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Synthesis of bifunctional chelating agents based on mono and diphosphonic derivatives of diethylenetriaminepentaacetic acid

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ABSTRACT

Bifunctional chelating agents (BFCAs) are small molecules containing a chelating unit, able to strongly coordinate a metal ion, and a reactive functional group, devised to form a stable covalent bond with another molecule. BFCAs are widely employed since their conjugation to a suitable biomolecule (e.g., a peptide or an antibody) allows the synthesis of diagnostic or therapeutic agents that specifically target diseased tissue with metals or radiometals. For this reason, BFCAs find application in diagnostic imaging, molecular imaging, and radiotherapy of cancer. The synthesis of new BFCAs based on a diethylenetriaminepentaacetic acid (DTPA) structure in which one or two carboxylic groups are replaced with phosphonic units is described. The phosphonic group, aside from being a classical isostere of the carboxylic acid in coordination chemistry, allows to modulate the physico-chemical properties of the ligands and of the corresponding complexes.

1. Introduction

The use of metal or radiometal complexes in medicine as therapeutic or diagnostic agents is an area of growing interest.[1–3] For diagnostic purposes, gadolinium complexes are employed as contrast agents in magnetic resonance imaging (MRI)[4–6] while complexes of ^{111}In or ^{68}Ga, for example, find application in single photon emission computed tomography (SPECT) or positron emission tomography (PET), respectively.[7–10] For therapy, and in particular in the treatment of some kind of tumors and metastases, complexes of β or α emitters, such as ^{90}Y, ^{177}Lu or ^{225}Ac, are usually studied and administered to patients.[7–12]

All these metal ions need to be strongly coordinated with a suitable ligand to guarantee a safe administration in vivo and prevent an undesirable deposition of toxic metal ions in tissues or organs different from the desired target. Polyaminopolycarboxylic derivatives, such as diethylenetriaminepentaacetic acid **1a** (DTPA) or 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid **2** (DOTA) (Fig. 1), are the ligands of choice and are widely employed because they provide very stable complexes with a wide variety of metal ions.[13]

The metal complex is usually covalently bound to a targeting vector (e.g., peptides[14–16] or monoclonal antibodies[17,18]) that allows a specific delivery to particular type of cells by a recognition process. The easiest way of linking a vector to a metal complex is by direct conjugation to a bifunctional chelating agent (BFCA) followed by deprotection of eventual protective groups and final complexation of the metal ion of choice.[19–21]

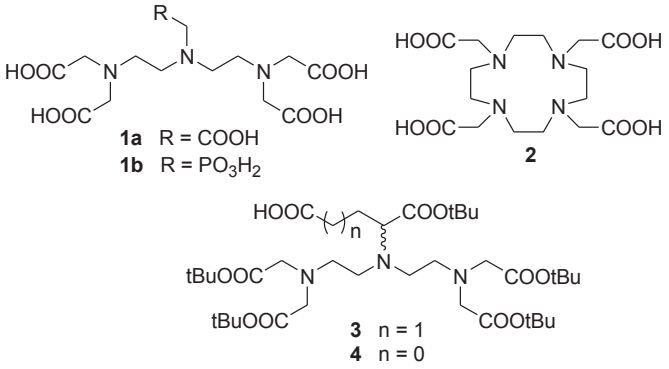

Fig. 1. Common chelating agents and bifunctional derivatives.

Among the huge number of polyaminopolycarboxylic bifunctional chelating agents reported in literature,[22] BFCA **3**[23] and **4**[24] (Fig. 1) found a broad spectrum of applications. For example, BFCA **3** has been conjugated to bile acids,[25,26] oxytocin,[27]

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aminoacids,[28] CCK8 peptides,[29] RGD (Arg-Gly-Asp) peptidomimetics,[30,31] while BFCA **4** has been exploited in the synthesis of a potential MRI contrast agent,[32] linked to a tamoxifen derivative,[33] and conjugated to a cyclic peptide for fibrin targeting.[34]

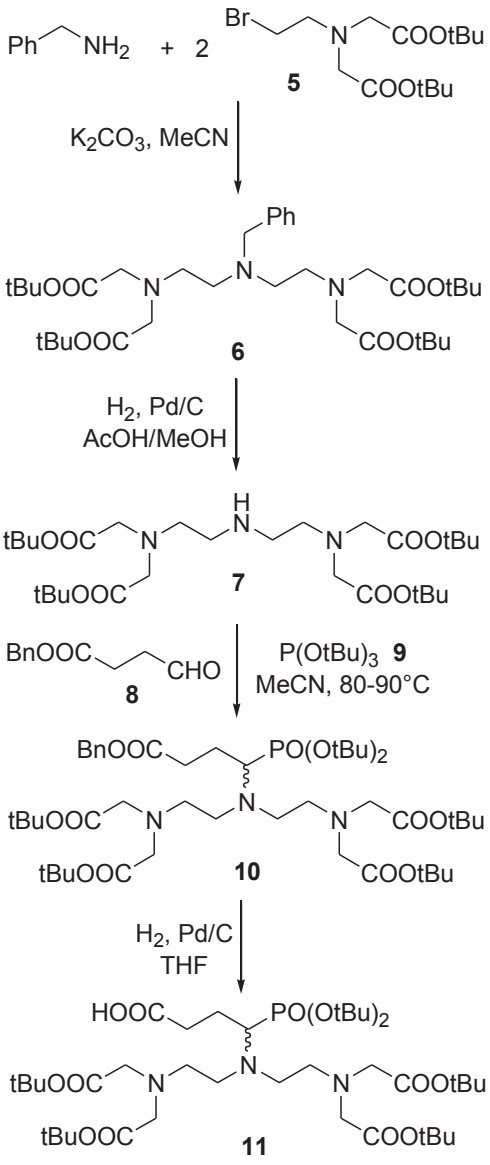
Efforts directed towards improvements of MRI contrast agents rely on different strategies involving structural variations of the ligand; among them the substitution of carboxylic groups with different acidic functionalities was extensively investigated, leading to the preparation of several derivatives, embodying more or less classical isosteres, such as phosphonic acid,[35,36] phosphinic acid,[37] acylsulphonamide,[38] and tetrazole.[39]

The phosphonic acid is particularly appealing as its size and acidic properties closely resemble the behavior of carboxylic groups.[40] Its tetrahedral deprotonated form ($-PO_3^{2-}$) occurring at physiological pH values offers multiple coordination modes, and residual anionic charges after complexation provide a beneficial effect on the solubility of the corresponding chelate, due to the establishment of an extended hydrogen bond network leading to improved solvation. Several examples of polydentate ligands embodying one[36] or more[41,42] phosphonic groups were reported for different purposes ranging from water corrosion inhibitors to diagnostic and therapeutic applications.

Phosphonic derivatives of the octadentate ligand DTPA (diethylenetriaminepentaacetic acid) are already known: the perphosphonated derivative (DTPMP)[43] is commercially available (Dequest® 2060), while the monophosphonic DTPA-analog **1b**[44] is reported to form thermodynamically very stable metal complexes, with stability constants comparable with the parent DTPA ligand.[45]

Despite the growing interest in phosphonic derivatives of polyaminocarboxylic ligands, it is surprising to observe only a few examples of bifunctional derivatives. A perphosphonic derivative (DOTP) of the macrocyclic ligand DOTA was decorated with different appendages, among them a *p*-aminophenyl residue amenable to use for conjugation purposes.[46] Moreover, two different cyclohexane-1,2-diamine tetraphosphonic ligands bearing ready-to-use isothiocyanate groups were designed for application in ^{153}Sm-based radioimmunotherapy.[47] To the best of our knowledge, the only BFCA with carboxylic and phosphonic moieties reported so far, is a triethylenetetraaminehexaacetic acid (TTHA) analog.[48]

We describe here the synthesis of two novel BFCA based on the DTPA structure but having one (Scheme 1, compound **11**) or two (Scheme 2, compound **18**) phosphonic group replacing the corresponding carboxylic moieties.



Scheme 1. Synthesis of BFCA **11**.

2. Results and discussion

The synthesis of the phosphonic derivatives **3** and **4** was realized adapting the original protocol of Rapoport,[49] widely applied for the easy assembly of DTPA derivatives and implying the double N-alkylation of a primary amine (representing the 'central' nitrogen atom of DTPA) with two molar equivalents of an *N*-(β-bromoethyl) iminodiacetate ester (representing the 'left' and 'right' wings of the DTPA).

The synthesis of monophosphonic BFCA **11** is shown in Scheme 1. Benzylamine was bisalkylated with bromoderivative **5**[49] in acetonitrile and in the presence of micronized K_2CO_3 as base. Compound **6** was then hydrogenated to give in good yield the symmetrical diethylenetriaminetetraacetic acid tetra-*t*-butyl ester **7**,[50] with the central secondary amine available for further functionalization. Reaction of **7** with the aldehyde–ester **8**[51] and tri-*t*-butylphosphite **9**[52] in refluxing acetonitrile produced the monophosphonic derivative **10**. Selective deprotection of the carboxylic ester located on the side chain by hydrogenolysis afforded the protected BFCA **11**.

The synthesis of diphosphonic BFCA **18** relied on a similar strategy, necessarily implying the modification of the *N*-(β-bromoethyl)iminodiacetate ester alkylating agent to include a (protected) phosphonate group. The novel bromoderivative **14** (Scheme 2) was synthesized by phosphonomethylation of *N*-(2-hydroxyethyl)glycine 1,1-dimethylethyl ester **12**[53] with paraformaldehyde and tri-*t*-butylphosphite **9**[52] to give the aminoalcohol **13**. Mesylation of the primary alcohol with the combination methanesulfonyl chloride/triethylamine in THF and a prompt treatment with lithium bromide generated the desired 'mixed' alkylating agent **14**.

The assembly of the BFCA continues with the bis-alkylation of the nitrogen atom of a suitable protected aminoacid. Esterification of aspartic acid 4-phenylmethyl ester **15** into its *t*-butyl ester derivative **16** was easily performed in *t*-BuOAc with perchloric acid, as reported by Taschner.[54] Treatment of **16** with two molar equivalents of the bromoderivative **14** in a buffered system gave compound **17**. As for the previous example, selective hydrogenation of the benzyl ester located on the side chain released the corresponding free carboxylic acid completing the synthesis of the diphosphonic BFCA **18** (Scheme 3).