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One-step synthesis of a new eight-membered cyclic ligand from glycine, formaldehyde and hypophosphorous acid

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Abstract—The eight-membered 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid was obtained with a one-step reaction of glycine, formaldehyde and hypophosphorous acid in acidic aqueous medium. A preliminary investigation of its coordination properties is reported.

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),[1] diagnostic-therapeutic radiopharmaceuticals[2] or fluorescent bioassays.[3] 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 substituted or modified derivatives.[4] Nevertheless an increasing interest is attracted by polyaminopolyphosphonic and -phosphinic acids, as witnessed in a recent review on their coordination properties.[5] Despite the scarce literature on α-aminoalkyl phosphinic acid, they represent a very useful class of organic compounds. The close similarity with α-aminocarboxylic acids suggests them as potential isosteric 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 complexes. In addition, the lower ionic charge relating to phosphonates helps to obtain easily neutral or almost neutral metal complexes, better tolerated in in vivo applications in view of the lower osmolarity of their solutions.

α-Aminoalkylphosphinic acids or bis(α-aminoalkyl)-phosphinic acids are easily prepared by reaction of amines, carbonyl compounds and hypophosphorous acid, their relative distribution depending mainly on the reactants ratio. This reaction, typically conducted in acidic medium, involves the preliminary formation of iminium ions from the carbonyl compound and the amine; the attack of the iminium ion to the hypophosphorous acid, which can be reiterated, afford α-aminoalkylphosphinic or bis(α-aminoalkyl)phosphinic acids, respectively.

To the best of our knowledge, there are no reports involving the reaction of hypophosphorous acid with formaldehyde and primary amines. A paper by Schmidt[6] describes the serendipitous discovery of α-aminophosphinic acids as products of the action of acetone on alkyl- or arylammonium hypophosphite. The reaction did not proceed beyond the α-aminoalkylphosphinic acid stage, either for the strictly stoichiometric amine:H_3PO_2 1:1 ratio or for the steric hindrance of the product to a second attack of iminium ions. Later, Maier[7] systematically studied the reaction of secondary amines in various stoichiometric ratios and experimental conditions, establishing the general rules to obtain these products, their purification and their physical and chemical properties. The same author

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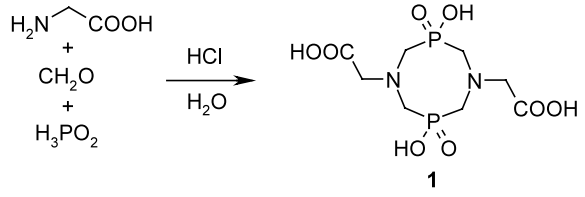
reacted iminodiacetic acid, formaldehyde and H_3PO_2 in acidic aqueous medium obtaining high yields of bis-[bis(carboxymethyl)aminomethyl]phosphinic acid,[8] later recognized as a good chelating agent for transition metal ions[9] and followed by three derivatives obtained from various imino(di)acids.[10]

Our interest in α-aminoalkylphosphinic and bis(α-aminoalkyl)phosphinic acids lies in their coordination ability towards metal ions, thereby providing useful structural motifs for the preparation of multi-sited ligands.[11,12] We were particularly interested (i) in assessing the behavior of primary aminoacids 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 $RN(CH_2^{+})_2$ dielectrophile), could give rise either to linear polymeric or to cyclic oligomeric products.

The reaction was then performed, adopting glycine as a model aminoacid in aq. HCl (Scheme 1). The strongly acidic medium is required to promote the second reaction of H_3PO_2 and to avoid the side reactions of the iminium ions 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 reactants, heat and very 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 30 min 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.

NMR analysis of the product showed a highly symmetrical molecule, (two signals in ^{1}H NMR and three signals in the ^{13}C NMR) with a molecular weight of 330 a.m.u., later characterized as 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid (**1**).[13] This heterocyclic ligand results from the assembly of 2 molecules of glycine, two molecules of H_3PO_2 and 4 molecules of formaldehyde; its striking feature is that each atom of this eight-membered ring is originated from eight single different molecules, representing a formal '1+1+1+1+1+1+1+1' cyclocondensation. The yield is satisfactory despite the number of elemental steps involved in the overall transformation and of the ring size, usually unfavorable for entropic reasons.



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Scheme 1.

The relative position of the functional groups is particularly interesting in view of the possible application of compound **1** as ligand for metal ions. The N-CH_2-COOH and N-CH_2-P(O)OH-CH_2-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 started a preliminary investigation on the binding properties of **1** towards Mn^{2+} and Gd^{3+}, two paramagnetic ions of choice in the design of contrast agents for MRI, with different chemical behaviors and whose magnetic features help in the investigation of the solution structures of the corresponding adducts.

The Mn^{2+} complex was prepared by addition of a stoichiometric amount of $MnCl_2$ to a solution of **1** while maintaining the pH at 7.0 by the addition of aq. NaOH. The longitudinal relaxivity R_{1p} (defined as the increase of the longitudinal relaxation rate of water protons in a 1.0 mM solution of the paramagnetic species) of the freshly prepared solution was 3.9 mM^{-1} s^{-1}, very similar to the value of 3.3 mM^{-1} s^{-1} reported for $[Mn(EDTA)]^{2-}$ and strongly indicative of a penta-coordinated metal ion. A slow dissociation process was clearly observable, and after 20 h the relaxivity value reached a limiting value of 8.8 mM^{-1} s^{-1} as a consequence of a higher hydration number for the metal ion.

The Gd^{3+} complex was prepared with a similar procedure; the observed relaxivity value is noteworthy (R_{1p} 11.8 mM^{-1} s^{-1}), in agreement with a hexacoordinated complex with three bound water molecules. The initial adduct is rather unstable, evolving slowly towards a second adduct with lower relaxivity (R_{1p} 8.5 mM^{-1} s^{-1}); this complex is more stable, being unchanged in a wide pH range (4<pH<8). Competitive titration with DTPA or EDTA provided an estimated log $K_{Gd(1)}$ of 17.6, relatively good for a hexacoordinating ligand. The coordination behavior of **1** with other metal ions is currently under investigation, as is the extension of this protocol to α-substituted aminoacids.

In conclusion, we report here the synthesis of an unusual medium-sized ring heterocyclic ligand, with mixed carboxylic-amino-phosphonic donating groups. The preparation is very easy, the molecule being assembled in one single reaction from readily available and cheap starting materials.

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13. Selected data for compound **1**: ^{1}H NMR (D_2O, pH 10) 3.87 ppm (s, 4H), 3.50 (d, 8H, $J_{CP}=9.3$ Hz); ^{13}C NMR (D_2O, pH 10) 178.5 ppm [C], 59.2 ppm [CH_2], 55.6 ppm [CH_2] (d, $J_{CP}=152$ Hz). ^{31}P NMR (D_2O, pH 10) 25.6 ppm. MS (MALDI-TOF) 331 a.m.u. (calcd for $C_8H_{16}N_2O_8P_2$: 330 a.m.u.). Anal. calcd for $C_8H_{16}N_2O_8P_2{\cdot}2H_2O$: 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.