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Sequestering agent for uranyl chelation: new binaphtyl ligands

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ABSTRACT

The synthesis of phosphonate, sulfocatecholamide (CAMS) and hydroxypyridinone (HOPO) binaphtyl ligands is presented. Their binding abilities for uranyl cation were determined by UV spectrophotometry in aqueous media versus pH. These titrations showed that the efficiency of these chelating agents depends on the nature of the chelating group. Each ligand shows a more or less pronounced affinity towards uranium. While the bisphosphonate compound did not show any affinity towards the uranyl ion, the BINHOPO derivative exhibits significant affinity at acidic and neutral pH while the BINCAMS is more efficient at basic pH.

1. Introduction

Commonly used as nuclear fuel in fission reactors for civilian purpose, uranium can be introduced into the human body in the case of internal contamination by ingestion, inhalation or through wounds. The hexavalent uranyl ion (UO_2^{2+}, U(VI)) was proven to be the most stable form in vivo[1] and is complexed in the blood by chelating agents such as proteins or carbonates. Distribution of toxic species and retention in target organs, such as kidneys, liver or marrow occur[2] after chelation, potentially inducing chemical intoxication, especially in the case of heavy metal contamination.[3] To avoid these effects, heavy metals must be eliminated from the body by administering nontoxic chelating agents able to form stable complex with uranyl ions so that the body can rapidly excrete the poison from blood and target organs. Thus toxic material concentrations and radiation doses, and subsequently tumour risks may be reduced. Until now, only a few ligands that are able to strongly bind U(VI) in vivo, promote its excretion and efficiently prevent or reduce deposition in kidneys and bones, the two main target organs of U(VI). Since the 1980's, several effective uranyl ligands were synthesised, based on different complexing functions. Phosphorus containing molecules, especially bisphosphonates, were found to be very effective uranyl ligands.[4–6] Few significant decorporation works have been reported so far concerning the decorporation efficacy of poly-phosphonated compounds,[7] particularly concerning ethane-1-hydroxy-1,1-bisphosphonate EHBP.[8–11] Decorporation with bidentate methylterphthalimide (MeTAM)-based chelating ligands was also studied and appeared not to be suitable for biological decorporation due to their high toxicity.[12] Sulfocatechol Tiron proved to be effective for U(VI) complexation in vivo within the physiological pH range,[13,14] but a modest successful reduction of acute U(VI) toxicity and reduction of body U(VI) with this ligand was observed. Therefore, multidentate analogues containing sulfocatecholamide (CAMS) or structurally analogous hydroxyl-pyridone (HOPO) units would be effective for in vivo chelation of U(VI).[15,16] Indeed, pioneering work performed by Raymond and co-workers on uranyl-sequestering agents based on 3-hydroxy-2(1*H*)-pyridinone (3,2-HOPO)[17] and sulfocatecholamide (CAMS) ligands resulted in two low-toxicity ligands 5-LICAM(S) and 5-LIO(Me-3,2-HOPO),[16] both efficient chelating agents of circulating U(VI) in the body. Recently, we described the synthesis and the evaluation of several 5-CAMS analogues incorporating various diamine skeletons such as the 5-CYCAMS (Fig. 1).[18] We also described several calixarene based compounds functionalized with (1,2)HOPO or CAMS chelating units.[19] In both case, the chelating properties towards uranium were studied in aqueous media by UV–Vis analysis and NMR spectroscopy and some of these showed pronounced affinity for the target ion. Since 1990, the enantiomeric atropoisomers of 1,1′-binaphthyl-2,2′-diol (Binol) have become among the most widely used ligands for both stoichiometric and catalytic asymmetric reactions.[20] 2,2′-Binaphthol

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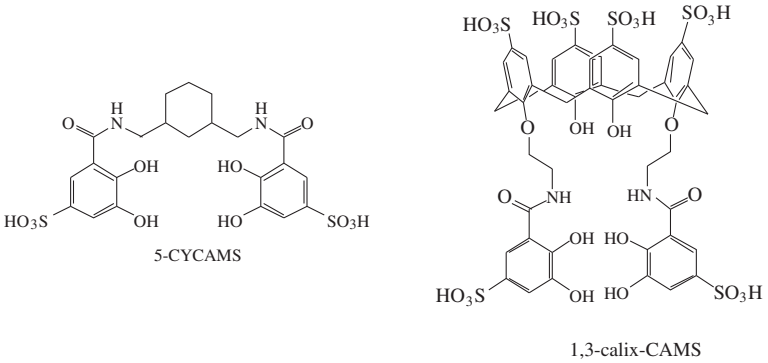

Figure 1. Uranyl 5-CAMS and 1,3-calix-CAMS.

(Binol) and its derivatives have generated particular interest because their versatile backbone can be modified, thereby affecting the reaction environment by influencing the properties of the metal centre. Substitution of Binol may affect not only the steric environment around the metal centre but also the electronic properties of the oxygen atoms, which are common constituents of the Lewis acidic–metal complexes.[21]

Recently, Yu reported a family of Binol derivatives exhibiting a good ability to complex lanthanides.[22,23] During the same period, new macrocyclic structures including Binol and salen units were studied and their uranium complexes isolated.[24,25] As far as we know, combination of the Binol structure with the chelating behaviour of sulfocatechol amides has not been reported in the literature as well as the phosphonate and HOPO derivatives. We present here the synthesis and the chelating properties of new racemic Binol derivatives containing phosphonate, HOPO or CAMS functions.

2. Results and discussion

The dibromo Binol **1** was obtained as described in the literature.[26] Heating **1** in triethylphosphite gave the bisdiethylphosphite Binol **2**. Deprotection of **2** was achieved by using trimethylsilyl bromide[27] without further purification to give **3** in 59% overall yield (Fig. 2). Acid chloride derivatives **4** and **5** were obtained by the reaction of oxalyl chloride with *O*-benzyl catechol[28,29] and *N*-benzyl HOPO[30–32] carboxylic acids preliminary synthesised following the previously described procedures[16] in dichloromoethane with a catalytic amount of DMF in quantitative yield. Bis-amide analogues **7** and **10** were obtained by condensation of the corresponding acid chloride derivatives **4** and **5** with the diamino-Binol **6** prepared according to a described procedure[33] in the presence of Et_3N (Fig. 3). Deprotection of the hydroxyl groups was achieved using HCl in acetic acid for the HOPO pendant arms to give the BINHOPO **11** in 98% yields. Hydrogenolysis of catechol **7** led to **8** in 98% yield.

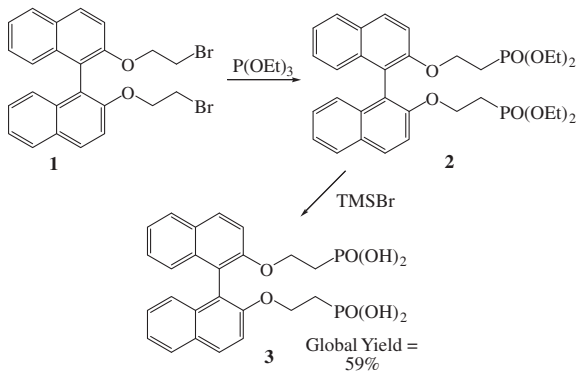

Figure 2. Access to bisphosphonate Binol compound.

Sulfonation of **8** in hot sulfuric acid followed by precipitation in diethyl ether gave the desired pure BINCAMS **9** in good yield. In parallel, sulfonation of BINHOPO **11** failed, leading to a complex mixture of partially polysulfonated compounds. Each component was fully characterised by ^1H NMR, ^{13}C NMR and mass spectroscopy.

The complexation behaviour of compounds **3**, **9** and **11** towards the uranyl cation was studied by the spectrophotometric method developed by Taran and co-workers,[4] based on a competitive uranium binding by using sulfochlorophenol SCP as a chromogenic chelate, assuming that 1:1 metal/ligand complexes are formed as it was also demonstrated through NMR studies in earlier works.[18,19] This latter was found highly suitable for a rapid screening of putative library of uranium ligand and compared with 5-LICAMS, synthesised as previously described by Raymond and coworkers (Table 1).[12] Globally, the bisphosphonate Binol **3** does not give satisfactory results while the Binol CAMS **9** gives slightly better results than the reference 5-LICAMS at pH 5.5. The HOPO Binol **11** exhibits high K_{cond} enhancement under basic conditions in accordance with previous findings.[18,19] At pH 7.4, none of the synthesised Binol displaced SCP/uranyl complexation equilibrium better than the 5-LICAMS. At pH 9, **11** exhibited a larger complexation efficiency ($\log K_{cond} = 21$) towards UO_2^{2+}. Except with the 1,3-calixCAMS,[19] such a very large stability constant has never been observed with CAMS ligands.

3. Experimental part

All the organic reagents used were pure commercial products from Aldrich, Acros, Fluka, Avocado, Lancaster & Maybridge. The solvents were purchased from Carlo Erba, Acros, Pro-Labo, Fluka & Aldrich. Anhydrous solvents came from Acros, anhydrous THF and dry CH_2Cl_2 were distilled. Flash chromatography was carried out on Merck Silica Si60 (40–63 mm). ^1H, ^{13}C NMR spectra were recorded on a Bruker AC-200 (200.13 MHz for ^1H, 50.32 MHz for ^{13}C) or AC-300 FT (300.13 MHz for ^1H, 75.46 MHz for ^{13}C) spectrometer; δ values are given in parts per million and J in hertz. Elemental analyses (C, H, N, S, O, F) were obtained from the Service Central d'Analyse of the CNRS (Solaize). High resolution mass spectra: HR LSIMS (Liquid Secondary Ionisation Mass Spectrometry: Thioglycerol), HR CIMS (Isobutan) and HR EIMS were carried out on a FinneganMAT 95xL by the UCBL Centre de Spectroscopie de Masse.

Compound **3**: To a magnetically stirred solution of Binol (1.303 g, 4.55 mmol) and triphenylphosphine (3.58 g, 13.6 mmol) in 40 mL dry THF at ambient temperature under N_2 atmosphere was added dropwise a mixture of 2-bromoethanol (0.97 mL,