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Synthesis and Acid Catalytic Activity of 1,5,3,7-Diazadiphosphocine-1,5-dicarboxylic Acids

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In order to synthesize new bioactive sompounds and contrasting agents, reactions of amino acids (glycine, aspartic acid and glutamic acid) with para formaldehyde 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-dioxoperhydro-diazadiphosphocine-1-yl]-succinic acid (**4b**) and 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-di-(2-glutaric acid) (**4c**). As shown in Table-1, the reactions of **4a-c** in presence of acid catalysts (all 100 % GC yields) gave only 8-phenyl-8-azabicyclo[3.2.1]octan-3-one (**5**) (**4a**; pH (1M) = 0.17, **4b**; pH (1M) = 0.15, **4c**; pH (1M) = 0.16). In case of inorganic acid catalysts, 8-phenyl-8-azabicyclo[3.2.1]octan-3-one (**5**) and N-phenyl pyrrole (**6**) (HCl: 5 = 89.4 and 6 = 10.3 %, H_2SO_4; 5 = 94.4 and 6 = 5.5 %, CH_3COOH: 5 = 13 and 6 = 7.8 %, citric acid: 5 = 80.6 and 6 = 18.7 %) were synthesized. Because of selective acid catalytic ability of **4a-c**, we will try reactivity studies as acid catalysts of **4a-c** about all acid catalytic reactions.

Keywords: Contrasting agent, 1,5,3,7-Diazadiphosphocine-1,5-dicarboxylic acids, Acid catalytic activity, Amino acids.

INTRODUCTION

Magnetic resonance imaging (MRI) is a powerful and non-invasive diagnostic technique useful in providing images of the inside of the human body[1]. Nowadays, around 30 % of all the magnetic resonance imaging scans are performed employing a contrast agent[2,3], which is an exogenous compound able to enhance the relaxation rates of water protons, In this way the quality of the magnetic resonance imaging images obtained is greatly improved.

An increasing interest is attracted by polyaminopolyphosphonic and - phosphinic acids, as witnessed in a recent review on their coordination properties[4]. Despite the less literature on α-aminoalkylphosphinic acid, they represent a useful class of organic compounds. The close similarity with α-amino carboxylic 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.

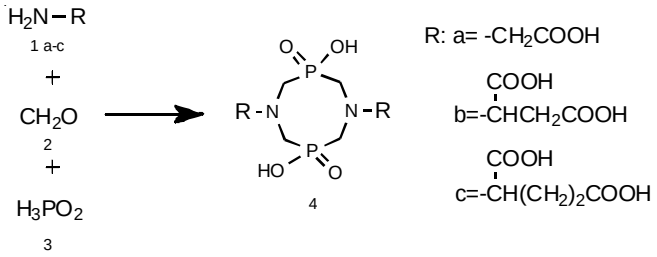
Our interest in α-aminoalkylphosphinic and *bis*(α-aminoalkyl) phosphinic acids lies in their coordination ability towards metal ions, thereby providing useful structural motifs for the preparation of multi-sited ligands[5,6]. We were particularly interested (i) in assessing the behaviour of primary 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 $RN(CH_2^+)_2$ dielectrophile), could give rise either to linear polymeric or to cyclic oligomeric products.

As a part of a research program related to the synthetic study of pharmacologically interesting compounds and good chelating agents for transition metal ions, we report here the synthesis of an unusual medium-sized ring heterocyclic ligand with mixed carboxylic-amino-phosphonic donating groups[7] and we research the reaction of aniline with 2,5-dimethoxytetrahydrofuran by the synthesized product (3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphonic-1,5-diacetic acid (**4a**), 2-[5-(1,2-dicarboxyethyl)-3,7-dihydroxy-3,7-dioxoperhydro-[1,5,3,7]diazadiphosphocan-1-yl]-succinic acid (**4b**), 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-di-(2-glutaric acid) (**4c**) as acid catalysts.

EXPERIMENTAL

Melting points were determined on an electrothermal capillary melting point apparatus and uncorected. TLC was performed on glass plates coated with silicon oxide (silica-gel 60 F_{254}) and compounds were visualized using a UV lamp. ^1H and ^{13}C NMR spectra were obtained with bruker AC2000 (200

MHz) and varian Gemeni (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. Except where noted, all starting amterial were purchased from Aldrich, Fluka, Fisher, Lancaster or TCI chemical companies and used as received. The following known compounds were prepared by literature procedures[7a]: ethanol, DMSO, hexane, chloroform, water, butanol, propanol and metahanol. Known compounds prepared by modified procedures have been included in the supplemental information.



3,7-Dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphos phonic-1,5-diacetic acid (4a): A mixture of glycine (**1a**) (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 for 0.5 h and then the clear solution was left standing 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 olution: m.p. 273-275 °C; IR (KBr, ν_{max}, cm^{-1}): 3445 (OH), 2999, 1718 (C=O), 1652; ^{1}H NMR (D_2O, PH 10, 200 MHz) δ; 3.87 (s, 4H), 3.50 (d, *J* = 9.3 Hz, 8H); ^{13}C NMR (D_2O), pH 10, 50 MHz) δ; 178.5, 59.2, 55.6; MS (MOLDI-TOF), *m/z* 331 (Anal. Calcd. C, 26.24; H, 5.50; N, 7.65; P, 16.92; Found; C, 26.50; H, 5.53; N, 7.36; P, 16.71).

2-[5-(1,2-Dicarboxylethyl-3,7-dihydroxy-3,7-dioxo-perhydro-[1,5,3,7]-diazadiphosphocan-1-yl]-succinic acid (4b): A mixture of L-aspartic acid (1.33 g, 0.01 mol), hypophosphorus acid (0.55 mL, 0.01 mol), para-formaldehyde (1.8 g, 0.02 mol) and 6 M HCl (10 mL) was stirred for 0.5 h. The clear solution was left standing 3 days. And then mixture was added ether, another separated with H_2O, dried *in vacuo*. A white solid product (0.17 g yield 7.8 %) was then collected: m.p. 238-240 °C; IR (KBr, ν_{max}, cm^{-1}) 3445 (OH), 2999, 1718 (C=O), 1652; ^{1}H NMR (D_2O, pH 10, 200 MHz) δ: 4.24 (t, *J* = 6.9 MHz, 2H), 3.48 (d, *J* = 9.2 MHz, 8H), 3.34 (m, 4H); ^{13}C NMR (D_2O, pH 10, 50 MHz) δ: 174.1, 173.4, 52.1, 50.8, 48.5.

3,7-Dihydroxy-3,7-dioxoprehydro-1,5,3,7-diazadi-phosphocine-1,5-di-(2-glutaric acid)(4c): A mixture of L-glutamic acid (1.47 g, 0.01 mol), hypophophrous acid (0.55 mL, 0.01 mol), para-formaldehyde (1.8 g 0.02 mol) and 6 M HCl (20 mL) was stirred for 0.5 h. The clear solution was left standing 3 days. In order to precipitate solid, the clear solution in refrogerator 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, ν_{max}, cm^{-1}) 3448 (OH), 2956, 1731 (C=O), 1655; ^{1}H NMR (D_2O, 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); ^{13}C NMR (D_2O, pH 10, 50 MHz) δ: 173.0, 172.6, 170.4, 169.7, 52.3, 51.5, 48.9, 25.8.

RESULTS AND DISCUSSION

As a part of existing study related to the synthetic study of pharmacologically interesting compounds and good chelating agents for transition metal ions, we here report the synthesis of an unusual medium signed ring heterocyclic ligand with mixed aminophosphonic donating group to synthesize 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid (**4a**),2-[5-(1,2-dicarboxylethyl)-3,7-dihydroxy-3,7-dioxoperhydro-diazadiphosphocan-1-yl]succinic acid (**4b**) and 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazaphos phocine-1,5-di-(2-glutaric acid) (**4c**). These reactions were then performed, adopting various aromatic groups and aminoethyl group with glycine 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 concentration of the reactant, heat and long reaction times led to expensive formation of polymeric product; 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 M solution in both reagents and adding para-formaldehyde in slight excess (3 equiv.) in one portion.

Complete dissolution was achived by stirring for 3 days. A white solid product was then collected by filteration, 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 characterized as 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphos phocine-1,5-diaceticacid (**4a**). This heterocyclic ligand results from the assembly of two molecules of glycine, two molecules of H_3PO_2 and four molecules of formaldehyde; its striking feature is that each atom of this eightmembered 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. In case of aspartic acid with para-formaldehyde and H_3PO_2, we could obtain 2-[5-(1,2-dicarboxyethyl)-3,7-dihydroxy-3,7-dioxoperhydro[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**.

The reaction of glutamic acid with para-formaldehyde and H_3PO_2 gave 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazaphosphocine-1,5-di-(2-glutaric acid) (**4c**). The relative position of the fuctional group is particulary interesting in view of the possible application of carboxylic acid (**4a**) as ligand for metal ions. The N-CH_2COOH 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 six donor atoms in a nearly ideal octahedral arrangement, highly advantageous for the complexation of the

hexa coordination transition metal ions. Hence we will start a preliminary investigation on the binding properties of carboxylic acid (**4a**) towards Mn^{2+} and Gd^{3+}, two paramagnetic ions of choice in the design of contrast agents for magnetic resonance imaging, with different chemacal behaviours and whose magnetic features help in the investigation of the solution structures of the corresponding adducts.

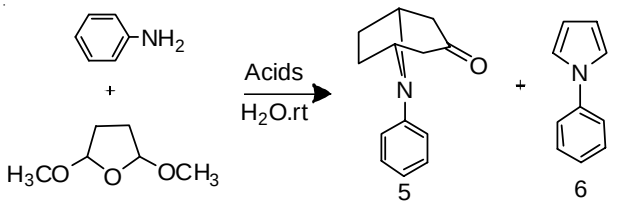
Comparision of catalytic ability for acids: In order to synthesize novel anticonvulsants, we researched that the reactions of amines with 2,5-dimethoxy-tetra hydrofuran and 1,3-acetonedicarboxylic acid as an acid catalyst and a reagent. In general reactions, synthetic yields of 8-aza-bicyclo[3.2.1]-octan-3-ones (**5**) were high than those of pyrroles (**6**) because reactions were done under room temperature.

As shown in Table-1, the reactions of **4a-c** so acid catalysts (all 100 % GC yields) gave only 8-phenyl-8-azabicyclo[3.2.1]-octan-3-one (**5**) (**4a**; pH (1M) = 0.17, **4b**; pH (1M) = 0.15, **4c**; pH (1M) = 0.16).

TABLE-1
COMPARISON OF CATALYTIC ABILITY OF ACIDS FOR THE REACTION OF ANILINE AND 2,5-DIMETOXYTETRAHYDROFURAN

Entry	Acid catalyst	pH (1M)	GC yield (%)	
			5	**6**
1	H_2O	6.8	13.4	3.7
2	HCl	0.15	89.4	10.3
3	H_2SO_4	0.2	94.4	5.5
4	CH_3COOH	1.05	13.0	7.8
5	Citric acid	1.51	80.6	18.7
6	**4a**	0.17	100	-
7	**4b**	0.15	100	-
8	**4c**	0.16	100	-

In case of inorganic acid catalysts, 8-phenyl-8-azabicyclo[3.2.1]octan-3-one (**5**) and N-phenyl pyrrole (**6**) (HCl: 5 = 89.4 and 6 = 10.3 %, H_2SO_4; 5 = 94.4 and 6 = 5.5 %, CH_3COOH: 5 = 13.0 and 6 = 7.8 %, citric acid: 5 = 80.6 % and 6 = 18.7 %) and were synthesized.



Because of selective acid catalytic ability of **4a-c**, we will try reactivity studies as acid catalysts of **4a-c** about all acid catalytic reactions.

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