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Synthesis of tetradentate mixed bisphosphonates—new hydroxypyridinonate ligands for metal chelation therapy

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Abstract—In a general study for developing better drugs suitable for Fe, Al, Co or lanthanide chelation therapy experiments, new mixed bisphosphonate-hydroxy pyridonates were synthesized. We demonstrate that the method using amidation reaction and dealkylation by concentrated hydrochloric acid gives excellent results for amino bisphosphonic acid ligands having at least two carbons between the amino group and the methylene bisphosphonic acid group. © 2002 Elsevier Science Ltd. All rights reserved.

During the past decade, a large number of laboratories have investigated the design of better chelating agents for the treatment of human metal intoxication¹ and/or associated pathologies. Among these metals with documented toxic effects, although not completely understood, iron,^{2,3} cobalt⁴ and aluminum^{5,6} are often cited. For example, aluminum poisoning has been associated with a number of human diseases in relation with neurological dysfunctions such as Alzheimer's disease.⁵

The purpose of this work is to investigate new chelating agents, **1** (Fig. 1) having mixed functional groups such as 1-hydroxy-2-pyridinone and aminobisphosphonic acid for the transport and/or delivery of these cations.

The 1-hydroxy-2-pyridinones which can be considered as cyclic hydroxamic acids, belong to the class of hard bidentate ligands. As such, they are able to complex hard metal ions like cobalt, iron or aluminum by two oxygen atoms yielding to five-membered ring chelates.^{6–8} With the aim to increase the chelating prop-

erties of these agents, we have synthesized polydentate hydroxypyridinones from activated 1-hydroxy-2-pyridinones and several amines such as spermine^{9,10} homospermine, triaminotriethylamine (TREN) and triaminotripropylamine (TRPN).¹¹ A number of studies showed that these ligands are also very efficient for actinide and/or lanthanide decorporations in vivo.^{12–15}

The aminobisphosphonate moiety is also interesting because of the strong chelating properties of the methylene bisphosphonic group. These non toxic derivatives are routinely used in skeletal scintigraphy for the delineation of metastases.¹⁶ They are also efficient for decorporation of actinides.¹⁷ Recently, we reported convenient and versatile methods in the synthesis of new phosphonated tripods.^{18,19} The corresponding bisphosphonic acids have also been demonstrated to be very efficient for chelating metal or metalloid ions such as iron, zinc, aluminum, or copper.^{20–23}

In this paper, we report the synthesis of new chelating agents **1** containing functional groups of different kind: a 1-hydroxy-2-pyridinone and various amino-bisphosphonic acids linked via an amide function.

For the synthesis of these new ligands, compound **2** is used as the starting material. It is prepared as previously described^{9,10} from 1-hydroxy-6-oxo-1,6-dihydro-pyridine-2-carboxylic acid (Scheme 1).

The various tetraethyl aminobisphosphonates: $n=0$ $R=H$, **3a**; $n=1$ $R=Me$, **3b**; $n=2$ $R=H$, **3c** have also been described.^{24–29}

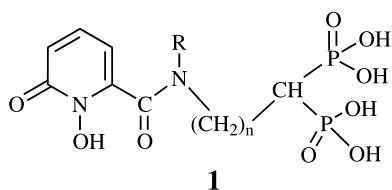
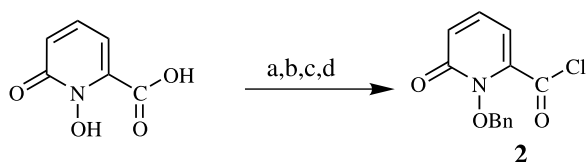


Figure 1.

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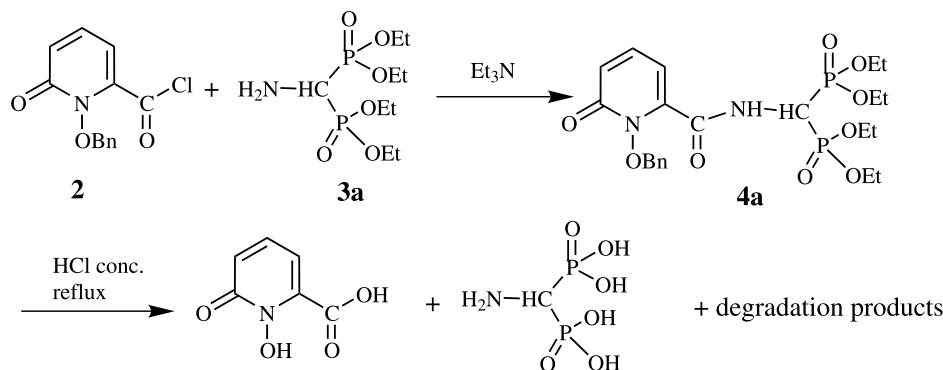
Scheme 1. Reagents and conditions: (a) SOCl_2 , MeOH; (b) K_2CO_3 ; BnBr in acetone; (c) NaOH; (d) $(\text{COCl})_2$ in CH_2Cl_2 .

The synthesis starts with a coupling reaction in which the protected acid chloride **2** is added to an equimolecular mixture of tetraethyl aminobisphosphonate **3** and triethylamine in CH_2Cl_2 . The mixture is refluxed for 15 min then stirred overnight at room temperature. The hydrolysis of phosphonate ethyl esters and the *N*-benzyloxy group of the pyridinone is carried out by concentrated hydrochloric acid under reflux. This procedure has already been used in the cleavage of similar benzyl group in the synthesis of LIHOPO, a powerful octadentate ligand derived from 1-hydroxy-2-pyridinone.¹⁰

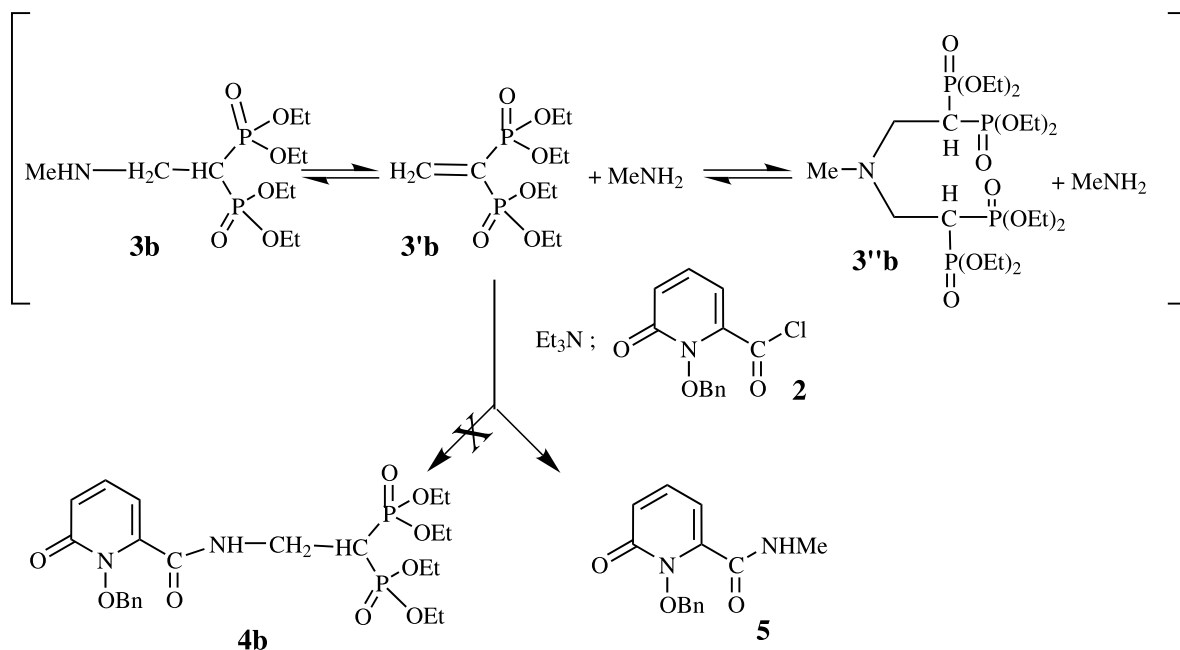
Our results show that the synthesis strongly depends on the aminobisphosphonate structure. In particular, the length of the carbon chain between the amino and the methylene bisphosphonic groups is of great importance.

When the amino group is directly bound to the methylene group ($n=0$, $\text{R}=\text{H}$, **3a**), the coupling reaction is very efficient and the intermediate **4a** is isolated in 94% yield. Refluxing **4a** for 15 min in concentrated hydrochloric acid gives only the dealkylation of phosphonic acid esters. Indeed, continuing hydrolysis overnight leads to the breaking of the amide bond and a partial decomposition of the products (Scheme 2). This HCl breaking of the amide bond in phosphonate derivatives has always previously been observed by Soroka.³⁰

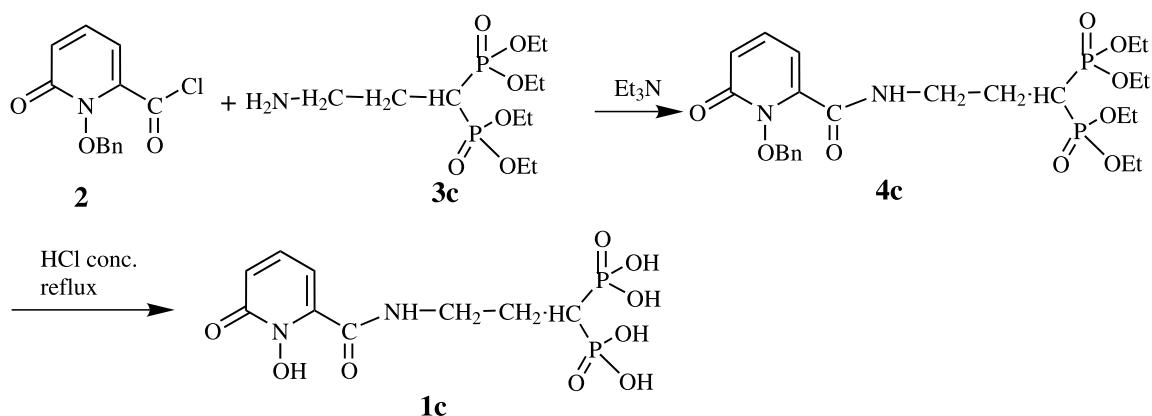
When a methylene group ($n=1$, $\text{R}=\text{Me}$) is present between the amino group and the tetraethyl methylene bisphosphonate as in **3b** (Scheme 3), an equilibrium



Scheme 2.



Scheme 3.



Scheme 4.

between the three species **3b**, **3'b** and **3''b** occurs. Although at 20°C the preponderant structure is **3b**, any small temperature variation leads to the rapid formation of the two others, the retro-Michael's reaction products **3'b** and **3''b** that may change the course of the reaction. Nevertheless, the use of benzoyl chloride instead of **2** in a model experiment showed that the expected coupling product **4** is normally formed.²⁹

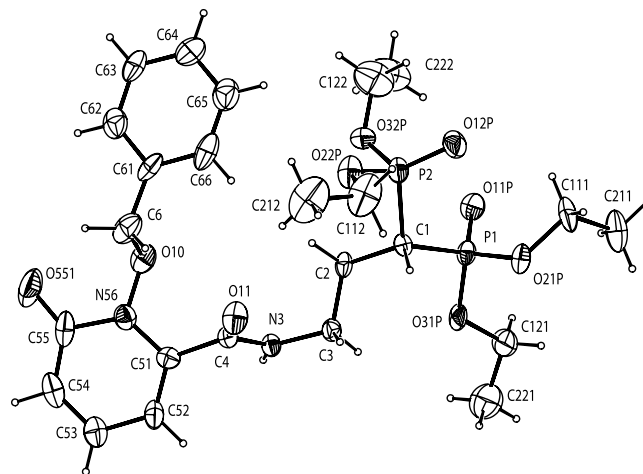
This result encouraged us to apply with confidence this method with to the 1-hydroxy-2-pyridinone derivative **2**. Unfortunately we obtained the useless product **5**, the result of coupling between methylamine and 1-hydroxy-2-pyridinone, instead of **4b**. All attempts to isolate **4b** failed, clearly showing that the equilibrium is shifted to the retro Michael species **3'b** and **3''b**. The methylamine thus formed is now more reactive than the tetraethyl aminobisphosphonate **3b** in the amidation reaction.

When at least two carbons are present, as in the case of tetraethyl aminobisphosphonate **3c** ($n=2$, $R=H$), the correct coupling reaction proceeds readily according to Scheme 4.

The intermediate **4c** is then isolated in 95% yield. Confirmation of its structure was attempted by X-ray diffraction. Despite numerous trials to prepare microcrystals, **4c** invariably led to powdery microcrystals. The better crystals were obtained from CCl_4 at room temperature. With a maximum dimension never exceeding 50 μm , not enough for standard diffractometers, crystals were carried out at the synchrotron W32 wiggler beam-line, LURE, Orsay³¹ (Fig. 2).

Refluxing **4c** in hydrochloric acid for 38 h, afforded the aminobisphosphonic acid coupled to the pyridinone, **1c**. In this step, no side reaction, like hydrolysis of the amide bond, was observed. Final work-up consisted in a neutralization of the solution using sodium hydroxide followed by ion-exchange chromatography on AG X8 H^+ resin to yield the mixed bisphosphonate–hydroxypyridinonate ligand **1c** in 92%.³²

In conclusion, we present a short and efficient procedure to prepare mixed bisphosphonate–hydroxypyridi-

Figure 2. ORTEP drawing of **4c**.

nonate ligands. We show that this method using amidation reaction and dealkylation by concentrated hydrochloric acid gives excellent results except for the aminobisphosphonic acid having a single carbon between the amino group and the methylene bisphosphonic acid group.

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31. Crystal data: $C_{24}H_{36}N_2O_9P_2$, space group $P2_1/c$, $a = 15.692(3)$, $b = 9.908(3)$, $c = 19.621(3)$ Å, $\beta = 111.75(9)^\circ$, $Z = 4$. Final $R = 0.059$ (using all 2274 Fobs). Temperature: 173 K. Data were deposited as a *cif* file with the Cambridge Crystallography Data Centre, 12, Union Road, CB2 1EZ Cambridge, UK, with ref. number CCDC 191294. Data are also available upon request (T.P.).
32. **1c**: 1H NMR (400 MHz, D_2O , pH 14) δ 1.44 (1H, dt, $J_{HP} = 17$ Hz, $J_{HH} = 5.5$ Hz), 1.60–1.80 (2H, m), 2.64 (2H, t, $J_{HH} = 7.7$ Hz), 6.22 (1H, d, $J_{HH} = 7.2$ Hz), 6.39 (1H, d, $J_{HH} = 8.6$ Hz), 7.14 (1H, dd, $J_{HH} = 7.2$, 8.6 Hz). ^{31}P NMR (162 MHz, D_2O , pH 14) δ 24.3. ^{13}C NMR (100.6 MHz, D_2O , pH 14) δ 24.5, 38.2 (t, $J_{PC} = 111$ Hz), 40.1, 106.4, 115.2, 133.9, 145.7, 162, 169.3.