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Polyols of a Cascade Type as a Water-Solubilizing Element of Carborane Derivatives for Boron Neutron Capture Therapy

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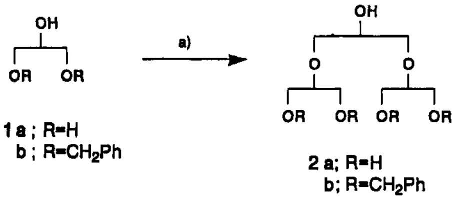
Summary: A practical method for the synthesis of polyols of a cascade type, as a water-solubilizing element of carborane derivatives for boron neutron capture therapy (BNCT), was developed. The carborane attached to the tetraol **6a** was dissolved in water in a concentration of 5.44 M.

Poor solubility in aqueous or biological media has been an obstacle to the effective delivery of potentially useful boron compounds to the tumor site. In the case of carboranes, conversion to the corresponding nido structures,[1] which may be isolated as sodium or potassium salts, has been used to prepare more soluble derivatives. However, a satisfactory level of solubility is not always achieved, and other sensitive groups in the molecule do not always survive the relatively severe reaction conditions for nido-structure formation. Furthermore, the stability of nido compounds in vivo is not well documented, and their ionic character suggests that interaction with reactive centers is highly probable. The nonpolar carboranes, on the other hand, are protected from such interactions to a large extent by the lipophilic character of the cage. There is, therefore, a need for nonionic water-soluble carborane derivatives that has generated increased interest in the synthesis of boron carriers to which carbohydrate or other polar, hydrophilic, functional groups are attached. Such compounds include hydroxyalkylated carboranes,[2] glycosyl carboranes,[3] carboranyl porphyrins,[4] and the carboranyl nucleoside derivatives or uridine, adenine, and guanine which are subunits of DNA.[5,6]

We report the synthesis of polyols of a cascade type as a new water-solubilizing element of carborane derivatives (Scheme I). *The cascade polyol has no asymmetric centers*, so that no diastereomers are formed when it is bonded to the C-terminal of *o*-carborane cages which may bear chiral or racemic biologically active molecules. This characteristic is very important for the synthesis of ^{10}B carriers. For example, chiral sugars are often used as a water solubilizing element, but diastereomers are produced if chiral or racemic carborane derivatives are bound.

To a vigorously stirred mixture of benzyl alcohol (1.0 mol), tetrabutylammonium iodide (0.05 mol), potassium hydroxide (0.75 mol), and water (3 mL) was added epichlorohydrin (0.25 mol) in portions and the mixture was heated for 40 h at 60–70 °C. The usual workup followed by purification by silica-gel column chromatography gave **1b** in 88% yield (0.219 mol) along with recovered benzyl alcohol (0.494 mol, 99%). A similar reaction of epichlorohydrin with **1b** gave **2b** in 88% along with **1b** recovered (99%). A higher homologue will be obtained by the repeated use of this ring-opening and substitution method. Removal of the benzyl group of **1b** and **2b** was accomplished using Pd(OH)$_2$ on charcoal to give **1a** and **2a**, respectively, but normally the debenzylation was carried out with the carborane bound polyol derivatives.

Scheme I. Synthesis of Polyols of a Cascade Type[a]

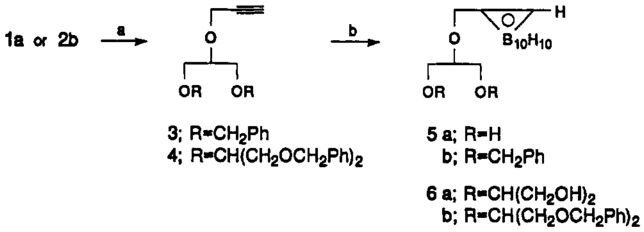


1a; R=H
b; R=CH$_2$Ph

2a; R=H
b; R=CH$_2$Ph

[a] Key: (a) epichlorohydrin, Bu$_4$NI, KOH, H$_2$O.

Scheme II. Synthesis of Water Soluble *o*-Carboranes[a]



3; R=CH$_2$Ph
4; R=CH(CH$_2$OCH$_2$Ph)$_2$

5a; R=H
b; R=CH$_2$Ph

6a; R=CH(CH$_2$OH)$_2$
b; R=CH(CH$_2$OCH$_2$Ph)$_2$

[a] Key: (a) propargyl bromide, NaH, DMF. (b) B$_{10}$H$_{14}$, CH$_3$CN, toluene.

The reaction of propargyl bromide with **1b** gave **3** in 67% yield, which was converted to **5b** in 48% yield upon treatment with decaborane. Hydrogenation of **5b** in the presence of Pd(OH)$_2$ on charcoal in acidic ethanol produced **5a** in 52% yield. Similarly, **2b** was converted to **4** in 55% yield, and subsequent hydroboration with decarborane produced **6b** in 47% yield. The hydrogenation afforded **6a** in 63% yield.

The solubility of **5a** and **6a** in water at room temperature (20 °C) was 0.67 mol/L and 5.44 mol/L, respectively. Precise solubility data of *o*-carborane derivatives previously prepared as ^{10}B carriers are not available. The solubility data of representative organic compounds or salts in water are following: DL-valine, 0.58 mol/L at 20 °C; sodium acetate·3H$_2$O, 3.30 mol/L at 20 °C; trichloroacetic acid, 5.65 mol/L at 25 °C.[7] Accordingly, it is now clear that the tetrol derivative **6a** is very soluble in water. We are in a position to use these cascade polyols as water-solubilizing elements not only for ^{10}B carriers but also for magnetic resonance imaging reagents such as certain porphyrins.

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Supplementary Material Available: Full characterization data for **1b**, **2b**, **3**, **4**, **5a,b**, and **6a,b**, along with the detailed synthetic procedures (12 pages). Ordering information is given on any current masthead page.

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