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Study on Reactivity of Five-Coordinate Bicycloazastannoxides III. New Method for Preparing β-Hydroxy-α-amino Acids

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ABSTRACT: *Five-coordinate bicycloazastannoxides containing a β-hydroxy-α-amino acid moiety were synthesized. By hydrolysis under the action of 10% HCl, five β-hydroxy-α-amino acids were prepared, and their structures were characterized by ^{1}H NMR spectroscopy, MS, and elemental analyses. The mechanism of the hydrolysis of the organotin (IV) complexes is discussed, and the yields of diastereomers are investigated by the HPLC method. This represents a new method for preparing β-hydroxyl-α-amino acids.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 183–186, 1999

β-Hydroxy-α-amino acids represent an important group of natural products. Condensation reactions of free Gly with aldehydes would seem to be the simplest way to prepare β-hydroxy-α-amino acids. However, this reaction can rarely be of synthetic value due to the low CH acidity of Gly and undesirable reactions of aldehydes or ketones leading to a predominance of side products. The use of Gly complexes with metal ions rather than free Gly improves the yield of desired reaction products [1,2]. Furthermore, the use of transition-metal complexes of Gly Schiff bases with salicylaldehyde [3] or pyruvic acid [4,5] instead of free $(Gly)_2$ complexes improves the yield and widens the scope of this synthetic pathway. However, organotin (IV) complexes with Schiff bases derived from α-amino acids and salicylaldehyde have not been investigated up to the present time.

In our earlier studies, we have determined by X-ray diffraction analysis that the structures of five-coordinate bicycloazastannoxides with Schiff bases derived from amino acids are similar to those of the metal vitamin B_6 chelates [6]. Recently, we investigated the condensation of five-coordinate bicycloazastannoxides with aldehydes [7] and first determined the thermodynamic α-CH acidity (*p*K*a* value) of these five-coordinate bicycloazastannoxides by the accurate spectrophotometeric method for measuring relative equilibrium acidities of weak carbon acids in dimethyl sulfoxide [8]. It was found that the effects of α-CH acidity and the stability of the α-carbanions on condensation reactions with aldehydes are important. The bulkiness of the amino acid moieties affects the α-CH acidity directly, and the effect of the bulkiness of amino acid moieties on their α-CH acidities could be correlated by the Taft equation. We have also observed that the chelation be-

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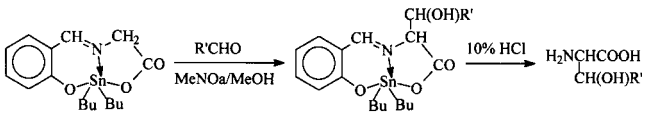
tween organotin (IV) and a Schiff-base ligand enhanced the α-CH acidity of the amino acid fragments, and the influence of the central atom (Sn) was discussed.

In this article, five five-coordinate bicyclostannoxides **(2–6)** were first synthesized by the condensation of complex **1** with aldehydes, α-thiophenaldehyde, *o*-anisaldehyde, *p*-anisaldehyde, 2-methylbenzaldehyde, and 4-methylbenzaldehyde, respectively. Then the hydrolysis of complexes **(2–6)** was investigated under the action of 10% HCl, and five β-hydroxy-α-amino acids were synthesized. Their structures were characterized by ^{1}H NMR spectroscopy, MS, and elemental analyses. The mechanism for the hydrolysis of the organotin (IV) complexes is discussed, and the related ratios of diastereomers have also been investigated by the HPLC method. The whole process from the condensation of complex **1** with aldehydes to the hydrolysis of complexes **(2–6)** imitates the chemical reaction in vivo that is catalyzed by pyridoxal phosphate coenzyme derivatives. This provides a new method for preparing β-hydroxy-α-amino acids.



	R′	R′
1	**2** C_4H_3S	**7** C_4H_3S
	3 *p*-MeOPh	**8** *p*-MeOPh
	4 *o*-MeOPh	**9** *o*-MeOPh
	5 2-MePh	**10** 2-MePh
	6 4-MePh	**11** 4-MePh

EXPERIMENTAL

General

Glycine was purchased from the Beijing Chemical Reagent Company. *o*-Anisaldehyde, *p*-anisaldehyde, 2-methylbenzaldehyde, 4-methylbenzaldehyde, and α-thiophenaldehyde were purchased from the Merk-Schuchardt Company. These compounds were purified by the general methods before being used. Sodium methoxide was prepared by adding metallic Na to methyl alcohol under argon with cooling. Dibutyltin (IV) complex **1** was prepared from dibutyltin dichloride (mp = 40°C) and the Schiff base derived from glycine [7].

Melting points were determined on a PHMK melting-point stage and are presented without corrections. Elemental analyses were carried out on a CHN corder M73 apparatus. ^{1}H and ^{119}Sn NMR spectra were recorded on a JNMPMX 90 MHz and a BRUKER Ac-P 200 spectrograph, respectively. The chemical shifts were reported as δ values with respect to $SiMe_4$ as internal reference. All runs were carried out on homogeneous systems. The mass spectra were obtained on a VG-7070E-HF instrument with electron bombardment of 70 eV. The IR spectra were recorded on a Nicolet FI-IR 50X spectrometer. The UV-vis spectra were obtained on a Specord UV-vis spectrophotometer. HPLC was carried out with a Varian 5060 Liquid Chromatograph on a Kromasil K 100-5u column (250 × 4.6 mm in column size).

Synthesis of Complexes **2, 3, 4, 5,** *and* **6**

To 1 mmole of complex **1** in 5 mL of a 1.5 N solution of CH_3ONa in methyl alcohol was added 3 mmole of α-thiophenaldehyde, and the mixture was stirred at 25°C under argon. The reaction was monitored by TLC using neutralized samples (SiO_2, $CHCl_3$-acetone, 5:1). When the composition of the reaction mixture ceased to change, it was neutralized with acetic acid to pH = 7. Methyl alcohol solvent was evaporated in vacuo. The residual yellow solid was washed with acetone until it became white. Acetone solvent was evaporated in vacuo, the residue was separated on a preparative-layer plate in $CHCl_3$-acetone (5:1) and further purified with THF-benzene (1:1). Complex **2** (a mixture of diastereomers in this and all succeeding cases) was obtained.

Yield of complex **2**: 67%, mp 110–112°C; UV-vis (CH_3OH) λ (log ε): 383.5 (2.70), 282.2 (3.00); ^{1}H NMR($CDCl_3$) δ 6.6–8.2 (8H, m, Ar), δ 4.25 (1H, d, α-CH), δ 3.4–3.7 (1H, m, β-CH); ^{119}Sn NMR (CDCl3) δ-208.3; IR (KCl) $\nu_{(C=O)}$ 1636, $\nu_{(C=N)}$ 1614, $\nu_{(Ph\text{-}O)}$ 1305, $\nu_{(Sn\text{-}O)}$ 547, $\nu_{(Sn\text{-}N)}$ 450; anal calcd. for $C_{22}H_{29}O_4NSSn$: C, 50.45; H, 5.56; N, 2.68. Found: C, 50.16; H, 5.33; N, 2.97.

Complex **3** was synthesized from **1** by condensation with *o*-anisaldehyde with a yield of 74.5%; mp 113–114.5°C [7].

Complex **4** was synthesized from **1** by condensation with *p*-anisaldehyde with a yield of 71.0%; mp 89–91°C [7].

Complex **5** was synthesized from **1** by condensation with 2-methylbenzaldehyde with a yield of 68.4%; mp 109–110.5°C [7].

Complex **6** was synthesized from **1** by condensation with 4-methylbenzaldehyde with a yield of 75.1%; mp 107–109°C [7].

Synthesis of β-Hydroxyl-α-amino Acids **7, 8, 9, 10,** *and* **11**

To 0.13 mmole of complex **2** in 6 mL of methyl alcohol was added 5 mL of 10% aqueous HCl solution, and the mixture was stirred at 50°C for a half hour. The colorless mixture was extracted with chloroform (3 × 5 mL) and neutralized with 5% aqueous ammonia to pH = 9. The aqueous extract was concen-

trated and placed on a Dowex-50 column (H^+ form, 50 mL). The column was washed with water and then with 5% aqueous ammonia. The eluant was chromatographed on a Dowex-50 column (a weak form) again. Product **7** (a mixture of diastereomers) was obtained. Yield of product **7**: 45%, mp 171–173°C; ^{1}H NMR (D_2O) δ 6.8–7.3 (3H, m, Ar); δ 5.3 (1H, d, α-CH); δ 3.7 (1H, d, β-CH). Anal. calcd for $C_7H_9NO_3S$: C, 45.02; H, 4.83; N, 7.40. Found: C, 45.15; H, 4.63; N, 7.27.

Product **8** (a mixture of diastereomers) was obtained by hydrolyzing complex **3** with 10% aqueous HCl solution according to the same procedure with a yield of 49%, mp 193°C; ^{1}H NMR (D_2O) δ 6.75–7.5 (5H, m, Ar); δ 5.55 (1H, d, α-CH); δ 4.15 (1H, d, β-CH); δ 3.8 (3H, s, OCH_3). Anal. calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.16; N, 6.64. Found: C, 56.37; H, 6.03; N, 6.31.

Product **9** (a mixture of diastereomers) was obtained by hydrolyzing complex **4** with 10% aqueous HCl solution according to the same procedure with a yield of 51%, mp 178–180°C; ^{1}H NMR (D_2O) δ 6.8–7.5 (5H, m, Ar); δ 5.5 (1H, d, α-CH); δ 4.2 (1H, d, β-CH); δ 3.75 (3H, s, OCH_3). Anal. calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.16; N, 6.64. Found: C, 56.58; H, 5.89; N, 6.05.

Product **10** (a mixture of diastereomers) was obtained by hydrolyzing complex **5** with 10% aqueous HCl solution according to the same procedure with a yield of 58%, mp 189–190°C; ^{1}H NMR (D_2O) δ 7.0–7.5 (5H, m, Ar); δ 5.2 (1H, d, α-CH); δ 3.85 (1H, d, β-CH); δ 2.1 (3H, s, CH_3). Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.54; H, 6.67; N, 7.18. Found: C, 61.41; H, 6.38; N, 7.09. MS spectrum: 113 (43.86%), 119 (46.85%), 105 (100%), 91 (69.23%), 77 (46.59%), and 44 (47%).

Product **11** (a mixture of diastereomers) was obtained by hydrolyzing complex **6** with 10% aqueous HCl solution according to the same procedure with a yield of 55%, mp 154–155°C; ^{1}H NMR (D_2O) δ 7.15 (5H, s, Ar); δ 5.1 (1H, d, α-CH); δ 3.8 (1H, d, β-CH); δ 2.1 (3H, s, CH_3). Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.54; H, 6.67; N, 7.18. Found: C, 61.63; H, 6.24; N, 7.17.

Determination of the Yield of β-Hydroxy-α-amino Acids and the Ratio of Their Diastereomers

Route A

1. Complex **2** was synthesized from complex **1** with α-thiophenealdehyde and purified according to the foregoing method.
2. To 0.13 mmole of complex **2** in 6 mL of methyl alcohol was added 5 mL of 10% aqueous HCl solution, and the mixture was stirred at 50°C for 1 hour. The mixture was diluted with methyl alcohol to 25 mL and 10 μL injected into the HPLC instrument. The yield of product **7** was obtained by the HPLC method. The conditions of HPLC, the retention times, and the yields are described in Table 1. The similar reactions for complexes **(3–6)** were carried out by the same method.

Route B. To 0.3 mmole of complex **1** in 5 mL of a 1.0 N methyl alcohol solution of CH_3ONa was added 0.3 mmole of α-thiophenealdehyde, and the mixture was stirred at 25°C under argon for 8 hours. Then 5 mL of 10% aqueous HCl solution was added into the reaction mixture, and the mixture continued to be stirred for another 2 hours at 50°C. The mixture was diluted with methyl alcohol to 25 mL and 10 μL injected into the HPLC instrument. The yield of product **7** was obtained by the HPLC method. The conditions of HPLC, the retention times, and the yields are described in Table 1. The similar condensations of complexes **1** with *o*-anisaldehyde, *p*-anisaldehyde, 2-methylbenzaldehyde, and 4-methylbenzaldehyde, and the related hydrolysis were carried out by the same method.

RESULTS AND DISCUSSION

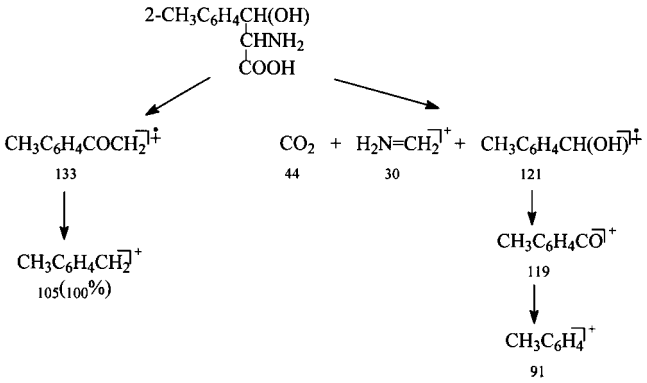
All of the β-hydroxy-α-amino acids are white solids. ^{1}H NMR spectra of products **7–11** are significant in identification of their structures. Compared with the organotin (IV) complexes (**2–6**), there is the disappearance of the peaks of the CH=N and Bu group in the products **(7–11)**. In addition, the peaks of the αCH of products **(7–11)** are shifted down field. These facts indicate that there is no coordination between N and Sn atoms, and the organotin (IV) complexes

TABLE 1 The Yields (%) of β-Hydroxyl-α-amino Acids from Complex **1** and the Ratios of Their Diastereomers

	Route A				
β-OH-α-a.a.	*Synthesis*	*HPLC*[b]	*Total*[c]	*Route B*	*Ratio of Diastereomers*[a]
7	30.15	50.85	34.07	25.53	48.4:51.6
8	36.51	54.17	40.35	27.96	42.5:57.5
9	36.21	59.43	42.19	27.12	39.0:61.0
10	39.67	65.58	45.14	33.31	42.3:57.7
11	41.31	62.05	46.60	27.97	45.5:54.5

[a]According to 500 MHz ^{1}H NMR data in D_2O.
[b]The yields for α-hydroxy-β-amino acids from **2,3,4,5,** and **6,** respectively, were determined by HPLC method.
[c]Total yields were calculated according to the yields of the reactions **1** → **2**, **1** → **3**, **1** → **4**, **1** → **5**, and **1** → **6** and the yields of the reactions **2** → **7, 3** → **8, 4** → **9, 5** → **10,** and **6** → **11,** respectively.
Conditions: Mobile phase: methyl alcohol–water 6:4(v/v); flow rate: 1.0 mL/min; detector: UV 254 nm; temperature: room temperature.

have been decomposed. Mass spectral data of product **10** also support the above results, and the splitting patterns are given.



It has been found that the organotin (IV) complexes **(1–6)** are stable under basic conditions, but in an acidic solution, they are hydrolyzed. Obviously, the Sn–O, Sn–N, and C = N bonds in the complexes **(2–6)** are sensitive to an acidic medium. They easily break under the action of acids, and the *β*-hydroxyl-*α*-amino acids are formed. The whole process from the condensation of complex **1** with aldehydes to the hydrolysis of complexes **2–6** imitates the chemical reaction in vivo, which is catalyzed by pyridoxal phosphate coenzyme derivatives. Since the pioneering work of Snell [9] and Martell [10], many studies have been carried out that mimic various vitamin B_6-dependent enzymes [11]. The procedure described herein provides a new method for preparing *β*-hydroxy-*α*-amino acids.

In this part, two routes for obtaining the *β*-hydroxy-*α*-amino acids were investigated by the HPLC method, and the data are gave in Table 1. All aldol condensations between **1** and various aldehydes were carried out in 1.0 N MeONa and at room temperature; the hydrolyses were carried out in acidic medium and at 50°C. The results show the following characteristics: (1) Route A is better than route B. (2) There are no remarkable differences in the yield with the various aldehydes. Obviously, the effect of the bulkiness of amino acid moieties on the hydrolysis may be ignored. (3) This is not a good path for an asymmetric synthesis of *β*-hydroxy-*α*-amino acids, according to the diastereomeric ratios. The X-ray data have shown that the Schiff-base ligand in the organotin (IV) complex containing the Gly is planar, and the angle between the five- and six-membered rings is close to 180° [8]. In addition, the proton in the CH = N group offers little steric hindrance in the condensation, so stereospecificity is not possible.

CONCLUSION

Five-coordinate bicycloazastannoxides with *β*-hydroxy-*α*-amino acids were synthesized by the condensation with aldehydes and furthermore hydrolyzed by 10%HCl; finally, a series of *β*-hydroxy-*α*-amino acids were formed. The foregoing whole process imitates the chemical reaction in vivo, which is catalyzed by pyridoxal phosphate coenzyme derivatives. It provides a new method for preparing for *β*-hydroxy-*α*-amino acids. Preparation of optically pure *α*-amino acids will be investigated by a series of asymmetric reactions of organotin (IV) complexes.

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