Synthesis of *S*-Alkyl and *S*-Acyl Derivatives of Mercaptoundecahydrododecaborate, a Possible Boron Carrier for Neutron Capture Therapy

Detlef Gabel,* Detlef Moller, Sven Harfst, Jens Rösler, and Hartmut Ketz

Department of Chemistry, University of Bremen, P.O. Box 330 440, W-2800 Bremen 33, Germany

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The synthesis of S-alkylated and S-acylated derivatives of mercaptoundecahydrododecaborate ($B_{12}H_{11}SH^{2-}$) (**1**) is described. Under conventional alkylation conditions, **1** reacts with primary alkyl halides to form S,S-bis-substituted sulfonium salts. With secondary halides, monoalkylation to thioethers is observed. The sulfonium salts act only as poor alkylating agents. The cyanoethyl-substituted sulfonium salt **3** was found to lose one substituent upon treatment with tetramethylammonium hydroxide, to yield the thioether **8**. Unsymmetrically substituted sulfonium salts were obtained through realkylation. Selective removal of the remaining cyanoethyl group yielded thioethers. Reaction of **1** with acid halides resulted in thioesters, which showed surprising stability toward hydrolysis.

Boron neutron capture therapy is a tumor therapy modality that is seeing a revival.[1,2] The potential of the boron-10 nucleus to capture thermal neutrons and thereby disintegrate into two densely ionizing particles can be exploited therapeutically, providing an incentive to synthesize appropriate boron compounds with tumor-accumulating or tumor-retaining properties. Suitable compounds should have the capability to be transported through the blood stream and to accumulate or be retained physiologically in tumor tissue. For treatment of glioma, mercaptoundecahydrododecaborate ($B_{12}H_{11}SH^{2-}$) (**1**) is used in Japan[3] and will be used in Europe.[4] Due to its ionic nature and the presence of a potentially reactive sulfhydryl group, it should be useful for the preparation of other tumor-seeking compounds. Recently, Nagasawa and Narisada[5] reported the preparation of carboxylic acid derivatives of **1** through S-alkylation with halogen derivatives of carboxylic acids.

We wish to report here that the reactivity of the SH group in **1** does not resemble that of carbon SH groups; rather, its reactivity resembles more closely that of an organic amino or hydroxy group.

Experimental Section

$[(CH_2{=}CHCH_2)_2SB_{12}H_{11}][N(CH_3)_4]$ (2). (a) The tetramethylammonium salt of **1** was converted to its sodium thiolate by titration with an equimolar amount of NaOH in water and recovered by lyophilization. This salt (1 g, 2.9 mmol) was suspended in 250 mL of acetonitrile. A solution of 1.3 mL (15 mmol) of allyl bromide in 40 mL of acetonitrile was added through a dropping funnel at room temperature over 10 min. After 24 h the solvent was removed under vaccum. The residue was suspended in acetonitrile, and the mixture was filtered to remove NaBr. Upon addition of diethyl ether, **2** precipitated. It was recrystallized from water to yield 420 mg (1.16 mmol, 40%) of star-shaped crystals (mp 170 °C). ^{1}H-NMR (360.1 MHz, DMSO-d_6, 25 °C, TMS): 5.94 (mult, $H_2C{=}CH$–), 5.40 (mult, $H_2C{=}CH$–), 3.58 (mult, –CH_2S–), 0.4–2.0 (mult, $B_{12}H_{11}$). IR (KBr): 3030, 2493, 1484, 1425, 1401, 1234, 1045, 991, 945, 823, 746, 720 cm^{-1}. Anal. Calcd for $C_{10}H_{28}B_{12}S\cdot{}^1/_2H_2O$: C, 35.52; H, 10.13; N, 4.14; B, 38.36; S, 9.48. Found: C, 34.91; H, 9.71; N, 4.24; B, 38.11; S, 10.01.

(b) The tetramethylammonium salt of **1** (1 g, 3.1 mmol) was suspended under stirring in acetonitrile (250 mL) in a one-neck flask equipped with a dropping funnel. A solution of allyl bromide (1.5 mL, 2.1 g, 17.3 mmol) in acetonitrile (40 mL) was added dropwise at room temperature over a period of 10 min to the reaction mixture. After 24 h the solvent was removed under vacuum and the obtained solid was redissolved in acetonitrile. The inorganic salts that precipitated were removed, and the product was precipitated with ether. The solid was filtered off and recrystallized from water to obtain 400 mg (1.21 mmol, 39.2%) of pale yellow cross-shaped crystals of **2**.

Table I. Derivatives Prepared

$B_{12}H_{11}SRR'^-$

	R	R′		R	R′
2	$-CH_2CH{=}CH_2$	=R	**5**	$-CH_2CH_2CN$	$-CH_2CH_2OCH{=}CH_2$
3	$-CH_2CH_2CN$	=R	**6**	$-CH_2CH_2CH_2CH_2-$	(cyclic)
4	$-CH_2CN$	=R			

$B_{12}H_{12}SR^{2-}$

	R		R
7	$-CH_2CN$	**10**	$-CH(CH_3)_2$
8	$-CH_2CH_2CN$	**11**	$-COCH_3$
9	$-CH_2CH_2OCH{=}CH_2$	**12**	$-COC_6H_5$

$[(NCCH_2CH_2)_2SB_{12}H_{11}][N(CH_3)_4]$ (3). This compound was prepared from β-bromopropionitrile analogously to **2** (preparation a), using 80% acetonitrile/20% water as reaction solvent, in which the thiolate anion of **1** is completely soluble. Yield: 830 mg (2.3 mmol, 78%) of colorless crystals, mp 250 °C dec. ^{1}H-NMR (360 MHz, CD_3CN, 25 °C): 3.38 and 2.98 (ABX$_2$, –SCH_2– and –CH_2CN), 3.08 (s, –NCH_3), 0.5–2.0 (mult, broad, $B_{12}H_{11}$). IR (KBr): 3032, 2998, 2959, 2929, 2500, 2250, 1484, 1423, 1327, 1285, 1255, 1226, 1068, 1045, 968, 949, 825, 741, 718 cm^{-1}. Anal. Calcd for $C_{10}H_{31}N_3B_{12}S$: C, 33.82; H, 8.80; N, 11.83; B, 36.53; S, 9.03. Found: C, 33.60; H, 8.64; N, 11.93; B, 36.25; S, 8.85.

$[(NCCH_2)_2SB_{12}H_{11}][N(CH_3)_4]$ (4). This compound was prepared from α-bromoacetonitrile analogously to **2** (preparation a). It was identified by ^{1}H-NMR and ^{13}C-NMR. Yield: 600 mg (1.8 mmol, 63%) of pale yellow crystals, mp 200 °C dec. HPLC showed the presence of residual amounts of **1** and **7**. ^{1}H-NMR (360 MHz, CD_3CN, 25 °C): 4.17 (AB, –CH_2CN), 3.08 (s, –NCH_3), 0.5–2.1 (mult, broad, $B_{12}H_{11}$). IR (KBr): 3030, 2970, 2920, 2526, 2257, 1483, 1400, 1390, 1284, 1243, 1226, 1170, 1143, 1060, 1043, 950, 913, 818, 721, 689, 503 cm^{-1}.[6]

$CH_2{=}CHOCH_2CH_2I$ (2-Iodoethyl Vinyl Ether). This compound was prepared from commercially available 2-chloroethyl vinyl ether by a Finkelstein reaction: A 10-mL (10-mmol) portion of 2-chloroethyl vinyl ether was added dropwise to 50 mL of a saturated solution of sodium iodide in dry acetone. After 24 h of stirring at 60 °C, the acetone was evaporated and the resulting slurry was eluted with 100 mL of dry diethyl ether. After evaporation of the solvent, the 2-iodoethyl vinyl ether was purified by fractional destillation in vacuo (15 hPa). Yield: 12 g (58%, 5.8 mmol) of colorless liquid, bp 50 °C (15 hPa). ^{1}H-NMR (360 MHz, CD_3CN, 25 °C): 6.47 (dd, $H_2C{=}CHO$–), 4.21 (dd, $=CH_{cis}H_{trans}$),

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(6) Compounds **4**, **7**, **6**, and **10** were identified through their NMR, IR, and mass spectra.

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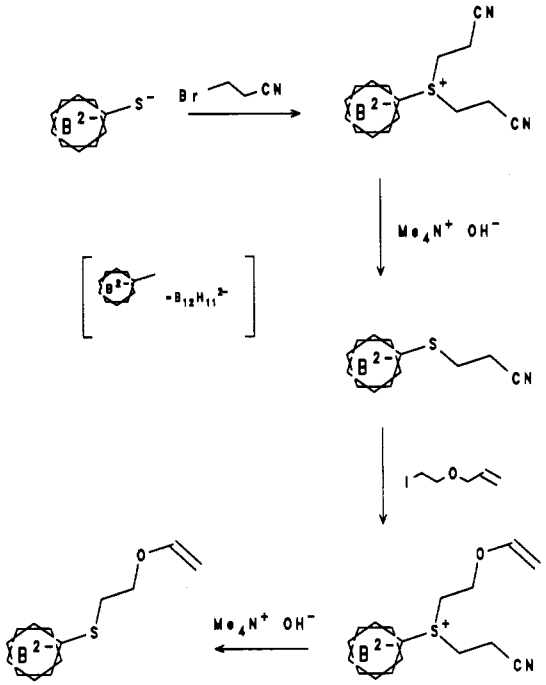
Scheme I. Reaction Sequence Leading to **9**



4.02 (dd, $=CH_{cis}H_{trans}$), 3.94 (t, $-OCH_2-$), 3.36 (t, ICH_2-). Anal. Calcd for C_4H_7IO: C, 24.26; H, 3.56; O, 8.08, I, 64.09. Found: C, 24.33; H, 3.50; O, 7.94; I, 63.95. The product can be stored in the refrigerator for several weeks without decomposition.

$[(NCCH_2CH_2)(CH_2{=}CHOCH_2CH_2)SB_{12}H_{11}][N(CH_3)_4]$ (5). This compound was prepared from **8** analogously to **2** (preparation a), using 2-iodoethyl vinyl ether as the halide source. The reaction solvent was 80% acetonitrile/20% water as described for **3**. Yield: 850 mg (2.3 mmol, 78%) of pale yellow crystals, mp 200 °C dec. ^{1}H-NMR (360 MHz, CD_3CN, 25 °C): 6.49 (dd, $-OCH{=}CH_2$), 4.38 (dd, $=CH_{cis}H_{trans}$), 4.10 (dd, $=CH_{cis}H_{trans}$), 4.10 (ABX_2, $-OCH_2-$), 3.46 and 3.24 (ABX$_2$, $-OCH_2CH_2-$), 3.30 (ABX$_2$, $NCCH_2CH_2-$), 3.08 (s, $-NCH_3$), 2.96 (ABX_2, $NCCH_2-$), 0.5–2.0 (mult, broad, $B_{12}H_{11}$). IR (KBr): 3031, 2995, 2963, 2927, 2497, 2253, 1618, 1483, 1420, 1324, 1286, 1210, 1193, 1072, 1045, 1017, 966, 947, 823, 723, 665 cm^{-1}. Anal. Calcd for $C_{11}H_{34}ON_2B_{12}S$: C, 35.5; H, 9.21; O, 4.28; N, 7.53; B, 34.86; S, 8.62. Found: C, 35.43; H, 9.05; N, 7.34; B, 34.70; S, 8.51.

$[(CH_2)_4SB_{12}H_{11}][N(CH_3)_4]$ (6). This compound was prepared analogously to **2** (preparation a), using 1,4-dibromobutane as the halide source. Yield: 800 mg (2.5 mmol, 85%) of white crystals, mp >340 °C dec. ^{1}H-NMR (360 MHz, CD_3CN, 25 °C): 3.23 (mult, $-SCH_2-$), 3.06 (s, $-NCH_3$), 2.08 (mult, $-SCH_2CH_2-$), 0.5–2.0 (mult, broad, $B_{12}H_{11}$). IR (KBr): 3029, 2945, 2497, 1482, 1420, 947, 824, 720 cm^{-1}.

$[NCCH_2SB_{12}H_{11}][N(CH_3)_4]_2$ (7). (a) This compound was prepared analogously to **2** (preparation a). The bromoacetonitrile solution (equimolar) was added dropwise and very slowly to the reaction mixture. The reaction process was monitored by HPLC. Addition of the nitrile was stopped when the peak for **1** had disappeared. The reaction mixture was refluxed for 1 h, and the solvent was then removed under vacuum. The residue was suspended in acetonitrile, and NaBr was filtered off. After evaporation of acetonitrile, the residue was recrystallized once from acetone (in which the sulfonium salt impurities have higher solubility) and once from water. The compound was identified by ^{1}H-NMR and ^{13}C-NMR. Yield: 450 mg (1.2 mmol, 43%) of pale green crystals, mp 260 °C HPLC showed the presence of residual amounts of **1** and **4**. ^{1}H-NMR (360 MHz, CD_3CN, 25 °C): 3.19 (s, broad, $-CH_2CN$), 3.08 (s, $-NCH_3$), 0.3–1.9 (mult, broad, $B_{12}H_{11}$). ^{13}C-NMR (DEPT, 90.556 MHz, CD_3CN, 25 °C): 121 (s, $-CN$), 54.5 (qua, $-CH_3$), 16.5 (t, $-CH_2-$). IR (KBr): 3029, 2980, 2955, 2884, 2828, 2486, 2236, 1483, 1394, 1281, 1133, 1060, 1047, 968, 947, 834, 717 cm^{-1}.

(b) **7** could also be identified in a syn-proportionation reaction from equimolar amounts of **1** (as its tris(tetramethylammonium) thiolate salt) and **4**. The reaction solvent was 80% acetonitrile/20% water. The suspension was refluxed for 24 h. The presence of **7** was deduced from the appearance of the appropriate HPLC peak and the disappearance of the peak for **1**.

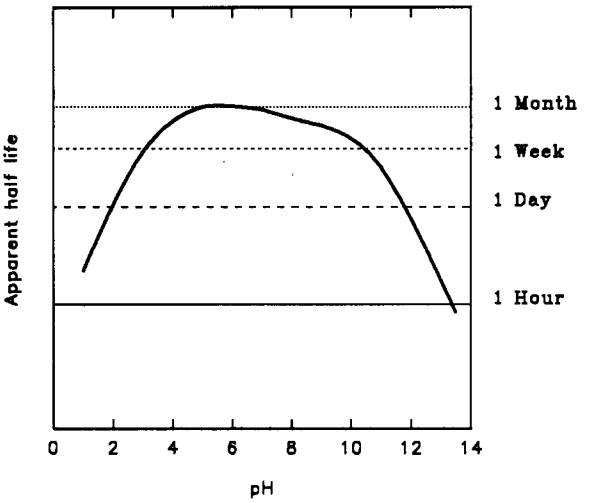


Figure 1. Apparent half-life of **11** in aqueous buffers of different pHs.

$[NCCH_2CH_2SB_{12}H_{11}][N(CH_3)_4]_2$ (8). A 1-g (2.8-mmol) sample of **3** was dissolved in the minimal amount of acetone at room temperature (ca. 100 mL). Tetramethylammonium hydroxide as a 20% solution in methanol was added in equimolar amounts. Compound **8** precipitated, was filtered off, and was recrystallized once from water. Yield: 950 mg (2.5 mmol, 90%) of colorless crystals, mp 285 °C dec. ^{1}H-NMR (360.1 MHz, DMSO-d_6, 25 °C): 3.08 (s, $-NCH_3$), 2.63 (td, $-CH_2CN$), 2.44 (t, broad, $-SCH_2-$), 0.2–1.8 (mult, broad, $B_{12}H_{11}$). IR (KBr): 3026, 2920, 2880, 2483, 2243, 1712, 1486, 1417, 1357, 1287, 1221, 1048, 949, 841, 720 cm^{-1}. Anal. Calcd for $C_{11}H_{39}N_3B_{12}S$: C, 35.21; H, 10.48; N, 11.19; B, 34.57; S, 8.55. Found: C, 35.29; H, 10.32; N, 10.99; B, 34.42; S, 8.36.

$[(CH_2{=}CHOCH_2CH_2)SB_{12}H_{11}][N(CH_3)_4]_2$ (9). This compound was prepared from **5** analogously to **8**. Yield: 950 mg (90%, 2.42 mmol) of colorless crystals, mp 245 °C dec. ^{1}H-NMR (360 MHz, CD_3CN, 25 °C): 6.46 (dd, $-OCH{=}CH_2$), 4.15 (dd, $=CH_{cis}H_{trans}$), 3.89 (dd, $=CH_{cis}H_{trans}$), 3.77 (t, $-OCH_2-$), 3.10 (s, $-NCH_3$), 2.57 (s, broad, $-SCH_2-$), 0.3–1.9 (mult, broad, $B_{12}H_{11}$). IR (KBr): 3026, 2968, 2926, 2862, 2482, 2362, 1616, 1486, 1320, 1286, 1205, 1048, 968, 960, 843, 823, 720 cm^{-1}. Anal. Calcd for $C_{12}H_{42}ON_2B_{12}S$: C, 36.74; H, 10.79; O, 4.08; N, 7.14; B, 33.07; S, 8.17. Found: C, 36.76; H, 10.59; N, 7.10; B, 32.93; S, 8.11.

$[(CH_3)_2CHSB_{12}H_{11}][N(CH_3)_4]$ (10). This compound was prepared analogously to **2** (preparation a), using 2-iodopropane as the halide source. ^{1}H-NMR showed the presence of small amounts (<5%) of the corresponding sulfonium salt. Yield: 850 mg (2.5 mmol, 85%). Mp: 250 °C dec. ^{1}H-NMR (360 MHz, CD_3CN, 25 °C): 3.50 (sep, $-SCH{=}$), 3.08 (s, $-NCH_3$), 1.48 (d, $=CHCH_3$), 0.4–2.1 (mult, broad, $B_{12}H_{11}$). IR (KBr): 3029, 2974, 2927, 2890, 2497, 1485, 1389, 1371, 1244, 1160, 1045, 948, 815, 720 cm^{-1}.

$[CH_3COSB_{12}H_{11}][N(CH_3)_4]_2$ (11). The tetramethylammonium salt of **1** (1 g, 3.1 mmol) was dissolved in acetonitrile (40 mL), and pyridine (4 mL, 50 mmol) was added. Then acetyl chloride (2 mL, 28 mmol) was added dropwise with ice-cooling. After 30 min of stirring at room temperature, the solvent was removed under vacuum. The obtained solid was dissolved in acetonitrile, precipitated with ether, and recrystallized from water to obtain white crystals of **11**. Yield: 1.09 g (2.99 mmol, 96.5%) of white crystals, mp 261 °C dec. ^{1}H-NMR (360 MHz, DMSO-d_6, 25 °C, TMS): 3.08 (s, $-NCH_3$), 2.34 (s, $-C(O)CH_3$), 0–2 (mult, broad, $B_{12}H_{11}$). IR (KBr): 3600, 3500–3400, 3020, 2950, 2900, 2480, 1990, 1650, 1480, 1450, 1420, 1350, 1280, 1110, 1050, 950, 840, 810, 720 cm^{-1}. Anal. Calcd for $C_{10}H_{38}B_{12}N_2OS$: C, 32.98; H, 10.52; N, 7.69; B, 35.63; O, 4.39; S, 8.8. Found: C, 32.85; H, 10.32; N, 7.58; B, 35.58; S, 8.69.

$[C_6H_5COSB_{12}H_{11}][N(CH_3)_4]_2$ (12). This compound was prepared analogously to **11**. Yield: 1.05 g (2.46 mmol, 79.5%) of white crystals, mp 312 °C dec. ^{1}H-NMR (360 MHz, DMSO-d_6, 25 °C, TMS): 7.85 (Ph $H_{2,6}$), 7.4 (Ph $H_{3,4,5}$), 3.1 (s, $-NH_3$), 0–2 (mult, broad, $B_{12}H_{11}$). IR (KBr): 3600, 3500–3400, 3020, 2950, 2900, 2480, 2000, 1650, 1580, 1480, 1450, 1420, 1310, 1280, 1200, 1170, 1050, 950, 910, 840, 820, 780, 720, 700 cm^{-1}. Anal. Calcd for $C_{15}H_{40}B_{12}N_2OS$: C, 42.26; H, 9.46; N, 6.57; B, 30.43; O, 3.75; S, 7.52. Found: C, 42.05; H, 9.32; N, 6.43; B, 30.26; S, 7.51.

Determination of the pK_a Value of $Cs_2B_{12}H_{11}SH$. A photometric method was used: The thiolate anion of **1** shows an ultraviolet absorption maximum at 247 nm ($\epsilon \approx 22\,000$). In this range ϵ for **1** is about 200. Therefore, the increase of absorbance was followed at 247 nm while a 10 mM solution of **1** with was titrated 10 M NaOH. By graphical analysis, an estimate of 13.4 for the pK_a was obtained. In a potentiometric titration of a solution of **1**, no pK_a between 2 and 12 was found.

Results and Discussion

Alkylation of **1** with most of the halides investigated invariably led to simultaneous appearance of mono- and bisalkylated products, often in the continued presence of unreacted thiol. With an excess of halide, bisalkylated sulfonium salts are obtained as a rule. The results reported by Nagasawa and Narisada[5] could not be reproduced. Invariably, S,S-disubstituted derivatives of $B_{12}H_{11}SH^{2-}$ were obtained with primary halides. Only with sterically hindered halides such as 2-iodopropane could the monoalkylated compound be obtained as the major product. Reaction rates varied considerably; thus, for **2** the reaction was complete within a few hours, whereas the formation of **3** was complete only after longer reaction times.

The appearance of the bisalkylated products could not be prevented by the use of the thiolate anion instead of the SH compound. This may be explained by the unusually high pK_a value of 13.4 for the SH group in **1**.

It was found that acetonitrile, sometimes with the addition of water, was a more suitable solvent for the alkylation than DMSO, previously used by Nagasawa and Narisada.[5] A suitable counterion for the negative charges was found to be the tetramethylammonium cation.

For some of the derivatives where no unreacted thiol was present (such as in the reaction mixture with cyanomethyl substituents), it was possible to separate the thioether from the sulfonium salt present, because of the higher solubility of the latter in acetone or acetonitrile.

The obtained sulfonium salts could, as a rule, not alkylate amines (reacting to form the corresponding thioethers) under conditions in which the carbon-centered sulfonium salts would. Only with the bis(cyanomethyl) and bis(cyanoethyl) derivatives, **3** and **4**, was removal of one of the substituents observed upon incubation with ethanolamine at room temperature. (This reaction was carried out in order to produce Δ2-oxazolines.) Here, also, a syn-proportionation to **7** was observed upon incubation of **1** and **4**.

With a strong base, such as tetramethylammonium hydroxide in acetone or acetonitrile, the bis(cyanoethyl) and bis(cyanomethyl) derivatives could be converted to the monosubstituted derivatives. For the bis(allyl) derivative, HPLC analysis showed that one of the substituents on the sulfur could be removed. Such reactions could possibly proceed in analogy to a Hofmann type degradation of quarternary ammonium salts. To this end, **6** was synthesized. Its Hofmann degradation should result in Δ3-butenyl-substituted $B_{12}H_{11}SH^{2-}$. However, the S-borylated tetrahydrothiophene derivative **6** did not undergo ring opening with tetramethylammonium hydroxide at room temperature. This could be due to the thermodynamic stability of the ring. However, in Hofmann eliminations of quarternay ammonium salts, five- and six-membered rings usually can be opened with ease.

The observed dealkylation of **2**–**4** could be explained by the α-CH acidity of the cyanoethyl group (with acrylonitrile the as leaving group), the relative electrophilicity of the α-carbon of the cyanomethyl group, and the higher reactivity of allyl derivatives (including S_N2' reactions) under conditions of nucleophilic substitution. Conventional elimination of the Hofmann type appears not to occur with these sulfonium salts.

It was found that the cyanoethyl group could be used as a convenient protective group for the sulfur of $B_{12}H_{11}SH^{2-}$. This is illustrated by the reaction of **3** to form **8**, and then further to form **5** and then **9**, resulting in a monosubstituted derivative. The overall yield from **1** (with purification of each intermediate) is 50%, which is acceptable for preparative purposes even with boron-10-enriched material. The cyanoethyl group has been utilized widely as a protecting group for phosphate esters, notably in oligonucleotide synthesis.[7]

The thioesters of **1** with carboxylic acids (compounds **11** and **12**) were found to be surprisingly stable against hydrolysis, with pseudo-first-order reaction rate constants similar to or smaller than those of organic esters. The thioester linkage between **1** and the carboxylate group could therefore be utilized in the preparation of water-stable derivatives for BNCT.

The *S*,*S*-dimethyl derivative of $B_{12}H_{11}SH^{2-}$ has been described before.[8] It was, however, obtained by a different route, in which the dimethylated sulfur was preformed and then incorporated into the molecule. Interestingly, Khan et al.[9] have described permethylation of sulfur in the isostructural $B_{11}CH_{12}^-$ cage under conditions similar to the ones employed here. Also for the sulfur-substituted *closo*-$B_{10}H_{10}^{2-}$ cage, alkylation to stable sulfonium salts has been described.[10]

In summary, the chemical properties of the sulfhydryl group of $B_{12}H_{11}SH^{2-}$ are different from those of organic thiols. The thioethers are readily alkylated to yield stable sulfonium salts. Only with a strong base and for selected organic groups can the sulfonium salts be converted to thioethers. Thioesters are stable enough to be used under physiological conditions without undue hydrolysis. These properties might be attributed to the strong electron-withdrawing character of the borate cage. Nevertheless, Alam et al.[11] observed that $B_{12}H_{11}SH^{2-}$ reacted with *N*-succinimidoyl 3-(2-pyridyldithio)propionate to form a disulfide-linked derivative, as commonly occurs with organic thiols.

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