977). The torsion angles ϕ_1(O5—C12—C8—N1) = 165.7(1) and ϕ_2(O4—C12—C8—N1) = 160(2) indicate a nearly coplanar arrangement of the carboxylic and N—H groups. The valence bonds are typical for the amino acid

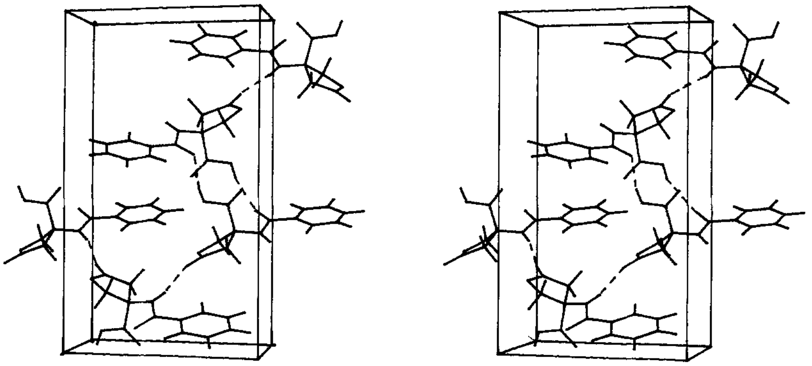

Fig. 2 The packing of 5 in the unit cell with intermolecular hydrogen bonds; *b* and *c* are parallel to the bottom and the side of the page, respectively, and the view is down *a*.

and peptide crystals (Ashida *et al.*, 1987). The valence angles at the C$^{\alpha}$(8) atom are deformed by cyclization of the two α,α substituents, and are from 102.0(1)° for the intraring C9—C8—C11 angle to 113.2(1)° for the N1—C8—C11 angle. The lactone ring adopts the envelope conformation with the C$^{\alpha}$(8) atom deflected from the ring plane. The ring is symmetrical with the $\Delta C_s(8)$ asymmetry parameter of 1.0(2)° (Duax and Norton, 1975). Figure 2 shows a stereoscopic view of the molecular packing in the unit cell. The molecules lie along *c* and are connected by intermolecular N—H · · · O and O—H · · · O hydrogen bonds in the infinite chains. The two hydrogen bonds N1—H1 · · · O3 and O5—H5 · · · O1 are 2.11(3) and 1.84(3) Å with angles N1—H1 · · · O3 and O5—H5 · · · O1 165(2) and 166(2)°; distances N1 · · · O3 and O5 · · · O1 are 2.935(2) and 2.654(3) Å. The strong O1 · · · H5 hydrogen bond evidently elongates the C7=O1 double bond to 1.242(2) Å.

Hydrolysis of *R*(+)-γ-lactone **5** by means of 5 *N* HCl led to (+)-α-hydroxymethylaspartic acid, $[\alpha]_D^{20}$ = +28.3° (*c* = 1, 2 *N* HCl). This result proves the *R*-configuration for the dextrorotatory enantiomer of α-hydroxymethylaspartic acid.

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Structure factor data have been deposited with the British Library, Boston Spa, Wetherby, West Yorkshire, UK as supplementary publication No. 60702 (14 pages).