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Synthesis of Alkoxy Derivatives of Dodecahydro-*closo*-dodecaborate Anion $[B_{12}H_{12}]^{2-}$

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Abstract

Dodecahydro-*closo*-dodecaborate anion $[B_{12}H_{12}]^{2-}$ is a stable non-toxic highly water-soluble boron-rich compound. Functionalized derivatives of this compound are of high interest as BNCT agents. There are however very few routes for the functionalizing of the cage. The present contribution describes a way to overcome this problem and to attach $[B_{12}H_{12}]^{2-}$ to organic molecules including biomolecules.A number of alkoxy derivatives of dodecahydro-*closo*-dodecaborate anion $[B_{12}H_{11}OR]^{2-}$ (R = Et, i-Pr, $C_{16}H_{33}$, allyl, benzyl, p-$CH_2C_6H_4CN$, p-$CH_2C_6H_4NO_2$, p-$CH_2CH_2C_6H_4NO_2$, and $CH_2CH_2N(CO)_2C_6H_4$) were prepared by the reaction of $(Bu_4N)_2[B_{12}H_{11}OH]$ with the corresponding alkyl bromides or iodides in acetone in the presence of K_2CO_3.

Keywords: Alkylation; Boron and compounds; Synthesis.

The increased current interest in the chemistry of the boron-rich dodecahydro-*closo*-dodecaborate anion $[B_{12}H_{12}]^{2-}$ (**1**) is due to the fast development of Boron Neutron Capture Therapy, which is a binary method for treatment of cancer in which a boron-containing substance is preferentially deposited in the tumour prior to irradiation by low energy neutrons. The interaction of the ^{10}B atom with a thermal neutron produces strongly cell-toxic ^4He and ^7Li, which destroy tumour cells [1,2]. Recently we developed a high-yield preparative method for

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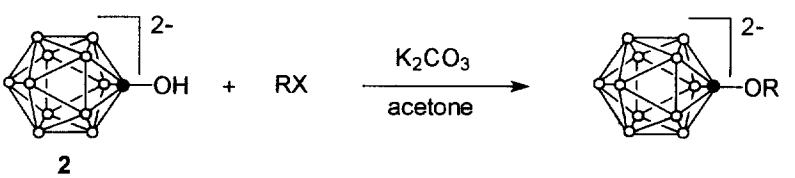
synthesis of the $[B_{12}H_{11}OH]^{2-}$ (**2**) anion *via* the 1-methyl-1-pyrrolinio-2-yloxy derivative of **1** [3], which opens the possibility for synthesis of water-soluble boron-rich tumour-seeking agents.

The preparation of ethoxy- and benzyloxy- derivatives of **1** by alkylation of **2** was reported recently [4]. However, the use of the strong basic conditions (5-fold excess of KOH in DMSO in combination with heating at 60°C during the work-up stage) prompted us to study other conditions to alkylate **2**. We found that gentle heating of a solution of $(Bu_4N)_2[B_{12}H_{11}OH]$ in acetone with an equimolar amount of alkylating agent in the presence of K_2CO_3 resulted in the formation of the corresponding alkoxy derivatives (Scheme 1).

In a typical experiment, 1.4 g (10 mmol) of K_2CO_3 and 2.75 mmol of the corresponding alkyl halide [ethyl iodide, isopropyl iodide, 1-bromohexadecane, allyl bromide, benzyl bromide, 4-cyano-benzylbromide, 4-nitrobenzylbromide, 4-nitrophenethylbromide, N-(2-bromoethyl)-phthalimide] were added to a solution of 1.6 g (2.5 mmol) of $(Bu_4N)_2[B_{12}H_{11}OH]$ in 50 ml acetone, and the reaction mixture was heated with stirring at 40-45°C for 12-14 h.



2

o = BH

● = B

X = Br, I

$R = C_2H_5$	**3** (41%)
$R = CH(CH_3)_2$	**4** (63%)
$R = (CH_2)_{15}CH_3$	**5** (47%)
$R = CH_2CH{=}CH_2$	**6** (58 %)
$R = CH_2C_6H_5$	**7** (67%)
$R = p\text{-}CH_2C_6H_4CN$	**8** (64%)
$R = p\text{-}CH_2C_6H_4NO_2$	**9** (70%)
$R = p\text{-}CH_2CH_2C_6H_4NO_2$	**10** (66%)
$R = p\text{-}CH_2CH_2N(CO)_2C_6H_4$	**11** (68%)

Scheme 1

The reaction mixture was then cooled to room temperature and filtered. The compounds **3**[1] and **4**[2] were isolated as caesium salts by addition of CsF in methanol to the filtrate followed by the

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[1] ^{11}B NMR data (Bruker ACP-200, $BF_3{*}Et_2O$ as an external standard) for **3** differ from that reported in [4] and are practically the same as those described by Preetz and Haeckel [5].

recrystallization of the precipitates obtained from water. Compound **5**[3] was isolated as a tetramethylammonium salt by the addition of solution of Me_4NCl in aqueous methanol. Compound **6**[4] was isolated as a tetraphenylphosphonium salt by precipitation with CsF followed by reprecipitation with Ph_4PCl from water. The aromatic compounds **7**[5], **8**[6], and **9**[7] were isolated as tetrabutylammonium salts by the addition of CsF in methanol to the filtrate followed by reprecipitation with Bu_4NBr from water. Compounds **10**[8] and **11**[9] were isolated as caesium salts by addition of CsF in methanol and recrystallization from water. The yields of the compounds were in the range of 40-70 %.

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2 ^{1}H NMR (DMSO-d_6): 3.74 (1H, m, -OC*H*$(CH_3)_2$), 0.93 (6H, d, J = 6 Hz, -OCH(CH_3)$_2$). ^{11}B NMR (DMSO-d_6): 4.6 (1B, s), -16.2 (5B, d, J = 150 Hz), -18.6 (5B, d, J = 138 Hz), -24.6 (1B, d , J = 129 Hz).

3 ^{1}H NMR (DMSO-d_6): 3.20 (2H, m, -OC$H_2$$(CH_2)_{14}CH_3$), 1.30-1.10 (28H, m, -OCH$_2$(CH_2)$_{14}$$CH_3$), 0.78 (3H, t, -OCH$_2$$(CH_2)_{14}$$CH_3$). ^{11}B NMR (DMSO-$d_6$): 7.2 (1B, s), -16.3 (5B, d), -17.7 (5B, d), -22.3 (1B, s).

4 ^{1}H NMR (DMSO-d_6): 5.85 (1H, m, -OCH$_2$$CH$=CH$_2$), 4.98-4.77 (2H, dd, -OCH$_2$CH=CH_2), 3.78 (2H, s, -OCH_2CH=CH$_2$). ^{13}C NMR (DMSO-d_6): 143.1 (-OCH$_2$(CH=CH$_2$), 113.2 (-OCH$_2$CH=(CH_2), 71.5 (-O(CH_2CH=CH$_2$).

5 ^{11}B NMR data for 7 differ from that reported in [4] and are the following (DMSO-d_6) 6.8 (1B, s), -16.5 (5B, d), -18.0 (5B, d), -22.8 (1B, d).

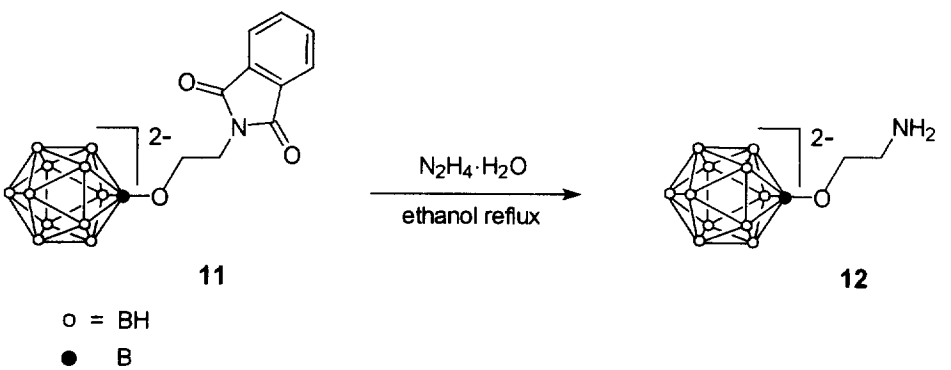
6 ^{1}H NMR (DMSO-d_6):7.68 (2H, d, J = 8.2 Hz, Ar-*H*), 7.48 (2H, d, J = 8.2 Hz, Ar-*H*), 4.49 (2H, s, OCH_2). ^{13}C NMR (DMSO-d_6): 153.1 (aromatic), 133.2 (aromatic), 128.8 (aromatic), 121.3 (CN), 109.8 (aromatic), 71.4 (CH_2). IR (Nujol):). IR (Nujol): 2469 (ν_{BH}), 2231 (ν_{CN}), 1609 ($\nu_{CC(Ar)}$), 1062 (ν_{BB}), 1040 (ν_{BB}), 1019 (ν_{BB}), 722 (ν_{BB}).

7 ^{1}H NMR (MeOH-d_4): 8.11 (2H, d, J = 8.8 Hz, Ar-*H*), 7.65 (2H, d, J = 8.8 Hz, Ar-*H*), 4.82 (2H, s, OCH_2). ^{13}C NMR (MeOH-d_4): 155.6 (aromatic), 149.5 (aromatic), 130.3 (aromatic), 125.5 (aromatic), 73.2 (CH_2). ^{11}B NMR (DMSO-d_6): 7.5 (1B, s), -16.3 (5B, d), -17.9 (5B, d), -22.8 (1B, d). IR (Nujol): 2468 (ν_{BH}), 1599 ($\nu_{CC(Ar)}$), 1519 (ν^a_{NO2}), 1343 (ν^s_{NO2}), 1070 (ν_{BB}), 1044 (ν_{BB}), 1013 (ν_{BB}), 721 (ν_{BB}).

8 ^{1}H NMR (DMSO-d_6): 8.11 (2H, d, J = 8.6 Hz, Ar-*H*), 7.51 (2H, d, J = 8.6 Hz, Ar-*H*), 3.52 (2H, t, J = 6.9 Hz, -OCH_2CH$_2$Ar), 2.84 (2H, t, J = 6.9 Hz, -OCH$_2$CH_2Ar). ^{13}C NMR (DMSO-d_6): 151.9 (aromatic), 147.3 (aromatic), 131.9 (aromatic), 124.7 (aromatic), 70.4 (-OCH$_2$CH$_2$Ar), 39.6 (-OCH$_2$CH$_2$Ar). IR (Nujol): 2469 (ν_{BH}), 1606 ($\nu_{CC(Ar)}$), 1517 (ν^a_{NO2}), 1348 (ν^s_{NO2}), 1062 (ν_{BB}), 1014 (ν_{BB}), 724 (ν_{BB}).

9 ^{1}H NMR (DMSO-d_6): 7.84 (4H, m, Ar-*H*), 3.57 (2H, t, J = 6.7 Hz, -OCH_2CH$_2$N-), 3.38 (2H, t, J = 6.7 Hz, -OCH$_2$CH_2N-). ^{13}C NMR (DMSO-d_6): 169.8 (C=O), 136.1 (aromatic), 133.5 (aromatic), 124.7 (aromatic), 67.1 (-OCH$_2$CH$_2$N-). ^{11}B NMR (DMSO-d_6): 6.3 (1B, s), -16.9 (5B, d) -18.2 (5B, d), -23.0 (1B, s). IR (Nujol): 2478 (ν_{BH}), 1771 ($\nu_{C=O}$), 1706 ($\nu_{C=O}$), 1059 (ν_{BB}), 1032 (ν_{BB}), 1014 (ν_{BB}), 725 (ν_{BB}).

The compounds prepared can be used for subsequent synthesis of functionalized derivatives of dodecahydro-*closo*-dodecaborate anion for BNCT. For example, treatment of the tetrabutylammonium salt of **11** with hydrazine hydrate in refluxing ethanol results in the formation of the amine **12**[10] which was isolated as a water-soluble caesium salt in 86 % yield (Scheme 2).



Scheme 2

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[10] ^{1}H NMR (D_2O): 3.67 (2H, t, J = 5.6 Hz, -OC*H*$_2$CH$_2$NH$_2$), 2.96 (2H, t, J = 5.6 Hz, -OCH$_2$C*H*$_2$NH$_2$). ^{13}C NMR (D_2O): 67.2 (-O*C*H$_2$CH$_2$NH$_2$), 41.2 (-OCH$_2$*C*H$_2$NH$_2$). IR (Nujol): 3368 (ν_{NH}), 3230 (ν_{NH}), 2478 (ν_{BH}), 1611 (δ_{NH}), 1063 (ν_{BB}), 1039 (ν_{BB}), 1015 (ν_{BB}), 723 (ν_{BB}).