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Synthesis and evaluation of 3-acyltetronic acid-containing metal complexing agents

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ABSTRACT

Potential metal chelators containing one or several acyltetronic acid moieties were prepared from cyclic or acyclic amines and polyamines, and from bis(phenols) by reaction with 1–4 equiv of 3-bromoacetyltetronic acid in the presence of potassium carbonate. The affinity constants of the chelating agents for toxic metallic cations Cd^{2+}, Cs^{+}, and Pb^{2+} and for dimethylarsinic acid were measured, at pH 7.5 and 9.3. Compound **4**, an acyclic triamine containing four acyltetronic moieties, was found to complex efficiently all the tested species.

1. Introduction

Organic compounds able to complex efficiently heavy metal cations can find application in the sensing of these cations or for their removal from contaminated waste.[1] It is thus of great value to identify new compounds having such properties. Several natural compounds containing a 3-acyltetronic acid moiety have been found to complex metal cations. Examples include the ionophore tetronasin[2] and the tyrosine phosphatase inhibitor RK-682[3] (Fig. 1). Copper complexes of 3-acyltetronic acids have been described,[4] as well as complexes of 3-alkoxycarbonyltetronic acids with salts of copper(II), cobalt(II) and zinc(II).[5]

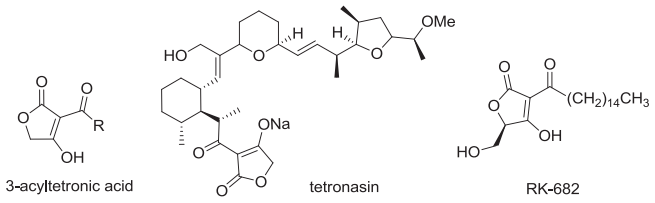

Fig. 1. Structures of 3-acyltetronic acids.

In this paper, we will describe the synthesis of a series of new chelating agents derived from amines or polyamines, containing one or several 3-acyltetronic acid moieties.[6,7] These compounds will then be evaluated as complexing agents for selected, highly toxic species, Pb^{2+}, Cd^{2+}, Cs^{+} and dimethylarsinic acid. Pb^{2+} is well known to cause health problems, such as kidney and neurological diseases.[8] Cadmium toxicity involves oxidative-stress and the alteration of the homeostasis of essential metals, such as copper and zinc. Water contamination by arsenic is one of the biggest health threats in several countries.[9] In humans and other mammals inorganic arsenic is converted to trivalent and pentavalent methylated metabolites, including dimethylarsinic acid. This compound has been largely employed as herbicide in agriculture. It has been reported to induce urinary bladder tumors in rats.[10] Moreover, it is genotoxic in human cells, causing decreased DNA production and shorter DNA strands.[11] Cesium is not required for biological processes and few is known about its toxicity.[12] Interest in finding agents able to complex the cesium cation stems largely from the wish to separate radioactive cesium generated in nuclear plants.[13] Such agents might also be employed for the decorporation of radioactive cesium. Radioactive cesium was dispersed in the environment following atmospheric nuclear explosions and also following the accidents of Chernobyl and Fukushima. Norbadione A (Fig. 2), a pigment isolated from the mushroom bay boletus (*Xerocomus badius*),[14] was shown to form a strong 1/1 complex with cesium chloride, owing to two chelating moieties that both

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participate to the complexation.[15] Likewise, we expected that by arranging one or several 3-acyltetronic acid moieties on a template constituted by an amine or a polyamine, would allow to obtain chelating agents able to complex the toxic cations Pb^{2+}, Cd^{2+}, Cs^{+}, as well as dimethylarsinic acid, depending on their structures.

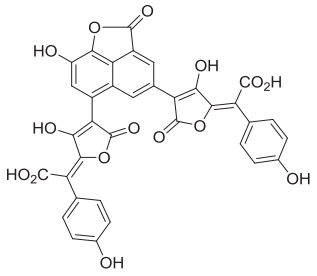


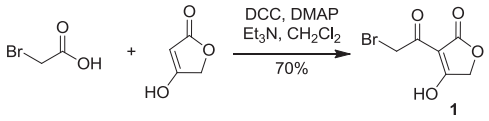
Fig. 2. Norbadione A.

2. Results and discussion

2.1. Synthesis of 3-acyltetronic acid-containing compounds

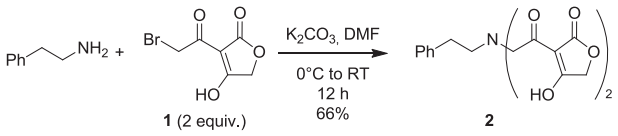
A synthesis of bis(acyltetronic acid) derived from dodecanedioic acid was recently reported,[16] according to the conditions described by Yoshii,[17] using DCC, DMAP, and triethylamine as reagents. Hence, this was a potentially attracting method for the preparation of the desired complexing agents. However, several attempts to obtain the acylation of ethylenediaminetetraacetic acid (EDTA) with 4 equiv of tetronic acid were unsuccessful.

Another possibility to access such compounds was then envisaged, starting from amines or polyamines and an electrophile containing already a 3-acyltetronic acid motif. For this purpose, 3-bromoacetyltetronic acid **1** was then prepared from tetronic acid and bromoacetic acid using the DCC/DMAP coupling (Scheme 1).



Scheme 1.

Several amines or polyamines were then efficiently converted to the corresponding adducts by reaction with 3-bromoacetyltetronic acid under mild conditions. For example, the dipodal adduct **2** was prepared as shown in Scheme 2, by treatment of phenethylamine with **1** (2 equiv) in the presence of K_2CO_3 (2 equiv) in DMF (0 °C to room temperature). Adduct **2** was obtained in 66% yield after purification by reverse phase chromatography (0.01 M HCO_2NH_4, pH 9/MeOH).



Scheme 2.

Using a similar protocol, with varying equivalents of **1** and K_2CO_3, depending on the number of possible alkylations, several adducts, tripodands **3**, acyclic tetrapodands **4**, **5**, **6**, aza-crown ethers derivatives **7**, **8**, **9**, were prepared from the corresponding amines and polyamines (Table 1). Two compounds derived from bis(phenols) were also prepared similarly, using 3 equiv of bromide **1** (entries 8, 9).

The preparation of the precursors of compounds **3**–**5** is described in Scheme 3. Amine **12**, precursor of **3**, was obtained by reaction of *N*-Boc-phenylalanine with tetronic acid in the presence of DCC/DMAP, followed by cleavage of the Boc (*tert*-butoxycarbonyl) group using trifluoroacetic acid. The known compounds **13** and **14**[18] were prepared as described. Compounds **6**–**11** were obtained from commercially available products.

2.2. Complexation studies

The absorption spectra of the chelators were recorded in the presence of varying concentrations of the following species: cadmium nitrate, cesium chloride, dimethylarsinic acid (DMA), lead(II) acetate. They were performed in two aqueous buffers, at pH=7.5 and 9.3, except for the cadmium species, which was insoluble at pH=9.3. Compound **11** was not evaluated, because of its low solubility in an aqueous medium. The spectra and the measured affinity constants were similar in the two buffers, which is in agreement with the fact that the enol functions of tetronic acids are not protonated in both neutral and basic media. In our experiments, the lower limit of the spectrophotometric detection was of about 0.1 μM of chelator, therefore this approach did not permit the measurements of affinities higher than 10^7.

The absorption spectra obtained with compound **4**, upon addition of Cd^{2+}, Cs^{+}, Pb^{2+} or dimethylarsinic acid, are indicated in Fig. 3. The analysis of the data by the SPECFIT32 program showed that for all the ligands, only monocomplexes were formed.[19]

Affinity constants (as log K) of the synthetic chelators for three metallic cations, Cd^{+}, Cs^{+}, and Pb^{2+} and organic dimethylarsinate are reported in Table 2. These values are also compared to those involving EDTA, which is considered as a universal chelator, since it forms very strong complexes with most metals.[20] EDTA seems also to form strong complexes with inorganic As(III) and to a lesser extent with inorganic As(V).[21] However, to the best of our knowledge, EDTA does not complex Cs^{+} or organic arsinates.

Compounds **2** and **3** have low affinities for the four species. This may be due to the lack of flexibility of the ligands in both chelators. Compound **9**, a tetra(acyltetronic acid) derived from cyclam (1,4,8,11-tetraazacyclotetradecane), seems to be a good chelator for Cd^{2+}. However, despite the fact that it is a tetrapod, it does not complex the other species. Its affinity for Cd^{2+} may be related to the presence of the four nitrogen atoms and the possible occurrence of a cage-like structure. Indeed, nitrogen is considered as a soft base and Cd^{2+} as a soft acid.[22] Compound **5**, which is an acyclic tetra(acyltetronic acid), is a very good chelator for Pb^{2+} and Cd^{2+}, with affinities higher than 10^7, and can also slightly complex Cs^{+} and dimethylarsinic acid. This can be due to the higher flexibility of the complexing tetronic ligands in comparison with **9**. Finally, compound **4**, which differs from **5** by the presence of two shorter spacers between nitrogen atoms, is capable of forming stable complexes with the four tested species. As with norbadione A and its derivatives, complex formation probably occurs by inclusion in a pseudo-cavity in which the chelating acyltetronic ligands surround the metallic species. This cavity can be compared to that of some calixarenes, which display similar affinities for Cs^{+}.[15d] The proposed chelators are less efficient than EDTA for the complexation of Cd^{2+} and Pb^{2+}. Therefore, the most interesting chelator seems to be **4**, which has a good affinity for Cs^{+}, and which is, to the best of our knowledge, the only organic molecule known to form a stable complex with an organic arsinate.

3. Conclusion

We have synthesized various compounds containing one or several 3-acyltetronic acid complexing moieties. They were obtained from a new precursor, 3-bromoacetyltetronic acid. Affinity