Synthesis of New Complexons: N-Hydroxy-α,α’-iminodipropionic- and N-Hydroxyiminodiacetic Acid

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Reaction conditions for the synthesis of N-hydroxy-α,α’-iminodipropionic acid, the ligand of naturally occurring amavadin, and N-hydroxyiminodiacetic acid, the first member of this class of complexons, have been investigated.

Amavadin (1), the complex of VO²⁺ with two molecules of N-hydroxy-α,α’-iminodipropionic acid (2a) is the only natural vanadium containing compound, the structure of which has been determined [1, 2].

\[
\begin{align*}
\text{NH}_2\text{OH} \cdot 2 \text{R'-CHX COOH} & \quad \text{Oxidation} \quad R-\text{CH-COOH} \\
\text{R-COOH} & \quad \text{Base} \quad -2 \text{HX} \\
\text{N-OH} & \quad \text{R'-CH-COOH} \\
\end{align*}
\]

First attempts to obtain 2 by oxidation of 3 with common oxidants such as hydrogen peroxide/sodium tungstate or sodium persulfate/silver nitrate were unsuccessful. Reaction of hydroxylamine with D,L-α-chloropropionic acid gave only modest yields [4]. Conditions for the reaction of hydroxylamine with D,L-α-bromopropionic- and bromoacetic acid were modified systematically. The formation of compounds 2 was checked by high pressure liquid chromatography. Under the conditions used for the synthesis of compound 2a in our preliminary report [3] (80 °C, sodium bicarbonate as base) the product decomposed rapidly and the resulting yield was only modest. Maximum yield was obtained at pH 7 and moderate temperature. Under these conditions, compound 2b could be obtained for the first time. Separation from the reaction mixture was achieved as described earlier [3] by precipitation of the zinc complex. The white precipitate was dissolved in dihydrochloric acid, adsorbed on a strongly acidic cation exchange resin and the product eluted with sodium hydroxide. In this way the free N-hydroxyiminio acids 2a and 2b could be readily prepared in 10 g amounts. The structure of these compounds was confirmed by field desorption mass spectrometry, nuclear magnetic resonance and elementary analysis.

In the case of compound 2a, two identical asymmetric carbon atoms are present. Hence an enan-

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tiomeric pair and an optically inactive meso-form are possible. Separation could be achieved by gas chromatography of the dimethylesters on Chirasil-Val [5, 6], a chiral stationary phase for gas liquid chromatography (see Fig. 1). Optically active 2a and the meso form showed sufficient difference in chemical shifts in the $^1$H NMR spectra to allow the determination of the amount of the meso-form present in optically active 2a (see Fig. 2).

Starting from optical active L-$\alpha$-bromopropionic acid with an optical purity in excess of 95% [7]. D,D-N-hydroxy-$\alpha,\alpha'$-iminopropionic acid (2a) was obtained. The product contained only about 9% of the meso-isomer as shown by $^1$H NMR spectroscopy and gas chromatography. The L,L-form of compound 2a was not detectable by gas chromatography. Further purification by preparative HPLC was not necessary. Determination of the absolute configuration of compound 2a was possible by its reduction to $\alpha,\alpha'$-imino-
dipropionic acid with zinc/acetic acid. The configuration of this compound was already determined in 1942 [8] (see also ref. [3]).

**Experimental**

D,L-α-Bromopropionic acid, bromoacetic acid and hydroxylamine hydrochloride were commercially available products. Lewatit S-100 ion exchange resin was purchased from Bayer AG and purified by standard procedures. L-α-Bromopropionic acid was obtained from L-alanine according to Fu and co-workers [9].

**N-Hydroxyiminodiacetic acid**

6.95 g (0.1 mol) hydroxylamine hydrochloride and 34.7 g (0.25 mol) bromoacetic acid were dissolved in 200 ml of water. The reaction mixture was kept at room temperature and titrated automatically (Impulsomat E 473 Metrohm, Herisau, Schweiz) to a pH of 7 using 10% sodium hydroxide solution. After 6 h the reaction mixture was acidified to pH 4 and 21.35 g (0.1 mol) zinc acetate dihydrate was added. After standing over night at room temperature the zinc complex of N-hydroxyiminodiacetic acid was collected and dried over diphosphorus pentoxide.

Yield: 12.1 g (56.7 mmol) = 56.7% d.Th. White powder; Fp. > 250 °C.

**Elementary analysis:** C₄H₇NO₅, M = 149.10
Calcd C 22.61 H 2.37 N 6.59, Zn 30.77.
Found C 22.59 H 2.50 N 6.38, Zn 29.20.

IR (KBr): 3420 (OH), 3240 (NH), 2930 (CH), 1655 and 1580 (CO) cm⁻¹.

**Chromatography on Ion-exchange Resin Lewatit S 100**

(Instead of Lewatit S 100 also Dowex 50 WX 8 50–100 mesh from Serva Fein Biochemica, Heidelberg, FRG, can be used.)

3.00 g (14.1 mmol) of the zinc complex from the above reaction were dissolved in 25 ml of water by dropwise addition of concentrated hydrochloric acid. The solution was loaded on a column (2.5×30 cm) containing strongly acidic cation exchange resin (Lewatit S 100) and eluted with 0.2 N sodium hydroxide solution. The fraction containing the product was concentrated to a volume of 100 ml and freeze dried.

Yield: 1.66 g (11.4 mmol) = 81% d.Th. White powder, Fp. 136 °C.

**Elementary analysis:** C₄H₇NO₅, M = 149.10
Calcd C 22.61 H 2.37 N 6.59, Zn 30.77.
Found C 22.59 H 2.50 N 6.38, Zn 29.20.

IR (KBr): 3420 (OH), 3240 (NH), 2930 (CH), 1650 (CO), 1585 (COO⁻ st as), 1420 (COO⁻ st sym) cm⁻¹.

**H NMR (D₂O):** δ = 3.85 (s); (Ref. 3-(Trimethylsilyl)propionic acid, sodium salt).

**FD-MS:** m/e 150 (100%, M+1), 149 (M⁺)

The substance had a purity of 98.0±1%, determined by titration against standard 0.1 N NaOH using phenolphthalein as indicator.

**N-Hydroxy-α,α’-iminodipropionic acid**

Analogous to the procedure previously described 0.05 mol of NH₂OH·HCl and 0.15 mol D,L-2-bromopropionic acid were allowed to react for 24 h at 40 °C and the zinc complex precipitated.

Yield: 6.70 g (27.9 mmol) = 55.7% d.Th. Fp. > 250 °C.

**Elementary analysis:** C₄H₇NO₅, M = 177.16
Calcd C 40.45 H 6.79 N 7.86.
Found C 40.27 H 6.58 N 7.68.

IR (KBr): 3400 (OH), 2995 (CH) and 1750 (CO) cm⁻¹.

**H NMR (D₂O):** δ = 4.12 (meso) and 4.05 (D,D+L,L) (q, J = 7 Hz; 2H, CH₂–CH); 1.46 (meso) and 1.43 (D,D+L,L) (d, J = 7 Hz; 6H, CH₂–CH); (Ref. 3-(Trimethylsilyl)propionic acid, sodium salt).

**FD-MS:** m/e 178 (100% M+1) and 175 (M⁺)

The substance had a purity of 95% determined by titration against standard 0.1 N NaOH solution.

Optically active L,L-N-hydroxy-α,α’-iminodipropionic acid showed [α]D = −25.8° (c=1, H₂O) (uncorrected, 9% meso-isomer present).

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