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Synthesis of 1,5,3,7-Diazadiphosphocine-1,5-dicarboxylic Acids and Their Esterifications

S.K. CHOI*, K.M. BANG, J.H. SONG, D.H. LEE, I.S. KIM, D.I. JUNG* and J.T. HAHN[†] Department of Chemistry, Dong-A University, Saha-Gu, Busan-604714, South Korea Fax: (82)(51)2007259; Tel: (82)(51)2007249, E-mail: dijung@dau.ac.kr

> In order to synthesize new bioactive compounds and contrasting agents, reactions of glycine and glutamic acid with paraformaldehyde and hypophosphorous acid were executed. Products are 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid (4a), 2-[5-(1,2-dicarboxyethyl)-3,7-dihydroxy-3,7-dioxo-315.715-[1,5,3,7]diazadiphosphocan-1-yl]-succinic acid (4b) and 3,7-dihydroxy-3,7dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-di-(2-glutaric acid) (4c). Esterification of 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid (4a) by treatment of methanol, ethanol and propanol were executed. 3,7-Dihydroxy-3,7-dioxoperhydro-1,5,3,7diazadiphosphocine-1,5-diacetic acid methyl ester (5a), 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid ethyl ester (5b) and 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid propyl ester (5c) were, respectively synthesized in good yields. In case of 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-di-(2-glutaric acid) (4c) by treatment of methanol, yielded 2-[5-(1,2-dicarboxyethyl)-3,7-dihydroxy-3,7-dioxo-315.715-[1,5,3,7]diazadiphosphocan-1-yl]-succinic acid methyl ester (5d).

> Key Words: Contrasting agent, Esterification, Amino acid, 1,5,3,7-Diazadiphosphocine-1,5-dicarboxylic acid.

INTRODUCTION

In the last few years, great efforts have been devoted to the development of efficient ligands for transition metal ions, in order to obtain complexes whose stability, physical properties and biodistribution could make them suitable for application as contrast agents for magnetic resonance imaging (MRI), diagnostic therapeutic radiopharmaceuticals or fluorescent bioassays¹⁻⁵.

Most of these ligands belong to the huge class of polyaminopolycarboxylic acids as diethylenetriaminopentaacetic acid (DTPA), 1,4,7,10-tetraazacyclododecane -1,4,7,10-tetraacetic acid (DOTA) and the great array of their substitued or modified derivatives. Nevertheless an increasing interest is attracted by polyaminopolyphosphonic and -phosphinic acids, as witnessed in a recent review on their coordination properties.

[†]Department of Beautycare, Young-Dong University, Chungcheongbuk-do-370-701, South Korea.

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Despite the scarce literature on α -aminoalkyl phosphinic acid, they represent a useful class of organic compounds. The close similarity with α -aminocarboxylic acids suggests them as potential isoteric substitutes of this ubiquitous moiety. Furthermore, alkylamino and *bis*-(alkylamino)phosphinic acids represent optimal structural scaffolds for the preparation of novel ligands with improved properties. In sharp contrast with carboxylic and phosphonic moieties, the bidentate phosphinic may be introduced as bridging group in linear or cyclic molecules, allowing the formation of a larger number of five-membered chelate rings, well known to provide high stability to the corresponding complexes⁶⁻¹⁰.

In addition, the lower ionic charge relating to phosphonates helps to obtain easily neutral or almost neutral metal complexes, better tolerated *in vivo* applications in view of the lower osmolarity of their solutions¹¹⁻¹⁴.

To the best of our knowledge, there are no reports involving the reaction of hypophosphorous acid with formaldehyde and primary amines.

Our interests in α -aminoalkylphosphinic acid and *bis*-(α -aminoalkyl)phosphinic acid lies in their coordination ability towards metal ions, thereby providing useful structural motifs for the preparation of multi-sited ligands. We were particularly interested (i) in assessing the behaviour of primary amino acids in the condition described above and (ii) in searching a route to obtain mixed carboxylic phosphinic ligands. The ditopic nature of hypophosphorous acid (a formal $^{-}P(O)(OH)^{-}$ dinucleophile) and of the primary amino group [a formal RN(CH₂⁺)₂ dielectrophile], could give rise either to linear polymeric or to cyclic oligomeric products¹¹.

As a part of a research program related to the synthetic study of pharmacologically interesting compounds and good chelating agents for transition metal ions, herein, the synthesis of an unusual medium-sized ring heterocyclic ligand with mixed carboxylic-amino-phosphonic donating groups is reported.

EXPERIMENTAL

Melting points were determined on an electrothermal capillary melting point apparatus and uncorrected. TLC was performed on glass plates coated with silicon oxide (silicagel 60F₂₅₄) and compounds were visualized using a UV lamp. ¹H and ¹³C NMR spectra were obtained with Bruker AC 2000 (200 MHz) and Varian Gemini (200 or 300 MHz) spectrometers. Mass spectra were measured with HP 5890 GC/ Mass (70 eV, EI). The organic solvents and chemicals were obtained from commercial products and purified by the appropriate methods before use. All starting materials were purchased from Aldrich, Fluka, Fisher, Lancaster, or TCI chemical companies and used as received. The following known compounds were prepared by literature procedures¹⁵: ethanol, DMSO, hexane, chloroform, water, butanol, propanol and methanol.

3,7-Dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid (4a): A mixture of glycine (0.75 g, 0.01 mol), hypophosphorous acid (0.55 mL, 0.01 mol), paraformaldehyde (1.8 g, 0.02 mol) and 6 M HCl (10 mL) was stirred 3096 Choi et al.

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for 0.5 h. And then the clear solution was left standing for 3 days. A white solid product (0.26 g, yield 8 %), was then collected by filteration, washed with a small amount of cold water, ethanol and dried *in vacuo*. Unreacted starting materials remained in solution: m.p. 273-275 °C; IR (KBr, v_{max} , cm⁻¹): 3445 (OH), 2999, 1718 (C=O), 1652; ¹H NMR (D₂O, pH 10, 200 MHz) δ 3.87 (s, 4H), 3.50 (d, *J* = 9.3 Hz, 8H); ¹³C NMR (D₂O, pH 10, 50 MHz) δ 178.5, 59.2, 55.6; MS (MALDI-TOF), m/z 331 (Anal. calcd (%). C 26.24; H, 5.50; N, 7.65; P, 16.92 found (%); C, 26.50; H, 5.33; N, 7.36; P, 16.71).

2-[5-(1,2-Dicarboxyethyl)-3,7-dihydroxy-3,7-dioxo-315.715-[1,5,3,7]diazadiphosphocan-1-yl]-succinic acid (4b): A mixture of L-aspartic acid (1.33 g, 0.01 mol), hypophosphorous acid (0.55 mL, 0.01 mol), paraformaldehyde (1.8 g, 0.02 mol) and 6 M HCl (10 mL) was stirred for 30 min. And then the clear solution was left standing 3 days. And then mixture was added ether, another separated with H₂O, dried *in vacuo*. A white solid product (0.17 g, yield 7.8 %) was then collected: m.p. 238-240 °C; IR (KBr, v_{max} , cm⁻¹): 3445 (OH), 2999, 1718 (C=O), 1652; ¹H NMR (D₂O, pH 10, 200 MHz) δ 4.24 (t, *J* = 6.9 Hz, 2H), 3.48 (d, *J* = 9.2 Hz, 8H), 3.34 (m, 4H); ¹³C NMR (D₂O, pH 10, 50 MHz) δ 174.1, 173.4, 52.1, 50.8, 48.5.

3,7-Dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-di-(2-glutaric acid) (4c): A mixture of L-glutamic acid (1.47 g, 0.01 mol), hypophosphorous acid (0.55 mL, 0.01 mol), paraformaldehyde (1.8 g, 0.02 mol), and 6 M HCl (20 mL) was stirred for 0.5 h. And then the clear solution was left standing 3 days. In order to precipitate solid, the clear solution in refrigerator was kept for 24 h. After filtering precipitated solid, it was washed by hexane and chloroform. A white solid product (0.32 g, yield 6.8 %) was then collected: m.p. 304-306 °C; IR (KBr, v_{max} , cm⁻¹): 3448 (OH), 2956, 1731 (C=O), 1655; ¹H NMR (D₂O, pH 10, 200 MHz) δ 4.27 (s, 2H), 3.50 (d, *J* = 9.3 Hz, 8H), 2.42 (t, *J* = 6.9 Hz, 4H), 2.08 (m, 4H); ¹³C NMR (D₂O, pH 10, 50 MHz) δ 173.0, 172.6, 170.4, 169.7, 52.3, 51.5, 48.9, 25.8.

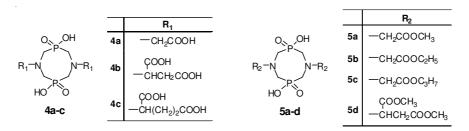
General procedure for the preparation of 5a-d: A mixture of synthesized 1,5-diacetic acid 4a/succinic acid 4b (3×10^{-3} mol) with coresponding alcohol (15 mL) as solvent and reagent was stirred for 0.5 h. After the reaction mixture was refluxed under N₂ for 24 h and dried. The organic layer was filtered and concentrated. A light green solid product then collected.

3,7-Dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid methyl ester (5a): Yield 74.5 %; m.p. 273-275 °C; IR (KBr, v_{max} , cm⁻¹): 3383, 1749 (C=O); ¹H NMR (D₂O, pH 10, 200 MHz) δ 4.12 (s, 4H), 3.57 (s, 6H), 3.42 (d, J = 9.3 Hz, 8H); ¹³C NMR (D₂O, pH 10, 50 MHz) δ 179.7, 68.2, 66.0, 64.8.

3,7-Dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid ethyl ester (5b): Yield 71.0 %; m.p. 312-314 °C; IR (KBr, v_{max} , cm⁻¹): 3385, 2930, 1750 (C=O); ¹H NMR (D₂O, pH 10, 200 MHz) δ 4.10 (s, 4H), 4.01(d, *J* = 7.1 Hz, 4H), 3.46 (d, *J* = 9.2 Hz, 8H), 1.20 (t, *J* = 7.1 Hz, 6H); ¹³C NMR (D₂O, pH 10, 50 MHz) δ 179.1, 74.8, 67.9, 68.4, 66.1, 24.6. Vol. 22, No. 4 (2010)

3,7-Dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid propyl ester (5c): Yield 69.4 %; m.p. 335-337 °C; IR (KBr, v_{max} , cm⁻¹): 3384, 2932, 1748 (C=O); ¹H NMR (D₂O, pH 10, 200 MHz) δ 4.05 (s, 4H), 3.86 (d, *J* = 6.7 Hz, 4H), 3.36 (d, *J* = 9.3 Hz, 8H), 1.75 (m, 4H), 0.99 (t, *J* = 7.4 Hz, 6H); ¹³C NMR (D₂O, pH 10, 50 MHz) δ 179.7, 80.0, 68.1, 66.0, 32.5, 20.8.

2-[5-(1,2-Dicarboxyethyl)-3,7-dihydroxy-3,7-dioxo-315.715-[1,5,3,7]-diazadiphosphocan-1-yl]succinic acid methyl ester (5d): Yield 74.5 %; IR (KBr, v_{max} , cm-1): 3383, 1749 (C=O); ¹H NMR (D₂O, pH 10, 200 MHz) δ 4.15 (s, 2H), 3.67 (s, 12H), 3.18 (m, 4H), 3.45 (d, J = 9.2 Hz, 8H); ¹³C NMR (D₂O, pH 10, 50 MHz) δ 174.5, 173.8, 69.6, 65.4, 64.9, 50.7.



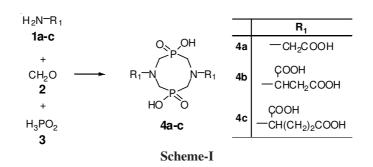
Structural diagram of 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-dicarboxylic acids (**4a-c**) and their derivatives (**5a-d**)

RESULTS AND DISCUSSION

As a part of research program related to the synthetic study of pharmacologically interesting compounds and good chelating agents for transition metal ions, the synthesis and esterification of an unusual medium sized ring heterocyclic ligand with mixed carboxylic aminophosphonic donating groups is reported. In order to synthesize 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid **4a**, the reaction was then performed, adopting glycine as a model amino acid in aq. HCl.

The strongly acidic medium is required to promote the second reaction of H_3PO_2 and to avoid the side reactions of the iminium ion such as the reduction by means of formaldehyde to N-methyl derivatives.

The reaction was found to be highly dependent on the experimental conditions employed. High concentrations of the reactant, heat and long reaction times led to extensive formation of polymeric products; conversely, low acidity (pH > 1) and low reactant concentrations gave rise to complex mixtures. A clean reaction was effected dissolving glycine and H_3PO_2 in 6 M HCl to obtain a 1.0 M solution in both reagents and adding paraformaldehyde in slight excess (3 equiv.) in one portion. Complete dissolution was achieved by stirring for 0.5 h and then the clear solution was left standing for 0.5 h and then the clear solution was left standing for 3 days. A white solid product was then collected by filtration, washed with a small amount of cold water, ethanol and dried *in vacuo*. 3098 Choi et al.



In case of aspartic acid with paraformaldehyde and H₃PO₂ we could obtain 2-[5-(1,2-dicarboxyethyl)-3,7-dihydroxy-3,7-dioxo-315.715-[1,5,3,7]-diazadiphosphocan-1-yl]-succinic acid (**4b**). Work-up step to get **4b** is very different and difficult than those of **4a** and **4c**. We remarked work-up step to get **4b** at the experimental section. The reaction of glutamic acid with paraformaldehyde and H₃PO₂ gave 3,7dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-di-(2-glutaric acid) (**4c**). Esterification of synthesized compound **4a** by methanol, ethanol and propanol gave acid ester compound **5a**, **5b**, **5c**. From these observations, this product was proposed to have the structure of 3,7-dihycholy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid methyl ester (**5a**). Structures of acid ester **5b** and acid ester **5c** were suggested by the similar manner as acid ester **5a**. In case of compound **4b** by methanol, we could get acid ester compound **5d**. Physical data of products **4a-c**, **5a-d** are as follows (Table-1).

The relative position of the functional groups is particulary interesting in view of the possible application of carboxylic acid **4a** as ligand for metal ions. The N-CH₂COOH and N-CH₂-P(O)OH-CH₂-N moieties are known to chelate efficiently through formation of five-membered rings with the metal atom. Furthermore, the latter is embraced by the six donor atoms in a nearly ideal octahedral arrangement, highly advantageous for the complexation of the hexacoordinated transition metal ions. Hence we will start a preliminary investigation on the binding properties of Vol. 22, No. 4 (2010)

TABLE-1 PHYSICAL DATA OF PRODUCTS 4a-c, 5a-d				
Entry	Product		m.p. (°C)	Yield (%) ^a
1		4a	273-275	8.0
2		4b	238-240	7.8
3		4 c	304-306	6.8
4	H ₃ cooc N N CoocH ₃ HO Co O _{2P} COH	5a	273-275	74.5
5	C_2H_5OOC N N COOC ₂ H ₅ HO R O ON OH	5b	312-314	71.0
6	C ₃ H ₇ OOC N N COOC ₃ H ₇ HO R O H ₃ COO C O P	5c	335-337	69.4
7	H ₃ COOC	5d	_	74.5

TABLE-1

a: Isolated yields.

carboxylic acid 4a towards Mn²⁺ and Gd³⁺, two paramagnetic ions of choice in the design of contrast agents for MRI, with different chemical behaviours and whose magnetic features help in the investigation of the solution structures of the corresponding adducts.

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