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Catechol-Bisphosphonate Conjugates: New Potential Chelating Agents for Metal Intoxication Therapy

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Abstract: In a quest for better chelating therapy drugs for the treatment of intoxication by Fe, Al, or actinides, two new series of mixed catechol-bisphosphonate through amide linkage were synthesized. Benzyl group was used as protecting group to avoid the breakage of amide by acid hydrolysis or imcomplete reaction in silylation-dealkylation using bromotrimethylsilane.

Keywords: Bisphosphonates, catechol, chelating agents, metal intoxication therapy.

In recent years, a great deal of attention has been focused on the development of more satisfactory chelating agent for the treatment of human metal intoxication. Accumulation of metal ions usually causes serious diseases. For example, a number of inherited diseases result from iron overloading[1], aluminum poisoning has been associated with neurological dysfunction[2].

The purpose of the present investigation is to synthesize new chelating agents **1** and **10** having mixed functional groups such as bisphosphonic acid and catechol in order to enhance binding affinity with concerned metal ions.

Bisphosphonates are widely used in the treatment of various diseases of bone mineral metabolism disorders[3]. Bisphosphonic acid ligand possesses well-known strong chelating properties owing to the formation of a three-dimensional structure capable of binding divalent metals ions such as Ca(II), Mg(II), Fe(II) in a bidentate manner. Bisphosphonates also have very high affinity for metal ions such as Cu(II)[4], Al(III) and Fe(III)[5].

Catechol ligand functional group is commonly found in the siderochromes which are low-molecular-weight compounds produced by microbes and involved in their cellular iron transports[6]. The catecholate anion is highly sensitive to oxidation, while amide substitution reduces this sensitivity[7]. Catecholate ligands incorporating a variety of electron withdrawing substituents have been extensively studied for their extraordinary high affinity with high oxidation state metals such as Fe(III)[8] and actinides such as uranium(IV) and thorium(IV)[9].

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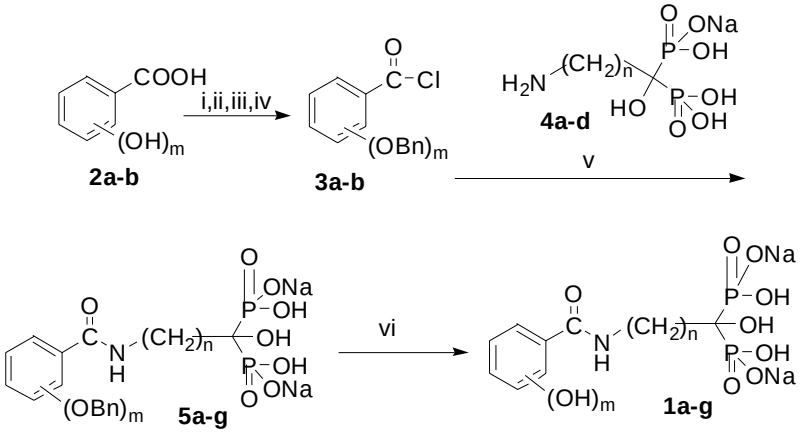
In this paper, we report the synthesis of new chelating agents **1** and **10** containing function group of catechol and bisphosphonate linked *via* an amide function.

Bisphosphonic acids are typically produced by acid hydrolysis or through silylation-dealkylation using bromotrimethylsilane[10]. But acid environment often causes decomposition of catechol and breakage of amide bond while the milder silylation-dealkylation method always leads to mixed products due to incomplete reaction. To avoid these inconvenience, we choose benzyl group to protect catechol and bisphosphonic acid which might be easily removed in neutral medium[11,12].

For the synthesis of new ligand **1**, compound benzoyl chloride **3** was used as starting materials. It was prepared from polyhydroxy benzoic acid **2** as previously described[13]. The solution of benzyl protected benzoyl chloride **3** in THF was added to the solution of monosodium salt of aminoalkylenebisphosphonic acid[14] in the presence of NaOH. After completion of reaction, the pH value of solution was adjusted to acidic and disodium salt of bisphosphonic acids **5** was obtained when the pH value was between 3-4. It's interesting that bisphosphonates **5** were hardly soluble in organic solvent and water, but the target product **1** dissolved in water, so the hydrogenolysis of benzyl protected bisphosphonates **5** could be carried out in water with Pd/C as catalyst in complete conversion. The product bisphosphonates **1**[15] was precipitated with alcohol from the aqueous solution (**Scheme 1**).

Scheme 1



2a,**3a**:2,3-; **2b**,**3b**:3,4-; **2c**,**3c**:3,4,5-; **4a**:n=2; **4b**:n=3; **4c**:n=4; **4d**:n=5; **5a**,**1a**:2,3-,n=3; **5b**,**1b**:3,4,5-,n=2; **5c**,**1c**:3,4-,n=2; **5d**,**1d**:2,3-,n=5; **5e**,**1e**:2,3-,n=2; **5f**,**1f:**3,4-,n=5; **5g**,**1g**:2,3-,n=4.

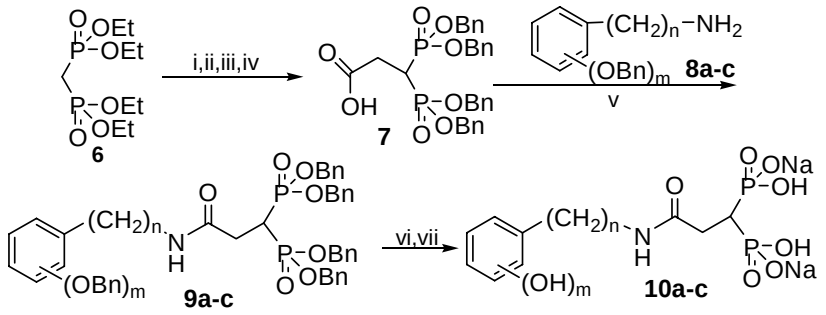
Reagents and conditions: (i)$SOCl_2$, MeOH, r.t.. (ii)BnBr, K_2CO_3, KI, acetone, reflux. (iii) NaOH/H_2O, THF, reflux. (iv)$SOCl_2$, benzene, reflux. (v) aq.NaOH/THF. (vi) H_2, Pd/C, H_2O, r.t..

Compounds synthesized are listed in **Table 1**. The length of the methylene chain and the number of phenolic groups can be varied as desired. This method avoided the acid

breakage of the amide bond in the synthesis of phosphonate[16] and bisphosphonate derivatives[17].

Then we next directed our efforts to the synthesis of ligand **10.** The desired 3,3-bis(dibenzyloxyphosphoryl)propanoic acid **7**[14] was prepared from tetraethyl methylenebisphosphonate. Coupling reaction of amine **8** with acid **7** was carried out in THF at room temperature using isobutyl chloroformate and N-methyl-morpholine (NMM) as the coupling agents in good yield. The amides **9** were then hydrogenated in methanol solution at atmospheric pressure using Pd/C as catalyst (**Scheme 2**). The free bisphosphonic acid is very hydroscopic while the sodium salt (see **Table 1**) is very stable at ambient temperature[18].

Scheme 2



8a,**9a**,**10a**:2,3-,n=0; **8b**,**9b**,**10b**:3,4-,n=0; **8c**,**9c**,**10c**:3,4-,n=2.

Reagengts and conditions: (i) aq. HCl, reflux. (ii) $HC(OBn)_3$,150℃. (iii) $BrCH_2CO_2tBu$, NaH, THF. (iv) CF_3COOH/CH_2Cl_2. (v) *i*-BuO_2CCl, NMM. (vi) H_2, Pd/C, r.t. (vii) $NaHCO_3$.

Table 1 Bisphosphonate **1** and **10** obtained.

Compound	Substitute	n	Yield (%)[a]	Formula
1a	2,3-dihydroxy	3	71.0[a]	$C_{11}H_{15}NNa_2O_{10}P_2.2H_2O$
1b	3,4,5-trihydroxy	2	36.0[a]	$C_{10}H_{13}NNa_2O_{11}P_2.H_2O$
1c	3,4-dihydroxy	2	46.8[a]	$C_{10}H_{13}NNa_2O_{10}P_2.0.5H_2O$
1d	2,3-dihydroxy	5	67.0[a]	$C_{13}H_{19}NNa_2O_{10}P_2$
1e	2,3-dihydroxy	2	51.0[a]	$C_{10}H_{13}NNa_2O_{10}P_2.0.5H_2O$
1f	3,4-dihydroxy	5	67.1[a]	$C_{13}H_{19}NNa_2O_{10}P_2$
1g	2,3-dihydroxy	4	61.7[a]	$C_{12}H_{17}NNa_2O_{10}P_2.1.5H_2O$
10a	2,3-dihydroxy	0	40.6[b]	$C_9H_{11}NNa_2O_9P_2.0.5H_2O$
10b	3,4-dihydroxy	0	42.7[b]	$C_9H_{11}NNa_2O_9P_2.1.5H_2O$
10c	3,4-dihydroxy	2	34.2[b]	$C_{11}H_{15}NNa_2O_9P_2.H_2O$

a) Yield calculated on the basis of compound **4**, b) Yield calculated on the basis of compound **8**.

In summary, two types of 1,1-bisphosphonic acids bearing catechol as chelating agents were efficiently prepared in satisfactory yields. We show that this method using benzyl as protecting group avoids the breaking of amide by harsh acid hydrolysis or imcomplete reaction in silylation-dealkylation using bromotrimethylsilane. Data on the chelating potency of the new bisphosphonates will be published elsewhere.

References and Notes

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15. Selected analytical data:
    1a: ^{1}HNMR(D_2O,600MHz, δ ppm): 1.88-2.02(m, 4H, CH_2CH_2), 3.38(t, 2H, *J*=6.8Hz, CH_2N), 6.83(t, 1H, *J*=8.1Hz, Ar-5H), 7.03(d, 1H, *J*=8.1Hz, Ar-4H), 7.22(d, 1H, *J*=8.1Hz, Ar-6H). ^{13}CNMR(D_2O, 100.6MHz): 26.1, 33.7, 42.7(3s, CH_2), 76.3(t, CP_2, J_{CP}=135Hz), 118.4, 120.8, 121.4,121.6, 146.6, 149.4(6s, Ar-H), 172.2(C(O)N). ^{31}PNMR(D_2O, 162MHz):18.9. Anal. calcd for $C_{11}H_{15}NNa_2O_{10}P_2.2H_2O$, C 28.40, H 4.12, N3.01, Found C 28.37, H 4.14, N 2.92.
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18. Selected analytical data:
    10a: ^{1}HNMR(D_2O,600MHz, δ ppm): 2.78(tt, 1H, *J*=6.8, 21.8Hz, CHP_2)，2.94(td, 2H, *J*=6.8, 15.0Hz, CH_2), 6.84-6.91(m, 3H, ArH). ^{13}CNMR(D_2O, 100MHz), 35.2(s, CH_2), 38.4(t, CHP_2, J_{CP}=105Hz), 117.0, 120.4, 122.5, 126.6, 141.6, 147.3(6s, Ar-H), 175.9(NHC=O). ^{31}PNMR (D_2O, 162MHz):19.6. Anal. calcd. For $C_9H_{11}NNa_2O_9P_2.0.5H_2O$, C 27.42, H 3.05, N 3.55, Found: C 27.81, H 3.37, N 3.44.

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