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Research paper

Synthesis and stability studies of derivatives of the 2-sulfanyl-*closo*-decaborate anion $[2\text{-}B_{10}H_9SH]^{2-}$

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ABSTRACT

By acylation of $[2\text{-}B_{10}H_9SH]^{2-}$ (**1**) with trifluoroacetic anhydride was synthesized the anion $[B_{10}H_9SCOCF_3]^{2-}$ (**2**). The alkaline and acid hydrolysis of the $[B_{10}H_9S(CH_2COOEt)_2]^-$ anion leading to the formation of $[B_{10}H_9S(CH_2COOH)_2]^-$ (**3**) gave evidence of high stability of sulfonium derivatives. While in phosphate buffer at pH = 5 the semi-hydrolysis time of thioesters $[B_{10}H_9SCOCH_3]^{2-}$, $[B_{10}H_9SCOCF_3]^{2-}$ (**2**), and $[B_{10}H_9SCOC_6H_5]^{2-}$ were 600, 17 and 168 h. The substituted *closo*-decaborates were characterized by IR and NMR (^1H, ^{11}B, ^{13}C) spectroscopy. The crystal structures of $(Bu_4N)_3[B_{10}H_9(CH_2COO)_2H]_2$ (**3**) and $Cs_5(Bu_4N)[B_{10}H_9SC(O)CF_3]_3$ (**2a**) were determined by X-ray diffraction. In structure **3**, anions were associated via strong O—H···O hydrogen bonds into centrosymmetric hexacharged tetramers. In structure **2a**, anions formed the environment of all cesium cations and chelated one of them due to Cs—O and Cs—HB bonds.

1. Introduction

Boron neutron capture therapy (BNCT) is a promising tool in treating malignant tumors, primarily intractable brain tumors. This method is used to treat mainly progressive or metastatic tumors in the cases when the possibilities of adjuvant therapy have been exhausted. The first encouraging results of BNCT in glioblastoma were obtained in Japan by Professor H. Hatanaka and his colleagues who used the sulfonyl derivative of the dodecaborate anion $[B_{12}H_{11}SH]^{2-}$ [1].

Presently, efforts are directed at preparing compounds exceeding the $[B_{12}H_{11}SH]^{2-}$ anion in selective accumulation in tumor cells [2,3].

In [4,5] methods for preparation of the sulfanyl derivative of the *closo*-decaborate anion $[2\text{-}B_{10}H_9SH]^{2-}$ (1) and its alkylated and acylated derivatives were described. In this work we studied stability of acylated $[B_{10}H_9SCOR]^{2-}$ and alkyl $[B_{10}H_9SR_2]^-$ derivatives in aqueous solutions at various pH values with the aim to elucidate the suitability of this class of compounds for BNCT purposes.

2. Experimental section

Elemental analysis for carbon, nitrogen, and hydrogen was carried out on a Carlo Erba CHNS3 FA 1108 Elemental Analyzer.

The boron content was determined on an inductively coupled plasma-atomic emission spectrometer iCAP 6300 Duo.

IR spectra were recorded at a resolution of 1 cm^{-1} on an Infralyum FT 02 Fourier transform spectrometer (Lumex Instruments Research and Production Company, St.-Petersburg, Russia) in the range 4000–300 cm^{-1}. Samples were prepared as suspensions in CCl_4.

NMR (^1H, ^{11}B, and ^{13}C) spectra of CD_3CN solutions were recorded on a Bruker Avance II 300 spectrometer operating at a frequency of 300.3, 96.32, and 75.49 MHz, respectively, using an internal deuterium lock. Tetramethylsilane and boron trifluoride etherate were used as external references.

NMR (^{19}F) spectra of DMSO d_6 solutions were recorded on a Bruker DPX 300 Avance spectrometer operating at a frequency of 300.0 MHz, using an internal deuterium lock.

pH control was performed by using phosphate buffered solutions with a molarity of 50 mM. Signals of the boron atoms of the apical peaks and of the ipso-atom of boron were used for the analysis of the hydrolysis process. The analysis was carried out

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by comparing the integrated signal intensities from the thioether and the sulfonium derivative. The signals for the analysis were taken the first 1, 2, 3, 5, 8, 12, 17, 24 h and then every subsequent 24 h.

The X-ray diffraction studies of crystals **3** and **2a**·0.5EtOH were performed on a Bruker APEX-II CCD diffractometer [6] (λMo = 0.71073 Å, ω scan mode). The diffraction data were processed using the SAINT program [6], and the absorption correction based on equivalent reflections was applied with the SADABS program [1]. Crystal data, details of data collection, and results of structure refinement are given in Table 1. Structure **3** was solved by the direct method (SHELXS-97 [7]), and structure **2a**·0.5EtOH was solved using the superflip method [8,9]. Both structures were refined by full-matrix least-squares procedures on F^2 (SHELXL-2014/7 [7,10]). In structure **3** the hydrogen atoms of the carboxyl groups were localized on a difference Fourier map and refined in the isotropic approximation. All other hydrogen atoms in **3** and all hydrogen atoms in **2a**·0.5EtOH were positioned geometrically and refined using the default mode of the riding model.

In structure **3** two of the three independent TBA cations are disordered. In **2a**·0.5EtOH the disordering covers the TBA cation, the CF_3 groups of the substituents of all *closo*-decaborate anions, and the ethanol molecule. The atoms of disordered elements were refined in the isotropic approximation, and all other non-hydrogen atoms were refined in the anisotropic approximation. Geometric restraints were applied to all TBA cations in **3** and disordered groups in **2a**·0.5EtOH. In particular, the C—F bond lengths were restrained to 1.322(5) Å. The anisotropic thermal parameters of two carbon atoms in **3** and three boron atoms in **2a**·0.5EtOH were restrained to approximate the isotropic behavior.

The structural disordering lowered the X-ray diffraction power of crystals **3** and **2a**·0.5EtOH. Both crystals were thin plates reflecting to θ_{max} ~21°. This resulted in rather low precision in bond lengths. However, there is no doubt that the structural models are correct.

The crystallographic data have been deposited with the Cambridge Crystallographic Data Center (CCDC nos 1560176 and 1560177).

Table 1
Crystal data, details of X-ray diffraction experiments, and parameters of structure refinement for **3** and **2a.**

Parameter	**2a**·0.5EtOH	**3**
Empirical formula	$C_{23}H_{65.50}B_{30}Cs_5F_9NO_{3.50}S_3$	$C_{56}H_{137}B_{20}N_3O_8S_2$
Formula weight	1668.29	1261.00
T, K	150(2)	150(2)
Crystal system	Triclinic	Monoclinic
Space group, *Z*	*P*1, 2	$P2_1/c$, 4
a, Å	13.3481(12)	17.7503(8)
b, Å	13.4210(13)	30.7787(13)
c, Å	21.074(3)	15.3864(7)
α, deg	92.101(2)	90
β, deg	107.994(2)	112.5560(10)
γ, deg	116.551(2)	90
V, Å^3	3143.4(6)	7763.0(6)
D_x, Mg/m^3	1.763	1.079
μ, mm^{-1}	3.028	0.116
F(0 0 0)	1585	2760
Crystal size, mm	0.20 × 0.10 × 0.01	0.28 × 0.16 × 0.06
θ range, deg	2.196–21.827	1.815–20.963
Reflections collected	19127	42590
Unique reflections, R_{int}	7493, 0.0956	8294, 0.0664
Completeness to θ_{max}	99.6%	99.9%
Max, min transmission	0.7447, 0.5876	0.7446, 0.6349
Data/restraints/parameters	7493/307/667	8294/130/784
Goodness-of-fit	0.981	1.008
*R*1, w*R*2 [$I > 2\sigma(I)$]	0.0487, 0.0828	0.0819, 0.2130
*R*1, w*R*2 (all data)	0.1097, 0.0983	0.1273, 0.2528
$\Delta\rho_{max}/\Delta\rho_{min}$, eÅ^{-3}	1.050/−0.712	0.827/−0.319

Crystal data, details of data collection, and results of structure refinement are summarized in Table 1.

(n-Bu_4N)$_2$[2-$B_{10}H_9SH$] (**1**) and n-Bu_4N[2-$B_{10}H_9S(CH_2COOEt)_2$] were obtained according to [5].

2.1. Synthesis of tetrabutylammonium 2-[bis (carboxymethyl)sulfonio]-closo-decaborate (n-Bu_4N)$_3$[2-$B_{10}H_9S(CH_2COO)_2H]_2$ (3)

A weighed portion (1 g, 1.8 mmol) of (*n*-Bu_4N)[2-$B_{10}H_9S(CH_2$-$COOEt)_2$] was dissolved in 40 ml of 50% ethanol; KOH (1 g, 18 mmol) was added, and the mixture was boiled under reflux for 2.5 h. After cooling to room temperature, the solution was treated with 2.3 ml of concentrated hydrochloric acid under thorough stirring and allowed to stand for 30 min. The solvent was distilled off on a rotary evaporator, and the precipitate was resuspended in 15 ml of distilled water and allowed to stand in an ultrasonic bath to form a flocculated suspension. The precipitate was filtered off and washed with distilled water (2 × 10 ml) and diethyl ether (2 × 10 ml), and then recrystallized from ethanol. Yield: 0.69 g (0.54 mmol, 60.4%). Anal. Calc. for $C_{56}H_{59}O_4NB_{10}S$ (%): C, 50.94; H, 10.88; N, 3.34; S, 5.09. Found (%): C, 51.51; H, 10.902 N, 3.41; S, 5.21. ^{1}H-NMR (CD_3CN, δ, ppm): 7.87 (s, 1H, $(CH_2COO)_2\underline{H}$), 3.68(d, 4H, J = 15.96, $SC\underline{H_A}H_B$), 3.60 (d, 4H, J = 15.96, $SCH_A\underline{H_B}$), 3.17 (m, 24H, *n*-Bu_4N^+), 1.67 (m, 24H, *n*-Bu_4N^+), 1.43 (m, 24H, *n*-Bu_4N^+), 1.03 (t, 36H, *n*-Bu_4N^+), 0.60–2.10 (m, 9H, $B_{10}H_9$). ^{13}C-NMR(CD_3CN, δ, ppm): 167.1 (C̲OO), 58.9 (*n*-Bu_4N^+), 46.0 (S̲CH_2), 23.7 (*n*-Bu_4N^+), 19.7 (*n*-Bu_4N^+), 13.4 (*n*-Bu_4N^+). ^{11}B-{1H} NMR (CD_3CN, δ, ppm): 4.6 (d, 1B), −3.1 (d, 1B), −15.4 (s, 1B), −24.4 (d, 5B), −28.5 (d, 2B). IR (CCl_4): 2962, 2926, 2876, 2874, 2478, 1734, 1559, 1464, 1472, 1400, 1375, 1330, 1208, 1196, 1175, 993, 939, 896 cm^{-1}.

2.2. Synthesis of tetrabutylammonium 2-(trifluoroacetylsulfanyl)-closo-decaborate (n-Bu_4N)$_2$[2-$B_{10}H_9SC(O)CF_3$] (2)

Triethylamine (1.65 ml, 12 mmol) was added to a solution of (n-Bu_4N)$_2$[2-$B_{10}H_9SH$] (1.00 g, 1.6 mmol) in 10 ml of acetonitrile. The mixture was cooled to −10 °C in an ice bath and 450 μl (3.2 mmol) of trifluoroacetic anhydride was added dropwise on stirring. After stirring for 30 min at room temperature, the solvent was distilled off on a rotary evaporator, 20 ml of distilled water was added, and the mixture was allowed to stand in an ultrasonic bath until a flocculent precipitate was formed. The precipitate was filtered off and washed with distilled water (2 × 10 ml) and diethyl ether (2 × 10 ml). Yield: 0.95 g (1.3 mmol, 81.3%). Anal. Calc. for $C_{34}H_{81}$-$N_2OB_{10}SF_3$ (%):C, 55.11; H, 11.35; N, 3.90; S, 4.46. Found (%): C, 55.31; H, 11.26; N, 3.79; S,4.35. ^{1}H-NMR (CD_3CN, δ, ppm): 3.14 (m, 8H, *n*-Bu_4N^+), 1.65 (m, 8H, *n*-Bu_4N^+), 1.41 (m, 8H, *n*-Bu_4N^+), 1.01 (t, 12H, *n*-Bu_4N^+), 0.60–2.10 (m, 9H, $B_{10}H_9$). ^{13}C-NMR (DMSO d_6, δ, ppm): 185.3 (C = O), 118.7 (CF_3). ^{11}B-{1H} NMR (CD_3-CN, δ, ppm): 1.7 (d, 1B), −0.4 (d, 1B), −18.5 (s, 1B), −24.5 (d, 4B), −26.3 (d, 3B). ^{19}F-NMR (DMSO d_6, δ, ppm): −75.21 (CF_3). IR (CCl_4): 2963, 2875, 2470, 1662, 1480, 1382, 1266, 1191, 1141, 935, 884 cm^{-1}.

2.3. Synthesis of pentacesium tetrabutylammonium tris[2-(trifluoroacetylsulfanyl)-closo-decaborate] semiethanolate $Cs_5(Bu_4N)$ [2-$B_{10}H_9SC(O)CF_3]_3$ 0.5EtOH A solution of 2

A solution of 2 (500 mg, 0.68 mmol) in 20 ml of ethanol was poured into a solution of cesium trifluoroacetate (370 mg, 1.5 mmol) in 10 ml of ethanol and thoroughly stirred. The precipitated crystals were filtered off and washed with 2 × 10 ml ethyl alcohol. Yield: 331 mg (0.20 mmol, 89.7%). Anal. Calc. for $C_{20}H_{66}N_1O_{3.5}B_{30}$-$S_3F_9Cs_5$ (%):C, 14.71; H, 4.07; N, 0.86; S, 5.89. Found (%): C, 14.65; H,