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Synthesis of carboxylic acids based on the *closo*-decaborate anion

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Dedicated to Professor Nikolai Kuznetsov on the occasion of his 80th birthday in recognition of his contribution to boron cluster chemistry.

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ABSTRACT

A series of new boron-containing carboxylic acids was prepared by the ring-opening reaction of cyclic oxonium derivatives of the *closo*-decaborate anion $[B_{10}H_{10}]^{2-}$ with methyl esters of hydroxybenzoic acids or the cyanide anion followed by hydrolysis of the obtained nitrile and esters. Acid hydrolysis of the esters results in protonation of the oxygen atom connected to the boron cage, with the formation of the corresponding *O*-protonated acids, isolated in the solid state. The compounds synthesized can be used in radionuclide diagnostics and boron neutron capture therapy of cancer.

1. Introduction

During the last decade, polyhedral boron compounds have attracted increasing interest due to their potential use in various fields [1], including the treatment of nuclear wastes [2,3], catalysis [4–7], material science [8–12] and the treatment of cancer [13]. Moreover, the synthesis of compounds for medical applications, primarily for boron-neutron capture therapy [14] of cancer, was one of the main driving forces for the development of boron hydride chemistry during the last two decades. Another important area of medical application of polyhedral boron compounds is radionuclide diagnostics and therapy [13b,15]. Polyhedral borane anions were found to be reasonable linkers for the attachment of radiohalogens to tumor-targeting proteins and peptides due to the high chemical stability of the boron–halogen bonds in these compounds as well as the absence of enzymatic systems for cleavage of the boron–halogen bond, due to the very exogenous nature of such compounds. Some years ago we reported the use of *closo*-dodecaborate anion derivatives as carriers of radiohalogen labels for indirect labeling of tumor-targeting proteins [16–17]. More recently, the *closo*-decaborate anion $[B_{10}H_{10}]^{2-}$ was proposed as an alternative boron carrier of radionuclide labels [18]. In comparison with $[B_{12}H_{12}]^{2-}$, the $[B_{10}H_{10}]^{2-}$ anion has the advantage of a much faster iodination reaction, which allows one to use it for selective direct labeling of antibodies in the presence of excess of tyrosine residues. It generated interest in the synthesis of *closo*-decaborate derivatives bearing terminal functional groups that are capable of binding to proteins, including isocyanates and carboxylic acids. Analysis of the literature data on the synthesis of *closo*-decaborate derivatives [19] revealed several examples of carboxylic acids derived from the $[B_{10}H_{10}]^{2-}$ anion [20–22] (Chart 1), however the properties of some of these compounds do not meet the requirements for prosthetic groups for protein radio-labeling. Compounds **A**–**C**, belonging to the first generation of *closo*-decaborate derived carboxylic acids [20a], are insoluble in water, whereas the synthesis of compound **D**, bearing a water-solubilizing gluconamide group, was difficult and gave a very low yield [20b]. The carboxylic group in compound **E** is affected by the strong electronic and steric effects of the boron cage. Compounds **F** and **H**–**J** contain potentially hydrolysable bonds that could result in the loss of the radiohalogen label. Finally, compound **G** looks very attractive, but it gives a rigid rather than a flexible linkage between the boron cage and the biomolecule, which is not always suitable.

Cyclic oxonium derivatives of polyhedral boron hydrides are known as useful synthons for the preparation of various boron-containing organic and bioorganic materials [23]. Breaking one carbon–oxygen bond results in moieties having a boron cluster separated from the functional fragment by spacer of 4–5 atoms. In such a way, molecules with a reasonably long spacer between

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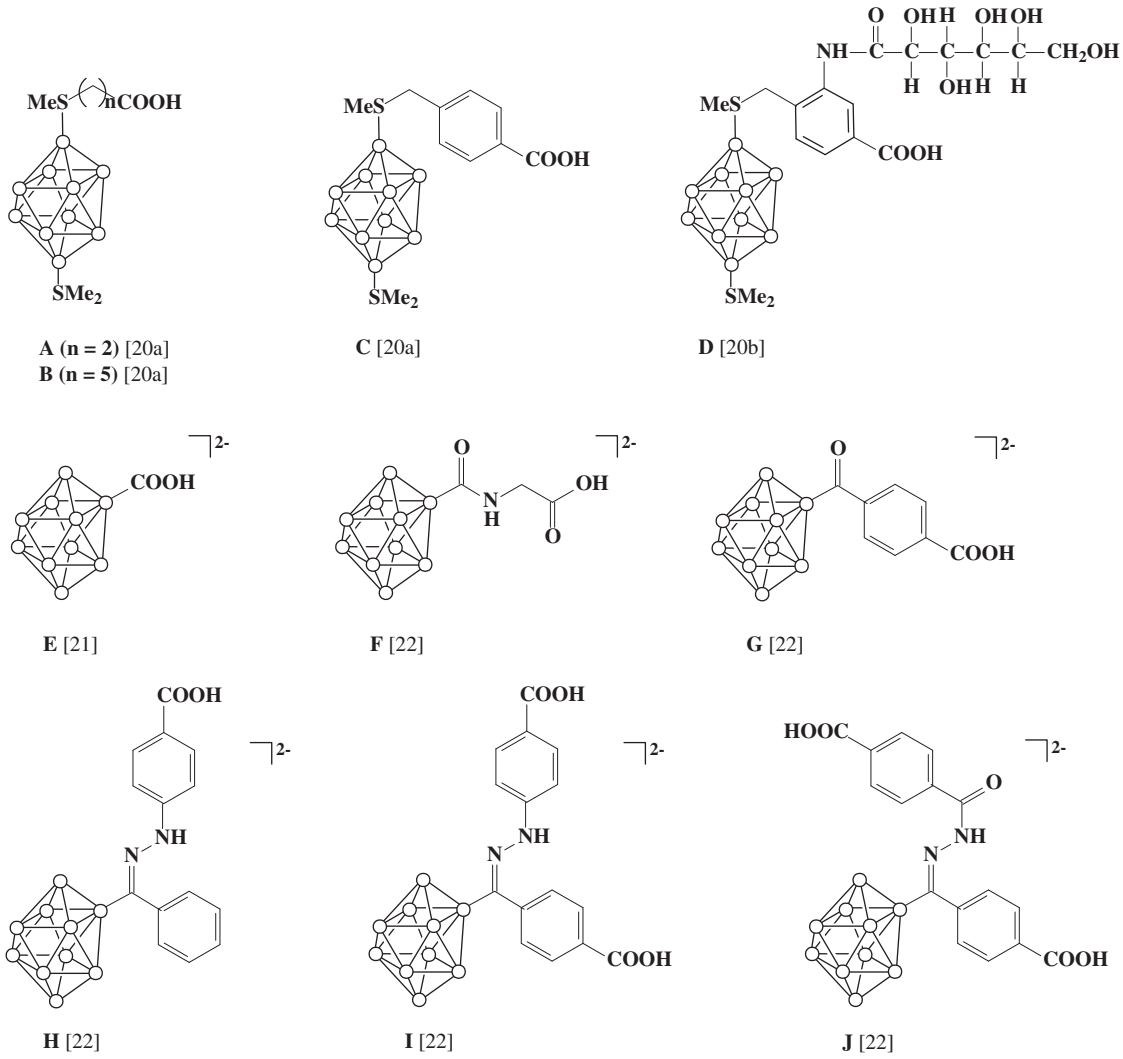

Chart 1. Carboxylic acids in the literature derived from the *closo*-decaborate anion. The bracketed numbers refer to the relevant literature references.

the boron cage and the property-determining part of molecule can be prepared. Moreover, the hydrophilic/lipophilic nature of the spacer can be affected by the proper choice of the initial substituent. Thus, the ring-opening of the tetrahydrofuran- and tetrahydropyrane-based derivatives produced compounds with lipophilic spacers, whereas 1,4-dioxane ring opening with *O*-nucleophiles gives compounds with the hydrophilic $-(CH_2CH_2O)_2-$ spacer. At present this approach has been used for the synthesis of more than 300 boron-containing compounds of various types, however the *closo*-decaborate ring-opening reactions described in the literature are limited to a few reports [24–26].

In this work we used the ring-opening reactions of the cyclic oxonium derivatives $[2\text{-}B_{10}H_9O(CH_2)_4]^-$ (**1**) and $[2\text{-}B_{10}H_9O(CH_2CH_2)_2O]^-$ (**2**) for the synthesis of *closo*-decaborate based carboxylic acids.

2. Results and discussion

The synthesis of a carboxylic acid based on the $[B_{12}H_{12}]^{2-}$ anion via the ring-opening reaction of a tetrahydrofuran derivative with the cyanide anion has been reported [27]. We used the same approach to prepare a similar acid based on the *closo*-decaborate anion. The reaction of **1** with sodium cyanide in the presence of an equimolar amount of tetrabutylammonium iodide at room temperature results in the required nitrile **3**, which can be readily converted to the corresponding acid **4** by alkaline hydrolysis (Scheme 1).

The ^1H NMR spectrum of **3** contains triplets of the opened tetrahydrofuran ring at 3.41 and 2.43 ppm, corresponding to the methylene groups attached to oxygen atom and cyanide group, respectively, and multiplet at 1.63 ppm corresponding to the aliphatic fragment of the chain. The IR spectrum contains a characteristic absorption band for the C≡N stretching at 2242 cm^{-1}. The hydrolysis of the cyano group results in the disappearance of the C≡N stretching the IR spectrum of **4** and the appearance of a new strong characteristic band of a carboxylic group at 1686 cm^{-1}.

It was demonstrated earlier that hydroxy benzoic acids react with cyclic oxonium derivatives of *nido*-carborane [28] and cobalt bis(dicarbollide) [29] in the presence of potassium carbonate to give the corresponding carboxylic acids as products of the ring opening reaction with the phenolate ion. In this work we decided to use the same approach for the synthesis of carboxylic acid derived from the *closo*-decaborate anion. However, the reaction of **1** with hydroxy benzoic acids in refluxing acetonitrile in the presence of potassium carbonate resulted in unexpected products of the tetrahydrofuran ring opening by both phenolate and carboxylate anions (Scheme 2).

A few examples of ring opening of 1,4-dioxane derivatives of cobalt bis(dicarbollide) by carboxylate anions have been described