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NEW EFFICIENT METHOD FOR THE SYNTHESIS OF THE WATER-SOLUBLE 1,2–$[B_{12}H_{10}(OH)_2]^{2-}$ ANION WITH THE EXOPOLYHEDRAL B-OH REACTION SITES FOR THE SUBSEQUENT MODIFICATION IN DEVELOPING BNCT PREPARATIONS

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Abstract

An original method for synthesis of a water-soluble derivative of the 1,2-$[B_{12}H_{10}(OH)_2]^{2-}$ boron cluster anion using alkaline hydrolysis of the products of interaction of bis(tetrabutylammonium) dodecahydro-closo-dodecaborate (2–) with the melt of benzene-1,2-dicarboxylic acid in an inert atmosphere is developed. The synthesized compounds were identified with the help of the elemental analysis and IR and ^{11}B spectroscopy of the nuclear magnetic resonance (NMR). It is shown that regioselectivity under the considered synthesis condition depends on the geometry of the selected synthesis reagent, namely, benzene-1,2-dicarboxylic acid.

Key words: *dodecahydro-closo-dodecaborate anion (2–), carboxylation, three-dimensional aromaticity, regioselectivity, NMR spectroscopy, IR spectroscopy*

1. INTRODUCTION

A three-dimensional aromatic behavior of binding in the boron cluster anion $[B_{12}H_{12}]^{2-}$ derevatives in many respects determines its behavior in the reactions of *exo*-polyhedral substitution with the preservation of the boron skeleton. The relevance of the study of $[B_{12}H_{12}]^{2-}$ reactivity and the mechanisms of formation of its substituted derivatives with *exo*-polyhedral functional groups is primarily due to the fact that new boron-containing substances and materials based on them (e.g., preparations for ^{10}B-neutron capture therapy of malignant tumors) cannot be constructed without such compounds.

Neutron capture therapy (NCT) is a noninvasive therapeutic modality for treating locally invasive malignant tumors such as primary brain tumors and recurrent head and neck cancer. It is a two-step procedure: first, the patient is injected with a tumor localizing drug containing a non-radioactive isotope that has a high propensity or cross section (σ) to capture slow neutrons. The cross section of the capture agent is many times greater than that of the other elements present in tissues such as hydrogen, oxygen and nitrogen. In the second step, the patient is radiated with epithermal neutrons, which after losing energy as they penetrate tissue, are absorbed by the capture agent which subsequently emits high-energy charged particles, thereby resulting in a biologically destructive nuclear reaction.

All of the clinical experience to date with NCT is with the non-radioactive isotope boron-10, and this is known as boron neutron capture therapy (BNCT). At this time, the use of other non-radioactive isotopes, such as gadolinium, has been limited, and to date, it has not been used clinically. BNCT has been evaluated clinically as an alternative to conventional radiation therapy for the treatment of malignant brain tumors (gliomas), and more recently, recurrent, locally advanced head and neck cancer.

Boron neutron capture therapy (BNCT) is based on the nuclear capture and fission reactions that occur when non-radioactive boron-10, which makes up approx 20% of natural elemental boron, is irradiated with neutrons of the appropriate energy to yield high energy alpha particles ("stripped" down ^4He nuclei) and high energy lithium-7 (^7Li) nuclei. The nuclear reaction is:

$$^{10}B + n_{th} \rightarrow [^{11}B] \rightarrow \alpha + {}^{7}Li + 2.31\ MeV.$$

Both the alpha particles and the lithium ions produce closely spaced ionizations in the immediate vicinity of the reaction, with a range of approximately 5–9 μm, or approximately the diameter of one cell. Their lethality is limited to boron containing cells. BNCT, therefore, can be regarded as both a biologically and a physically targeted type of radiation therapy. The success of BNCT is dependent upon the selective delivery of sufficient amounts of ^{10}B to the tumor with only small amounts localized in the surrounding normal tissues. Thus, normal

tissues, if they have not taken up boron-10, can be spared from the nuclear capture and fission reactions. Normal tissue tolerance is determined by the nuclear capture reactions that occur with normal tissue hydrogen and nitrogen.

A wide variety of boron delivery agents have been synthesized, but only two of these currently are being used in clinical trials. The first, which has been used primarily in Japan, is a polyhedral borane anion, sodium borocaptate or BSH ($Na_2B_{12}H_{11}SH$), and the second is a dihydroxyboryl derivative of phenylalanine, referred to as boronophenylalanine or BPA. The latter has been used in clinical trials in the United States, Europe, Japan and more recently, Argentina and Taiwan. Following administration of either BPA or BSH by intravenous infusion, the tumor site is irradiated with neutrons, the source of which has been specially modified nuclear reactors. Up to 1994, low-energy (< 0.5 eV) thermal neutron beams were used primarily in Japan, but since they have a limited depth of penetration in tissues, higher energy (> 0.5eV < 10 keV) epithermal neutron beams, which have a greater depth of penetration, have been used in clinical trials in the United States, Europe, and Japan.

In theory BNCT is a highly selective type of radiation therapy that can selectively target the tumor at the cellular level without causing radiation damage to the adjacent normal cells and tissues. Doses up to 60–70 Gy can be delivered to the tumor cells in one or two applications compared to 6–7 weeks for conventional external beam photon irradiation. However, the effectiveness of BNCT is dependent upon a relatively homogeneous distribution of ^{10}B within the tumor, and this is still one of the key stumbling blocks that have limited its success.

The first stage of the development of BNCT preparations based on polyhedral $[B_{12}H_{12}]^{2-}$ boron anion consists in the introduction of primary substituent (reaction site) in the *closo*-dodecaborate system, which subsequently can be modified. In the present study, efficient method for the synthesis of *closo*-dodecaborate anion derivatives in using hydroxyl group as the primary substituent are suggested.

The aim of this study, namely, the analysis of the interaction of bis(tetrabutylammonium) dodecahydro-*closo*-dodecaborate (2–) with the melt of benzene-1,2-dicarboxylic acid in an inert atmosphere, was dictated by the necessity of searching for new methods for introduction of functional oxygen-containing groups as *exo*-polyhedral substitutes.

It is known that regioselectivity of a chemical reaction depends in some cases on the geometry of the selected reagent. This paper considered this approach to functionalization of the *closo*-dodecarborate anion.

2. EXPERIMENTAL

The $[B_{12}H_{12}]^{2-}$ anion was fabricated in the form of the triethylammonium salt using pyrolysis of a decarborane-14 solution. To obtain $K_2[B_{12}H_{12}]$ the triethylammonium salt was dissolved in a stoichiometric amount of an aqueous solution of potassium hydroxide, and the solution was then boiled to remove the remains of triethylamine. The residue obtained after evaporation and cooling of the solution was recrystallized from the ethyl alcohol and dried until constant mass at the temperature of 70°C. The bis(tetrabutylammonium) dodecahydro-*closo*-dodecaborate (2–) ($(TBA_2[B_{12}H_{12}])$ was prepared using the ion exchange reaction by adding a 10% aqueous solution of TBABr to the aqueous solution of $K_2[B_{12}H_{12}]$. The formed residue was filtered, washed in diethyl alcohol, and dried in vacuum. Before use, argon was dried with the help of successive passage through calcium chloride, phosphoric anhydride, and a molecular sieve with the diameter of 3–4 Å.

2.1. Synthesis of Carboxylate-Substituted $[C_6H_4(C(O)O)_2–B_{12}H_{10}]^{2-}$ Derivative

5.0 g of $(TBA)_2[B_{12}H_{12}]$ were added to 50 mL of benzene-1,2-dicarboxylic acid that was premelted in a dry argon atmosphere. The mixture was slowly heated. Gradual dissolution of the salt was observed at 185–190°C; liberation of hydrogen was observed at 190–195°C. Upon completion of the gas liberation, the mixture continued to be held at the temperature of 200–205°C for 1 h (the volume of the liberated hydrogen was measured with the help of a gas burette: the calculated volume was 357 cm^3, while the measured one was 351 cm^3). The yellow reaction mass was cooled, and the target compound was extracted using recrystallization from toluene. Then it was dried in an exiccator in vacuum over paraffin chips to remove traces of toluene and over phosphorus pentaoxide until a constant mass. 4.0 g of $(TBA)_2[C_6H_4(C(O)O)_2–B_{12}H_{10}]$ was obtained; the yield was 78% of the theoretical one.

2.2. Synthesis of $[B_{12}H_{10}(OH)_2]^{2-}$ Hydroxy-Substituted Derivative

A charge of carboxylate-substituted derivative salt was dissolved in 50 mL of an alcohol solution that contained an equivalent amount of sodium hydroxide, and the solution was boiled with a backflow condenser for 2 h. Then the solvent was reduced in vacuum and the obtained dry residue was dissolved in hot water. The residue formed upon cooling of the solution to 0°C was filtered, dissolved in a small amount of dichloromethane, dried over anhydrous sodium sulfate, and concentrated in vacuum. The obtained dry residue was recrystallized from acetonitrile and dried in vacuum above phosphorous pentaoxide until constant mass. The yield of the target product was 98% of the theoretical one.

The elemental analysis for carbon, hydrogen, nitrogen, and sulfur was performed using an Elemental Analyser EA 1108 (Carlo Erba) automated gas analyzer. Boron was estimated using the method of atomic absorption spectroscopy with a PerkinElmer spectrophotometer (HGA–700, model 2100 with electrothermal atomization).

The IR spectra were recorded with an Avatar 330 spectrometer in the range of 400–4000 cm^{-1}. The specimens were prepared in the form of a powder by joint abrasion of the analyzed substance with potassium bromide.

The NMR ^{11}B spectra of the solutions of the synthesized compounds were recorded with a Bruker Avance 400 spectrometer at the operating frequency of 128.3 MHz with inner stabilization over deuterium with respect to boron trifluoride etherate using CD_3CN as a solvent.

3. RESULTS AND DISCUSSION

Dodecahydro-*closo*-dodecaborate anion (2–) reacts with a melt of benzene-1,2-dicarboxylic acid at the temperature of 190–195°C in the dry argon atmosphere. This is accompanied by formation of the $[C_6H_4(C(O)O)_2–B_{12}H_{10}]^{2–}$ carboxylate-substituted derivative whose alkaline hydrolysis yields formation of a corresponding $[B_{12}H_{10}(OH)_2]^{2–}$ hydroxyl-substituted derivative (Fig. 1).

In the analyzed reaction, benzene-1,2-dicarboxylic acid serves as a reagent and a solvent. The synthesis was performed using tetrabutylammonium salt, which dissolves well in benzene-1,2-dicarboxylic acid. It is necessary to sustain a temperature regime and excess pressure in the reaction medium, otherwise benzene-1,2-dicarboxylic acid becomes charred.

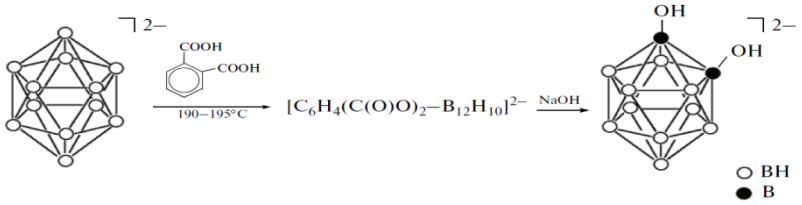

Fig. 1. Schematic of synthesis of water-soluble derivative of the 1,2-$[B_{12}H_{10}(OH)_2]^{2–}$ boron cluster anion

The data of the elemental analysis of the synthesized compounds are presented in Table 1. Owing to high hydrophily of the hydroxyl-substituted derivative, Table 1 lists the data for bis(tetraphenylphosphonium)di(hydroxyl)decahydro-*closo*-dodecarborate (2–) ($(TPP)_2[B_{12}H_{10}(OH)_2]$) obtained by refluxing hot aqueous solutions of tetrabutylammonium salt of the hydroxyl-substituted derivative and tetraphenylphosphonium chloride.

Table 1. Elemental analysis data on synthesized compounds

Compound	Concentration of elements[#], wt %			
	B	C	N	H
$(TBA)_2[C_6H_4(C(O)O)_2 – B_{12}H_{10}]$	16.2/16.4	70.1/60.9	3.7/3.6	11.2/10.9
$(TPP)_2[B_{12}H_{10}(OH)_2]$	15.1/15.2	67.7/67.6	–/–	6.3/6.1

[#]experiment/calculation

The process of substitution manifests itself in the formation of intense absorption bands in the IR spectrum (Table 2) at 1667 and 1269 cm^{-1} which correspond to valence vibrations of C=O and C–O bonds of the carboxylate group. Two sharp maxima at 3653 and 3645 cm^{-1} in the IR spectrum of the product of alkaline hydrolysis of the carboxylate-derivative correspond to valence vibrations of the O–H bond of the hydroxyl group.

Table 2. Ascription of the most informative absorption bands observed in IR spectra of synthesized compounds

Compound	Absorption bands, cm^{-1}					
	ν_{B-H}	$\nu_{C=O}$	ν_{C-O}	ν_{B-O}	ν_{O-H}	ν_{B-B}
$(TBA)_2[C_6H_4(C(O)O)_2 - B_{12}H_{10}]$	2 479	1 667	1 269	1 165	–	1 028
$(TBA)_2[B_{12}H_{10}(OH)_2]$	2 475	–	–	–	3 653 3 645	1 011

The interpretation of the isomeric structure of the compound which is formed as the result of nucleophilic substitution in the *closo*-dodecaborate anion in the process of its interaction with benzene-1,2-dicarbonxylic acid based on the data of the ^{11}B NMR spectrum is highly complicated by intense signal broadening. However, a corresponding hydroxyl-substituted product with analogous mutual positioning of substitutes is formed during hydrolysis in a three-dimensional aromatic system.

The $^{11}B\{^1H\}$ NMR spectrum of $[B_{12}H_{10}(OH)_2]^{2-}$ contains five signals with the integral intensity ratio of 2 : 2 : 4 : 2 : 2 with the chemical shifts of 3.72, –16.16, –18.13, –21.51, and –25.23 ppm (Fig. 2, Table 3). A singlet with the chemical shear of 3.72 ppm appears in the ^{11}B NMR spectrum in the absence of broadband suppression of the B–H spin–spin interaction (SSI), while four signals initiated by boron atoms that are related to hydrogen split into doublets. In general, three isomers can be formed, namely, 1,2- (ortho-), 1,7- (meta-), or 1,12- (para-). Both the ortho- and the meta-isomers correspond to the C_{2V} point group of symmetry that yields the appearance of five maxima in the ^{11}B NMR spectrum, while the para-isomer corresponds to the C_{5V} point group of symmetry (two maxima appear in the ^{11}B NMR spectrum). Since five signals are observed, the compound is either an ortho- or a meta-isomer.

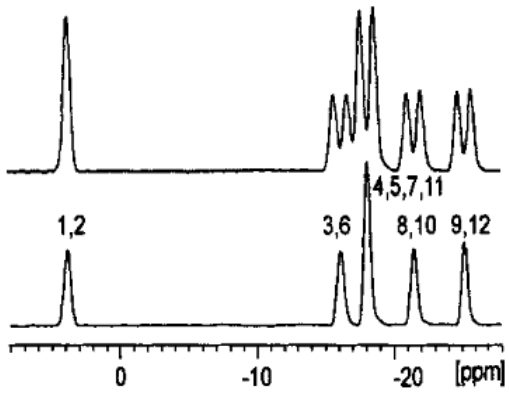

Fig. 2. ^{11}B- и $^{11}B\{^1H\}$ NMR spectra of 1,2-$(TBA)_2[B_{12}H_{10}(OH)_2]$ in CD_3CN

Table 3. Data of ^{11}B NMR spectroscopy of 1,2-$(TBA)_2[B_{12}H_{10}(OH)_2]$ in CD_3CN

Multiplicity in the absence of broad-band suppression of the B–H[##] SSI	Chemical shift δ, ppm	SSI constant $^1J(^{11}B,^1H)$, Hz	Integral intensity	Ascription
s	3.72	–	2	B(1, 2)
d	–16.16	121.3	2	B(3, 6)
d	–18.13	126.8	4	B(4, 5, 7, 11)
d	–21.51	129.1	2	B(8, 10)
d	–25.23	129.1	2	B(9, 12)

[##]*s* – singlet, *d* – doublet

Owing to the fact that regioselectivity under the analyzed synthesis conditions depends on the geometry of the selected reagent (benzene-1,2-dicarboxylic acid), it can be assumed that hydrolysis of the carboxylation reaction product yields formation of the 1,2-$(TBA)_2[B_{12}H_{10}(OH)_2]$ ortho-isomer.

The nucleophilic attack of the boron skeleton by a molecule of benzene-1,2-dicarbonxylic acid is accomplished almost simultaneously on two positions. This is accompanied by the formation of only a disubstituted derivative with *exo*-polyhedral B–O bonds since ^{11}B NMR spectroscopy of the carboxylate-derivative revealed no monohydroxy-substituted products. The attack of the substrate by more than one molecule of benzene-1,2-dicarboxylic acid is limited by the temperature of melting (with decomposition) of the acid itself.

4. CONCLUSIONS

An original method for the synthesis of a water-soluble derivative of the 1,2-$[B_{12}H_{10}(OH)_2]^{2-}$ boron cluster anion using alkaline hydrolysis of the product of interaction of bis(tetrabutylammonium) dodecahydro-*closo*-dodecaborate (2–) with the melt of benzene-1,2-dicarboxylic acid in an inert atmosphere is developed.

It was found that an attack of the boron skeleton by a molecule of benzene-1,2-dicarboxylic acid is accomplished almost simultaneously on two positions with the formation of only a dihydroxy derivative. An attack of the substrate by more than one molecule of benzene-1,2-dicarboxylic acid is limited by the temperature of melting (with decomposition) of the acid itself.

It is shown that regioselectivity under the analyzed synthesis conditions depends on the geometry of the selected reagent, namely, benzene-1,2-dicarboxylic acid.

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