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Oxidation products of cesium monomercaptoundecahydro-*closo*-dodecaborate(2 −)

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Abstract

When an aqueous solution of boron-10-enriched cesium monomercaptoundecahydro-*closo*-dodecaborate(2 −), $Cs_2{}^{10}B_{12}H_{11}SH$ (**1b**) was allowed to stand for a long period in contact with air, several oxidation products, separable by HPLC, were formed. Disulfide $Cs_4{}^{10}B_{12}H_{11}SS{}^{10}B_{12}H_{11}$ (**2b**), thiolsulfinate $Cs_4{}^{10}B_{12}H_{11}SSO{}^{10}B_{12}H_{11}$ (**3b**), and sulfinylsulfone $Cs_4{}^{10}B_{12}H_{11}SOSO_2{}^{10}B_{12}H_{11}$ (**4b**) were prepared stepwise by the reaction of the thiol $Cs_2{}^{10}B_{12}H_{11}SH$ (**1b**) with an oxidizing agent. Oxidation of disulfide **2b** with an equivalent amount of *m*-chloroperbenzoic acid (MCPBA) quantitatively gave the thiolsulfinate, **3b**. Further oxidation proceeded on treating **3b** with an excess of MCPBA. When two equivalents of MCPBA were used, the sulfinylsulfone **4b** was formed predominantly and isolated as the cesium salt. The characterization of the oxidation products is described.

Introduction

The boron-10-enriched compound $Na_2{}^{10}B_{12}H_{11}SH$ (**1a**) and its derivatives are useful reagents in boron neutron capture therapy. Since 1968, H. Hatanaka has been successful with clinical therapy of brain tumors using **1a** [1]. We have synthesized **1a** for this therapy and published several studies [2–4]. Throughout our work, we experienced considerable difficulty in isolating the thiol compound as a pure salt, because of contamination with small amounts of oxidation products formed by autoxidation of **1a**. The oxidation of organic sulfur compounds has been studied by many workers; various intermediates, such as disulfide, thiolsulfinate, α-disulfoxide, and sulfinylsulfone, have been reported [5–7]. Soloway et al. have reported the isolation of oxidation products, such as $B_{12}H_{11}SSB_{12}H_{11}(4-)$ and $B_{12}H_{11}SSOB_{12}H_{11}(4-)$ from the reaction of $B_{12}H_{11}SH(2-)$ with hydrogen peroxide [8,9]. We have examined the further oxidation of these compounds with MCPBA in a stepwise manner and have obtained several products.

Here we describe the oxidation and characterization of these boron compounds.

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Results and discussion

Autoxidation of $Cs_2{}^{10}B_{12}H_{11}SH$ *(1b) in aqueous solution*

When an aqueous solution of **1b** was allowed to stand for a long period, several oxidation products formed. They were separated by HPLC as shown in Table 1, with the retention time serving as the method of identification. The disulfide **2b**, thiolsulfinate **3b**, and sulfinylsulfone **4b** were identified by comparing their retention times with those of the authentic samples which had been made by reaction of **2b** with MCPBA. As shown in Table 1, the relative intensity of **1b** decreased over time, while those of **2b** and **3b** increased gradually. After 45 days, the oxidation had proceeded further to give the new oxidation product, **4b**. After 76 days, the peaks of **1b** and **2b** had disappeared completely and the relative intensities of **3b** and **4b** had increased.

When an aqueous solution of **2b** was monitored by HPLC in a similar way, **3b** and **4b** were found as shown in Table 1. The peak of **2b** decreased while that of **3b** increased gradually. After 23 days, the peak of **2b** had disappeared entirely and **3b** was observed as the major product together with other oxidation products. After 45 days, the relative intensity of **3b** had gradually decreased, whereas that of **4b** was increasing. After 76 days, further oxidation was slow. These results suggest that the autoxidation of **1b** in aqueous solution proceeds via **2b** and **3b** as intermediates.

Table 1

HPLC of **1b** and **2b** in an aqueous solution

	Period/d	Retention time [a]/min (relative intensity [b])				
		1b	**2b**	Unknown	**4b**	**3b**
1b	0	5.5 (100)	–	–	–	–
	22	5.10 (74.9)	11.84 (9.2)	–	–	22.40 (15.9)
	45	5.24 (5.3)	11.92 (8.4)	14.22 (5.6)	16.16 (4.5)	22.80 (76.2)
	76	–	–	14.22 (8.1)	16.24 (8.9)	23.80 (83.0)
2b	0	– –	12.68 (100)	–	–	–
	2	– –	12.32 (98.2)	–	–	22.70 (1.8)
	23	– –	– –	13.64 (8.4)	15.64 (11.8)	21.92 (79.8)
	45	– –	– –	13.80 (14.2)	15.74 (16.4)	22.04 (69.3)
	76	–	–	13.84 (13.2)	15.80 (18.8)	22.18 (68.0)

1b: $Cs_2{}^{10}B_{12}H_{11}SH$, **2b**: $Cs_4{}^{10}B_{12}H_{11}SS^{10}B_{12}H_{11}$,
3b: $Cs_4{}^{10}B_{12}H_{11}SSO^{10}B_{12}H_{11}$, **4b**: $Cs_4{}^{10}B_{12}H_{11}SOSO_2{}^{10}B_{12}H_{11}$

[a] The retention time served as the method of identification. [b] Small peaks of impurities were excluded.

Oxidation of $Cs_4B_{12}H_{11}SSB_{12}H_{11}$ (2b)

Wellum et al. reported the isolation and some of the properties of disulfide **2b** which had been prepared by the oxidation of $Cs_2B_{12}H_{11}SH$ (**1b**) with iodosobenzoate [8]. We also examined the oxidation reaction of **1b** with nickel peroxide and obtained the same disulfide $Cs_4B_{12}SSB_{12}H_{11}$ (**2b**) [3].

When **2b** was treated with an equivalent of MCPBA in H_2O-CH_2Cl_2 at room temperature, thiolsulfinate **3b** was formed (eq. 1).

$$\underset{(\mathbf{2b})}{Cs_4B_{12}H_{11}SSB_{12}H_{11}} + MCPBA \rightarrow \underset{(\mathbf{3b})}{Cs_4B_{12}H_{11}SSOB_{12}H_{11}} \quad (1)$$

$$\underset{(\mathbf{3b})}{Cs_4B_{12}H_{11}SSOB_{12}H_{11}} + 2MCPBA \rightarrow \underset{(\mathbf{4b})}{Cs_4B_{12}H_{11}SOSO_2B_{12}H_{11}} \quad (2)$$

HPLC of the reaction product showed a single peak with a retention time of 22.4 min, and the peak of the starting material had disappeared completely. Thus the oxidation of **2b** to **3b** proceeds quantitatively with an equivalent amount of MCPBA. The cesium salt **3b** could be converted to its ammonium salt **3c** on a cation exchange resin (see Experimental). The formation of **3c** is confirmed by the elemental analysis and the spectral data. When more than an equivalent amount of oxidant was used, the amount of **3b** decreased gradually, and the oxidation proceeded further. When two equivalents of MCPBA were used with respect to **3b**, the main product was sulfinylsulfone **4b** (eq. 2).

Characterization of $B_{12}H_{11}SOSO_2B_{12}H_{11}(4-)$

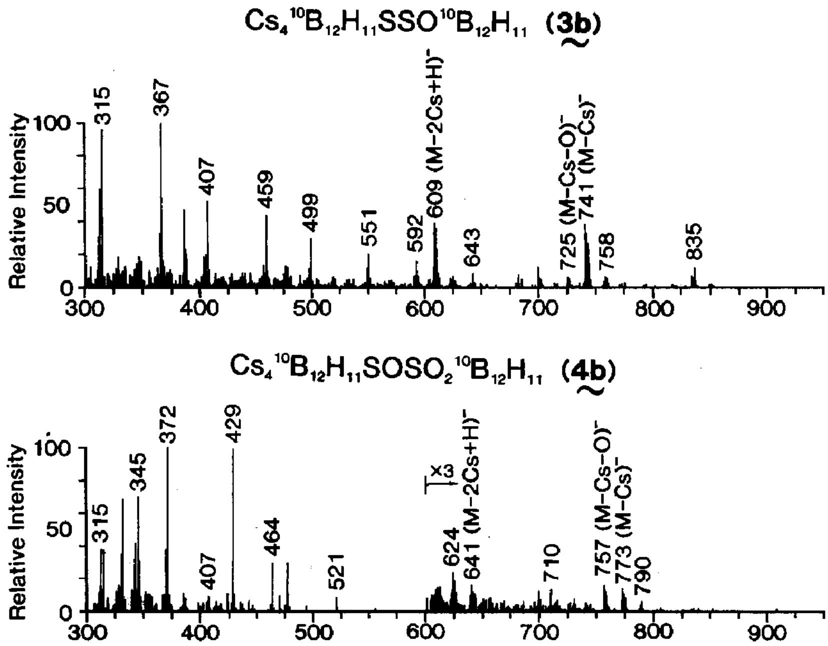
The formation of $B_{12}H_{11}SOSO_2B_{12}H_{11}(4-)$ by the oxidation of $B_{12}H_{11}SSB_{12}H_{11}$ $(4-)$ with MCPBA in a stepwise manner is confirmed by both the chemical analysis and the spectral data.

The tetramethylammonium salt **4c** was prepared similarly. The formulation of the tetramethylammonium salt is consistent with the calculated value for $[(CH_3)_4N]_4{}^{10}B_{12}H_{11}SOSO_2{}^{10}B_{12}H_{11} \cdot 1.5H_2O$ (**4c**) (see Experimental). The water content was determined by the weight loss at 110 °C in the method used in our laboratories [11]. The IR spectrum of **4c** showed features similar to those of **3c** with additional bands at 1235 and 1102 cm^{-1} which are characteristic of sulfones, and suggests that ${}^{10}B_{12}H_{11}SOSO_2{}^{10}B_{12}H_{11}$ exists as a sulfinylsulfone with the $-SO-SO_2-$ structure [12]. The IR spectrum of the cesium salt **4b** also showed similar absorption bands at 1205 and 1100 cm^{-1} which also point to this structure. The weak band at 462 cm^{-1} in the IR spectra of **4b** and **4c** probably corresponds to the S–S stretching frequencies.

We have also attempted the interesting reaction reported by Tsu-Lok Ho et al. involving the use of titanium(III) ion for the reduction of sulfoxides to sulfides [13]. The reduction of sulfinylsulfone **4c** with $TiCl_3$ successfully gave the disulfide **2c** as identified from its IR spectrum and by HPLC. This result shows that the S–S bond exists in the structure of sulfinylsulfone.

Mass spectra of $Cs_4{}^{10}B_{12}H_{11}SSO^{10}B_{12}H_{11} \cdot H_2O$ (3b) and $Cs_4{}^{10}B_{12}H_{11}SOSO_2{}^{10}B_{12}H_{11} \cdot 2.7H_2O$ (4b)

The negative ion liquid secondary ion mass spectra (NILSIMS) of **3b** and **4b** are shown in Fig. 1, and the elemental compositions of main fragment ion peaks



$Cs_4{}^{10}B_{12}H_{11}SSO^{10}B_{12}H_{11}$ (**3b**)

$Cs_4{}^{10}B_{12}H_{11}SOSO_2{}^{10}B_{12}H_{11}$ (**4b**)

Fig. 1. Partial mass spectra of **3b** and **4b**

obtained by high resolution NILSIMS are shown in Table 2. The ion peak pattern shows the typical envelope shape, since these boron compounds consist of 24 boron atoms enriched with over 95.6% of ^{10}B as estimated from the peak intensities in Fig. 1. The high-resolution mass spectral data (Table 2) permitted the following analysis of the mass spectral fragmentation and hence the elucidation of the structures. Although the $[M-H]^-$ peaks corresponding to the elimination of the proton from the molecules were not observed, significant peaks $[M-Cs]^-$ owing to loss of the cesium cation from the molecules were observed at m/z 741 (observed accurate mass number 741.1384, $^{10}B_{24}H_{22}OS_2Cs_3$) for **3b** and 773 (773.1276, $^{10}B_{24}H_{22}O_3S_2Cs_3$) for **4b**. The fragment ion peaks corresponding to the $[M-Cs-O]^-$ were detected at m/z 725 (725.1425, $^{10}B_{24}H_{22}S_2Cs_3$) for **3b** and 757 (757.1326, $^{10}B_{24}H_{22}O_2S_2Cs_3$) for **4b**. Furthermore, one of the cesium atoms in the ions of $[M-Cs]^-$ was replaced by a hydrogen atom to afford the ion $[M-2Cs+H]^-$ which appeared at m/z 609 (609.2399, $^{10}B_{24}H_{23}OS_2Cs_2$) for **3b** and 641 (641.2295, $^{10}B_{24}H_{23}O_3S_2Cs_2$) for **4b**. As shown in Table 2, the difference in the mass numbers of **3b** and **4b** is 32 which corresponds to two oxygen atoms. These findings indicate that the anionic part of **4b** consists of $^{10}B_{12}H_{11}SOSO_2{}^{10}B_{12}H_{11}$. The anionic part of **4b** can also be prepared chemically by oxidation of **3b** with two equivalents of MCPBA (eq. 2).

Experimental

Physical measurements. HPLC was conducted with a Nucleosil $_{10}C_{18}$ column (4 × 300 mm) in 5 mmol tetrabutylammonium phosphate solution (pH 7)/CH_3OH (55 : 45) as the mobile phase and detected at 254 nm by use of a JASCO TWINCLE liquid chromatograph equipped with a variable wavelength UV-detector (Japan Electroscopic Co., Tokyo). Infrared spectra were recorded with a JASCO A-702

Table 2

High resolution mass spectra of cesium salts (3b and 4b)

$Cs_4{}^{10}B_{12}H_{11}SSO^{10}B_{12}H_{11}$ (3b) [a]			$Cs_4{}^{10}B_{12}H_{11}SOSO_2{}^{10}B_{12}H_{11}$ (4b) [b]		
m/z	Relative intensities [b]	Elemental composition	*m/z*	Relative intensities [b]	Elemental composition
609	100	$^{10}B_{24}H_{23}OS_2Cs_2 = [M-2Cs+H]^-$	641	108	$^{10}B_{24}H_{23}O_3S_2Cs_2 = [M-2Cs-H]^-$
610	91	$^{10}B_{23}{}^{11}BH_{23}OS_2Cs_2$	642	85	$^{10}B_{23}{}^{11}BH_{23}O_3S_2Cs_2$
611	65	$^{10}B_{22}{}^{11}B_2H_{23}OS_2Cs_2$	643	64	$^{10}B_{22}{}^{11}B_2H_{23}O_3S_2Cs_2$
725	26	$^{10}B_{24}H_{22}S_2Cs_3 = [M-Cs-O]^-$	757	109	$^{10}B_{24}H_{22}O_2S_2Cs_3 = [M-Cs-O]^-$
726	26	$^{10}B_{23}{}^{11}BH_{22}S_2Cs_3$	758	93	$^{10}B_{23}{}^{11}BH_{22}O_2S_2Cs_3$
727	24	$^{10}B_{22}{}^{11}B_2H_{22}S_2Cs_3$	759	59	$^{10}B_{22}{}^{11}B_2H_{22}O_2S_2Cs_3$
728	17	$^{10}B_{21}{}^{11}B_3H_{22}S_2Cs_3$	760	57	$^{10}B_{21}{}^{11}B_3H_{22}O_2S_2Cs_3$
741	100	$^{10}B_{24}H_{22}OS_2Cs_3 = [M-Cs]^-$	773	100	$^{10}B_{24}H_{22}O_3S_2Cs_3 = [M-Cs]^-$
742	86	$^{10}B_{23}{}^{11}BH_{22}OS_2Cs_3$	774	83	$^{10}B_{23}{}^{11}BH_{22}O_3S_2Cs_3$
743	73	$^{10}B_{22}{}^{11}B_2H_{22}OS_2Cs_3$	775	78	$^{10}B_{22}{}^{11}B_2H_{22}O_3S_2Cs_3$

[a] Boron-10-enriched compounds (^{10}B, 95.64%) were used. [b] Relative intensities are given as percentage of the $(M-Cs)^-$ peak.

spectrometer in the range 4000–200 cm^{-1}, as Nujol mulls. The following descriptions are used: vs, very strong; m, medium; w, weak; vw, very weak; sh, shoulder; br, broad.

Mass spectra (NILSIMS and high resolution NILSIMS) were recorded with a Hitachi M-90 double focusing mass spectrometer. The sample solutions (in glycerol) were placed on the silver emitter and bombarded with xenon cations accelerated to 14 kV. High resolution NILSIMS were measured by a peak-matching technique with polyethylene glycol as an internal standard.

Materials. $Cs_2B_{12}H_{11}SH$ was prepared by a procedure described previously [3]. Nickel peroxide was prepared by a standard method [10]. MCPBA was obtained from Nakarai Chemical Co., Japan.

Synthesis of $Cs_4B_{12}H_{11}SSB_{12}H_{11}$ (2b)

Nickel peroxide (0.88 g) was added to 2.4 g (5.24 mmol) of **1b** in 20 ml of distilled water at room temperature with vigorous stirring. The reaction mixture was washed with 50 ml of hot water. The aqueous layer was concentrated to a final volume of approximately 10 ml. The white precipitate was recrystallized from water and dried to give 1.71 g (74.0%) of **2b** as the unhydrated salt. IR (cm^{-1}, rel. int.): 2475 vs, 1075 sh, 1059 m, 980 sh, 978 m, 948 vw, 842 m, 819 vw, 722 m. ^{10}B-enriched $Cs_4{}^{10}B_{12}H_{11}SS^{10}B_{12}H_{11}$ was prepared similarly. IR (cm^{-1}, rel. int.): 2490 vs, 1090 sh, 1068 m, 992 m, 862 m, 730 w.

Synthesis of $[(CH_3)_4N]_4B_{12}H_{11}SSOB_{12}H_{11}$ 2.5 H_2O (3c)

To 538 mg (0.61 mmol) of **2b** in 60 ml of distilled water was added 131.6 mg of MCPBA in 12 ml of CH_2Cl_2 with stirring at room temperature for 2.5 h. The organic layer was separated off and the aqueous layer was washed three times with CH_2Cl_2. The aqueous layer was concentrated to about 5 ml and converted to the acid on an ion exchange resin [Amberlite IR-120 (H^+)]. The pH was then raised to 7.0 by the addition of a 10% aqueous solution of tetramethylammonium hydroxide (2.3 mmol). Concentration by rotary evaporator and cooling to 0 °C, gave white crystals which were isolated by filtration. Cooling of the mother liquor yielded a second crop. The total yield of the air-dried crystals was 270 mg (0.40 mmol, 65.6%). The water content was determined by the weighing-tube method developed in our laboratory [11]. IR (cm^{-1}, rel. int.): 3620 m, 3300 w, 3200 w, 2500 vs, 1610 w, 1480 s, 1455 s, 1410 w, 1270 m, 1045 m, 950 s, 837 m, 816 w, 717 m, 477 w. Anal. Found: C, 27.63; H, 10.89; N, 7.93; S, 8.54; B, 35.40; H_2O, 5.71. $[(CH_3)_4N]_4B_{24}H_{22}S_2O \cdot 2.5$ H_2O calcd.: C 27.32; H, 10.75; N, 7.96; S, 9.11; B, 36.88; H_2O, 5.68%. The IR spectrum agrees well with that published previously for **3c** [9].

The ^{10}B-enriched **3c** was prepared similarly from ^{10}B-enriched **2b**. IR (cm^{-1}, rel. int.): 3612 m, 3352 br, 3032 w, 2496 vs, 1609 vw, 1485 s, 1460 m, 1288 vw, 1087 w, 1066 m, 995 w, 949 m, 854 w, 478 vw.

Synthesis of $Cs_4B_{12}H_{11}SSOB_{12}H_{11} \cdot H_2O$ (3b)

A solution of 146 mg (0.208 mmol) of **2b** in 5 ml of distilled water was converted to the acid by passage through a cation exchange resin [Amberlite IR-120 (H^+)]. The pH of the solution was raised to 7.0 by addition of an aqueous solution of cesium hydroxide (0.835 mmol). The precipitate was filtered and washed several times with CH_3OH and crystallized from H_2O–CH_3OH to give 190 mg (0.208

mmol). The conversion ratio under cation exchange was almost 100%. IR (cm^{-1}, rel. int.): 3570 m, 3330 w, 2495 vs. 1605 vw, 1345 w, 1058 m, 1025 w, 1015 m, 999 w, 979 w, 840 m, 819 vw, 723 m, 460 vw.

The ^{10}B-enriched **3b** was prepared similarly as the monohydrate salt. IR (cm^{-1}, rel. int.): 3596 m, 2500 vs, 1601 w, 1090 w, 1069 m, 1000 m, 966 m, 857 m, 850 w, 538 vw, 473 w. MS: *m/z* 741 $[M-\mathrm{Cs}]^-$.

Synthesis of $[(CH_3)_4N]_4B_{12}H_{11}SOSO_2B_{12}H_{11} \cdot 1.5H_2O$ *(4c)*

To 44.0 mg (0.50 mmol) of ^{10}B-enriched **3b** in 50 ml of distilled water was added 225 mg (1.30) mmol of MCPBA in 20 ml of CH_2Cl_2 at room temperature for 2 h with vigorous stirring. The reaction mixture was transferred to a separating funnel and washed three times with CH_2Cl_2. The aqueous solution was concentrated to about 5 ml and converted to the acid on an ion exchange resin, then the pH was raised to 7.0 by addition of tetramethylammonium hydroxide. The solution was concentrated and cooled to 0 ° C. The resulting solid was purified by recrystallization from H_2O. The yield of **4c** was 251 mg (0.36 mmol, 72.0%). IR (cm^{-1}, rel. int.): 3590 m, 3540 m, 3035 m, 2496 vs, 1632 w, 1487 m, 1235 m, 1121 w, 1103 m, 1063 m, 998 ws, 960 w, 950 m, 531 w, 505 w, 462 vw. Anal. Found: C, 27.36; H, 10.67; N, 7.87; S, 8.67; B, 34.55; H_2O, 3.42. $[(CH_3)_4N]_4B_{24}H_{22}S_2O_3 \cdot 1.5H_2O$ calcd.: C, 27.54; H, 10.54; N, 8.03; S. 9.19; B, 34.39; H_2O, 3.72%.

Synthesis of $Cs_4B_{12}H_{11}SOSO_2B_{12}H_{11} \cdot 2.7H_2O$ *(4b)*

$[(CH_3)_4N]_4B_{12}H_{11}SOSO_2B_{12}H_{11} \cdot 1.5H_2O$ (**4c**) was transformed into the cesium salt **4b** on the ion exchange resin as described above. The water content was determined by use of the weighing-tube method developed in our laboratory. IR (cm^{-1}, rel. int.): 3585 m, 3380 br, 2495 vs, 1615 br, 1482 m, 1205 br, 1120 sh, 1100 br, 1067 m, 980 m, 946 m, 606 w, 574 w, 538 w, 462 vw. MS: *m/z* 773 $[M-\mathrm{Cs}]^-$.

Reduction of $Cs_4B_{12}H_{11}SOSO_2B_{12}H_{11}$ *(4b)*

To 20 mg of **4b** in 0.5 ml of water was added 27 mg of $TiCl_3$ powder under nitrogen at room temperature. After the purple solution had become a turbid brown suspension, the reaction mixture was concentrated to dryness and washed with a small amount of water and CH_3OH. The resulting pale yellow solid was treated with H_2O–MeOH. The sulfide was identified as $Cs_4B_{12}H_{11}SSB_{12}H_{11}$ by comparison with the IR and HPLC data of an authentic sample. IR (cm^{-1}, rel. int.): 2470 vs, 1058 s, 975 m, 842 m. HPLC: 11.92 min. (authentic sample, 11.87 min.)

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