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SYNTHESIS OF NEW CHIRAL MACROCYCLIC TETRAOXO POLYAMINES CONTAINING PYRIDINE RING AND FUNCTIONAL ARMS

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Abstract Seven new chiral macrocyclic tetraoxo polyamines containing pyridine ring and functional arms derived from L-histidine, L-alanine, L-leucine and L-phenylalanine, respectively, have been synthesized and characterized by MS, ^{1}H NMR and elemental analysis.

Polyazamacrocycles are widely studied for potential applications in transition metal coordination chemistry related to metal ion sequestration, biomimetic catalysis, enzyme functions, diagnostic and therapeutic medicine, and molecular recognition.[1] In recent years considerable attention has been addressed to the polyazamacrocycles bearing a variety of functional arms such as pyridine, pyrazole and hydroxyalkyl.[2] However, there are only a few examples dealing with imidazole arms. Imidazole is the important biological ligand and functional group, and the imidazole residue of histidine as the active sites of enzymes and proteins is well recognized.[3] More recently, the tetra-azamacrocycles with imidazole arms

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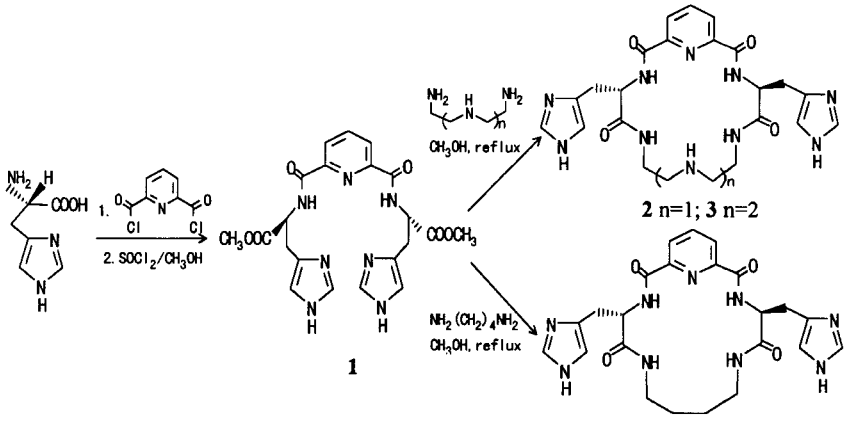
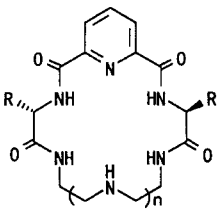
were synthesized for biomimetic purposes.[4] Therefore, it appeared worthwhile pursuing further to explore the synthesis of polyazamacrocycles with imidazole pendants.

On the other hand, there is a continuing interest in the synthesis of the macrocyclic oxo polyamines because their structures bear the dual features of macrocyclic polyamines and oligopeptides.[5] Following our own interest in the design, synthesis and use of imidazole-containing macrocycles[6] as well as pyridine-containing macrocycles[7], we report herein the convenient synthesis of novel chiral macrocyclic tetraoxo polyamines containing pyridine ring and imidazole arms **2-4**. Pyridine unit incorporated into a macrocyclic framework is able to provide the proper rigidity, and participate in complexation through its nitrogen donor atom. The introduction of chiral unit into the macrocyclic ring is expected to deduce the effective discrimination of enantiomers of guest, which have attracted attention on the enzyme mimic. The synthesis of **2-4** is summaried in Scheme 1 and is based upon the macrocyclizations via aminolysis of the dihistidine dimethyl esters **1** with commerically available polyamines. This strategy has the advantage that polyamine precursors are used directly without N-protection, and that the key intermediate **1** was also used directly without protection technique of the imidazole ring.

Bridged histidines are versatile intermediates for the synthesis of various useful chiral imidazole derivatives. Histidine derivatives, however, are generally considered to be difficult to prepare. Therefore, it is necessary to develop the convenient and efficient synthesis of these bridged products. First, highly chemoselective preparation of the bridged histidine was investigated. Inital attempt to form **1** by coupling histidine methyl ester with 2,6-bis(chlorocarbonyl)pyridine was unsuccessful due to serious side reactions. Subsequently we found that the direct coupling of histidine and the acid chloride could be carried out to give the bridged histidine in an excellent yield when a mixed solvent system consisting of aqueous KOH with dissolved histidine and tetrahydrofuran (THF) with dissolved 2,6-bis(chlorocarbonyl)pyridine was allowed to react with vigorous stirring at 0-5 ℃ (the temperature should go no higher). This strategy successfully avoided the acylation of the imidazole ring and the hydrolysis of 2,6-bis(chlorocarbonyl)pyridine.

Scheme 1





5-8

Compd.	5	6	7	8
R	CH_3	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	CH_2Ph
n	1	1	2	1

More interestingly, a dramatic solvent effect was observed. Under the same reaction conditions, the use of chloroform or dichloromethane instead of tetrahydrofuran gave no the desired product except for the hydrolysis of the acid chloride. By adding a water-soluble solvent as a cosolvent such as tetrahydrofuran, 2,6-bis(chlorocarbonyl)pyridine smoothly reacted with amino of histidine, and its hydrolysis was avoided efficiently. It is especially pointed out that a tetrahydrofuran solution of 2,6-bis(chlorocarbonyl)pyridine and one equivalent of aqueous KOH should be added simultaneously drop by drop; otherwise the poor yield (<10%) was obtained. We next investigated the conversion of the bridged histidine to the diester derivative **1**, and found that the bridged histidine smoothly esterified in a good yield in the presence of $SOCl_2$ at 0 ℃.

The final macrocyclization was accomplished by reaction of equimolar amounts of the dihistidine dimethyl ester **1** and the corresponding polyamines in refluxing

methanol under normal dilution conditions for 72 h . The 1: 1 cyclization was the main cyclization process observed in these reactions, and title compounds **2-4** were isolated by column chromatography on silica gel in *ca.* 5-10% yield. Attempts were made to improve upon the macrocyclization yield. Unfortunately, both the use of high dilution conditions and the replacement of the dimethyl ester with the diethyl ester had little effect on the reaction.

According to the procedure mentioned above, we also synthesized a series of new chiral macrocyclic tetraoxo polyamines containing pyridine ring and functional arms **5-8** derived from L-alanine, L-leucine and L-phenylalanine, respectively.

The synthetic approach insures that the two side arms of these macrocycles will be oriented in an *anti* fashion. Incorportion of functionalized side chains into a macrocyclic oxo polyamine structure may further modulate its coordination geometry, ring conformation, steric effect, and redox properties. These chiral macrocycles can be used for the purposes of chiral recognition, enzyme models and catalysis of asymmetric oxidation, and modificated further for various uses. Biomimetic studies of these macrocycles and their metal ion complexes are in progress.

Experimental

General methods and materials

Melting points were taken on a micro-melting apparatus and uncorrected. ^{1}H NMR spectra were recorded at 400 MHz, and chemical shifts in ppm are reported relative to internal Me_4Si. Mass spectra data were recorded on a Finnigan MAT 4510 spectrometer. Elemental analyses were performed with a Carlo Erba 1106 instrument. Optical rotations were taken on a WZZ-1 polarimeter. L-alanine, L-leucine, L-phenylalanine and L-histidine were purchased from Sino-American Biotechnology Company for use without further purificatoin. 2,6-bis(chlorocarbonyl)pyridine were prepared according to literature procedure.[8] Chloroform and tetrahydrofuran were purified according to the standard methods. Diethylenetriamine, triethylenetetramine and 1,4-dibutylamine were distilled in

vacuo. All other chemicals and reagents were obtained commercially and used without further purification.

The preparation of the dihistidine dimethyl ester 1

L-histidine (2.5 g, 16.1 mmol) was dissolved in 8.5 mL of 2 mol.dm^{-3} aqueous KOH and cooled to 0-5 ℃. Subsequently 20 mL of THF was added. To this vigorously stirred solution were added simultaneously a solution of 4 mL of 4 mol.dm^{-3} aqueous KOH and a solution of 2,6-bis(chlorocarbonyl)pyridine (1.65 g, 8.1 mmol) in 12 mL of THF over 3-4 h. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred at this temperature for 30 min. THF was then removed. The aqueous phase was diluted with 20 mL of H_2O, and acidified by stirring with a solution of 3 mL of formic acid. Acetone (20 mL) was then added to result in a white precipitate. The mixture was filtered. The crude product was recrystallized from H_2O, and dried to give the bridged histidine (92.9%). m.p. 241-242 ℃.

The bridged histidine (2.0 g, 4.5 mmol) was suspended in 25 mL of methanol and cooled down to 0 ℃ in an ice bath. $SOCl_2$ (0.8 mL) was added dropwise with stirring over 1 h. After the addition was complete, the mixture was stirred at the same temperature for another 24 h. H_2O (20 mL) was then added. The mixture was treated with $NH_3.H_2O$ until the pH was 8.0. The precipitate was recrystallized from H_2O, and dried to gain the bridged diester **1** as a white solid in a 92.5% yield. m.p. 191-193 ℃. MS (m/z): 469 (M^+, 100).

General procedure for the synthesis of ***2-8***

Diamino acid dimethyl esters (11.8 mmol) and the corresponding polyamines (11.8 mmol) were heated at reflux in anhydrous methanol (80 mL) under a nitrogen atmosphere for 72 h, followed by concentration to a pale yellow solid. This solid was purified by column chromatography on silica gel.

(4S,14S)-4,14-Bis(4-imidazolylmethyl)-2,5,13,16-tetraoxo-3,6,9,12,15,21-hexaaza

bicyclo[15.3.1]heneicosa-1(21),17,19-triene **2** was obtained as a white solid by column chromatography ($CHCl_3$: CH_3OH: $NH_3{\cdot}H_2O$=5: 2: 0.2) in a 6.2% yield; m.p. 215-218 ℃; $[\alpha]_D^{25}$=+4.5 (c=0.5, CH_3OH). δ_H (400 MHz, DMSO-d_6): 1.91 (br, 1H, amine NH), 2.67 (m, 4H, CH_2NHCH_2), 3.34 (m, 4H, 2CONHCH_2), 3.65 (d, J=6.6 Hz, 4H, 2ImCH_2), 4.93 (br, 2H, asymmetric methine), 6.74 (s, 2H, 2ImH-5), 7.53 (s, 2H, 2Im2-H), 8.04 (br, 2H, 2CH_2NHCO), 8.14 (br, 3H, HPy), 10.1 (d, J=9.4 Hz, 2H, 2PyCO*NH*). Anal. calcd. for $C_{23}H_{28}N_{10}O_4$: C, 54.32, H, 5.55, N, 27.55; found: C, 54.01, H, 5.90, N, 27.29. MS (m/z): 509 (M^+, 10).

(4S,17S)-4,17-Bis(4-imidazolylmethyl)-2,5,16,19-tetraoxo-3,6,9,12,15,18,24-heptaazabicyclo[18.3.1]tetracosa-1(24),20,22-triene **3** was obtained as a white solid by column chromatography ($CHCl_3$: CH_3OH: $NH_3{\cdot}H_2O$=5: 2: 0.3) in a 5.3% yield; m.p. 217-219 ℃; $[\alpha]_D^{25}$= +23.4 (c=0.5, CH_3OH). δ_H (400 MHz, DMSO-d_6): 2.01 (br, 2H, amine NH), 2.50 (m, 8H, CH_2NHCH_2), 3.38 (m, 4H, 2CONHCH_2), 4.00 (d, J=6.4 Hz, 4H, 2ImCH_2), 4.61 (m, 2H, asymmetric methine), 7.04 (m, 4H, 2Im5-H, 2Im2-H), 7.66 (m, 2H, 2CH_2NHCO), 8.17 (br, 3H, HPy), 9.53 (br, 2H, 2PyCO*NH*). Anal. calcd. for $C_{25}H_{33}N_{11}O_4$: C, 54.43, H, 6.03, N, 27.94; found: C, 54.19, H, 6.31, N, 27.65. MS (m/z): 552 (M^+,15).

(4S,13S)-4,13-Bis(4-imidazolylmethyl)-2,5,12,15-tetraoxo-3,6,11,14,20-pentaazabicyclo[14.3.1]eicosa-1(20),16,18-triene **4** was obtained as a white solid by column chromatography ($CHCl_3$: CH_3OH =1: 1) in a 7.1% yield; m.p. 208-210 ℃; $[\alpha]_D^{25}$=+19.9 (c=0.5, CH_3OH). δ_H (400 MHz, DMSO-d_6): 1.16 (m, 4H, $CH_2(CH_2)_2CH_2$), 2.50 (m, 4H, 2CONHCH_2), 3.68 (d, J=6.8 Hz, 4H, 2ImCH_2), 4.65 (m, 2H, asymmetric methine), 6.74 (m, 4H, 2Im5-H, 2Im2-H), 7.38 (m, 2H, 2CH_2NHCO), 8.19 (s, 3H, HPy), 9.29 (br, 2H, PyCO*NH*). Anal. calcd. for $C_{23}H_{27}N_9O_4$: C, 55.97, H, 5.51, N, 25.55; found: C, 55.69, H, 5.80, N, 25.54. MS (m/z): 494 (M^+, 20).

(4S,14S)-4,14-Dimethyl-2,5,13,16-tetraoxo-3,6,9,12,15,21-hexaazabicyclo[15.3.1]heneicosa-1(21),17,19-triene **5** was obtained as a white solid by column chromatography ($CHCl_3$: CH_3OH=10: 1) in a 9.6% yield; m.p. 280 ℃(decomp.);

$[\alpha]_D^{25}$ = +52.2 (c=1.0, $CHCl_3$). δ_H (400 MHz, DMSO-d_6): 1.24 (d, J=5.4 Hz, 6H, $2CH_3$), 2.33 (br, 1H, amine NH), 2.67 (m, 4H, CH_2NHCH_2), 3.89 (m, 4H, $2CONHCH_2$), 4.54 (m, 2H, asymmetric methine), 7.64 (br, 2H, $2CH_2NHCO$), 8.08 (br, 3H, HPy), 9.35 (br, 2H, 2PyCO*NH*). Anal. calcd. for $C_{17}H_{24}N_6O_4$: C, 54.24, H, 6.43, N, 22.33; found: C, 53.88, H, 6.32, N, 22.02. MS (m/z): 377 (M^++1, 90).

(4S,14S)-4,14-Diisobutyl-2,5,13,16-tetraoxo-3,6,9,12,15,21-hexaazabicyclo[15.3.1]heneicosa-1(21),17,19-triene ***6*** was obtained as a white solid by column chromatography ($CHCl_3$: CH_3OH=100: 5) in a 5.9% yield; m.p. 170-171 ℃; $[\alpha]_D^{25}$ =-9.2 (c=1.0, $CHCl_3$). δ_H (400 MHz, DMSO-d_6): 0.91 (d, J=5.6 Hz, 12H, $4CH_3$), 1.25 (m, 6H, $2CH_2CH$(*Leu*)), 2.41 (br s, 1H, amine NH), 2.78 (m, 4H, CH_2NHCH_2), 3.67 (m, 4H, $2CONHCH_2$), 4.56 (m, 2H, asymmetric methine), 7.63 (br, 2H, $2CH_2NHCO$), 8.06 (br, 3H, HPy), 9.13 (d, J=9.0 Hz, 2H, 2PyCO*NH*). Anal. calcd. for $C_{23}H_{36}N_6O_4$: C, 59.97, H, 7.88, N, 18.25; found: C, 59.87, H, 8.15, N, 18.03. MS (m/z): 461 (M^+,100).

(4S,17S)-4,17-Diisobutyl-2,5,16,19-tetraoxo-3,6,9,12,15,18,24-heptaazabicyclo[18.3.1]tetracosa-1(24),20,22-triene ***7*** was obtained as a white solid by column chromatography ($CHCl_3$: CH_3OH=3.5: 1) in a 5.1% yield; m.p. 174-177 ℃; $[\alpha]_D^{25}$ =-10.9 (c=1.0, $CHCl_3$). δ_H (400 MHz, DMSO-d_6): 0.88 (d, J=6.0 Hz, 12H, $4CH_3$), 1.24 (m, 6H, $2CH_2CH$(*Leu*)), 1.94 (br, 2H, amine NH), 2.52 (m, 8H, CH_2NHCH_2), 3.41 (m, 4H, $2CONHCH_2$), 4.52 (m, 2H, asymmetric methine), 6.08 (br, 2H, $2CH_2NHCO$), 8.19 (br, 3H, HPy), 9.48 (d, J=8.2 Hz, 2H, 2PyCO*NH*). Anal. calcd. for $C_{25}H_{41}N_7O_4$: C, 59.62, H, 8.21, N, 19.47; found: C, 59.23, H, 8.41, N, 19.24. MS (m/z): 505 (M^++1, 20).

(4S,14S)-4,14-Dibenzyl-2,5,13,16-tetraoxo-3,6,9,12,15,21-hexaazabicyclo[15.3.1]heneicosa-1(21),17,19-triene ***8*** was obtained as a white solid by column chromatography ($CHCl_3$: CH_3OH=10: 1) in a 5.2% yield; m.p. 284-286 ℃; $[\alpha]_D^{25}$ =-10.0 (c=1.0, $CHCl_3$). δ_H (400 MHz, DMSO-d_6): 2.00 (br, 1H, amine NH), 2.71 (m, 4H, CH_2NHCH_2), 3.65 (m, 4H, $2CONHCH_2$), 4.01 (d, J=6.4 Hz, 4H, $2PhCH_2CH$), 4.22 (m, 2H, asymmetric methine), 7.28 (br, 2H, $2CH_2NHCO$), 7.68 (m,10H, 2HPh), 8.04 (br, 3H, HPy), 9.38 (d, J=8.2 Hz,

2H, 2PyCO*NH*). Anal. calcd. for $C_{29}H_{32}N_6O_4$: C, 65.89, H, 6.10, N, 15.90; found: C, 65.69, H, 6.22, N, 15.71. MS (m/z): 528 (M^+, 15).

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