Review

The chemistry of the azanonaborane cluster $RNH_2-B_8H_{11}NHR$

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Dedicated to M. Frederick Hawthorne on the occasion of its 75th birthday

Abstract

The preparation and properties of the $R^1R^2NH-B_8H_{11}NHR$ cluster are described. The cluster is stable to aqueous solutions and can be made water-soluble by the introduction of a few hydrophilic groups. This makes the cluster a good candidate as the boron moiety in compounds for boron neutron capture therapy. The chemistry of the cluster preparation, the stability of the cluster, and conditions for reactions of the organic moieties are reviewed. Pyridine derivatives of the cluster show electronic interaction between the cluster and the pyridine.
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1. Introduction

Neutral polyhedral clusters containing boron are usually hydrophobic entities, and often are chemically labile. One of the exceptions to this is the $R^1R^2NH-B_8H_{11}NH-R$ cluster (Fig. 1), which has been described originally by Hawthorne and co-workers [1]. Its structure was determined by Lipscomb and co-workers [2].

The cluster might be considered a hypho cluster, based on the electron count when the bridging nitrogen is not taken into account. Due to this, one would expect the cluster to be highly reactive, and unstable especially toward water and other protic solvents. The cluster with R being an isopropyl group can, however, be recrystallized from water–ethanol mixtures. This fact indicates an unexpected stability of the cluster, probably unmatched by any other hypho cluster. It also indicates that the cluster is moderately water-soluble. The exploration of its chemistry, and the application especially in boron neutron capture therapy, is therefore worthwhile.

A general synthesis for the cluster with different amines has been worked out [3]. The cluster reacts with alkines to an N-bridge arachno 10-vertex species [4]. With $[RhCl_2(\eta^5-C_5Me_2]$, two rhodium atoms are incorporated into the cluster to a 10-vertex closo-type geometry.

Recently, the chemistry of this cluster has been investigated further. The reaction mechanism of its formation was elucidated, and the substitution and reactions of the organic substituents as well as its potential in boron neutron capture therapy (BNCT) and other applications have been investigated.

2. Formation of the cluster

The cluster is formed by the reaction of a primary amine with the $B_9H_{13}S(CH_3)_2$ cluster, which is obtained by the reaction of $B_{10}H_{12}[S(CH_3)_2]_2$ with methanol. The reaction was known to proceed step-wise, and the first amine, which replaces the dimethylsulfide ligand was known to end up as the bridging nitrogen in the cluster. The second amine occupies the exo position in the final cluster. The reaction requires a total of 3 mol of amine, two of which remain in the cluster, and the third is needed to form a BH_3–amine adduct. Sometimes, separation by chromatography of this adduct and the

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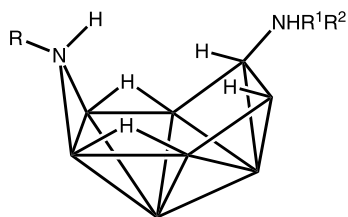*E-mail address:* gabel@chemie.uni-bremen.de (D. Gabel).

Fig. 1. Structure of the B_8N cluster. Every corner of the cluster represents one boron atom and one hydrogen atom (which are omitted for clarity reasons).

product was found to be difficult, and then the addition of acetone was helpful in destroying the BH_3 by oxidation.

The reaction of $B_9H_{13}S(CH_3)_2$ with aminoalcohols does not lead to pure products, probably due to side reactions of the hydroxyl group with the cluster. Protecting groups of the hydroxy function or their introduction through, e.g. hydroboration [5] after cluster formation are suitable alternatives.

In the process of formation of the cluster, the origin of the boron atom eliminated was of interest, as well as the way the remaining atoms rearrange. This was investigated by using decaborane(14) labelled at different positions with Br, D, and ethyl, and following the positions of the labels through the intermediate nonaborane cluster to the final product. These investigations showed that a firmly integrated boron atom, the boron atom 1 in the nonaborane cluster, leaves the cluster (Table 1).

Table 1
Nonaborane derivatives with B substituents and the position of the substituent in the azanonaborane cluster [6]

Substituent	Position in B_9 Cluster	Position in B_8N Cluster
Br	1	Missing
Ethyl	7	5
Ethyl	2	2
Br	2	2
Br	6	4
D	1, 2, 3, 7	2,5,7 or 2,4,6

A mechanism for the reaction has been proposed [6]. The experimental basis for the proposed mechanism is the fate of the boron atoms B^1, B^2, B^6, and B^7 (on the basis of the single label experiments) and B^3 (concluded from the tetradeuterated B_9 cluster) (see Fig. 2). The ethyl group in the final cluster is connected to B^6 (based on computed ^{11}B-NMR chemical shifts). The fate of the boron atoms B^5, B^8, and B^9 has not been clarified, but the proposed mechanism would require only a minimal rearrangement of the bonds (one DSD rearrangement and the closing of the cluster after the loss of B^1). The loss of B^1, which is *not* part of the open face, is surprising.

3. Stability and reactivity of the cluster

When the cluster is to be integrated into other organic moieties, the required reactions must be compatible with the stability of the cluster. We therefore investigated the reactivity toward a series of commonly employed reaction conditions. Acidic conditions lead to a loss of the cluster. Basic conditions (i.e. the presence of hydroxide ions or excess of amines) usually do not degrade the cluster. An exception is the reaction of $B_9H_{13}S(CH_3)_2$ with diaminoethane, which does not result in the formation of the RNH_2–$B_8H_{11}NHR$ cluster, but in gradual degradation. In the case of excess of amines other than the one which is bound in the exo position, exchange rections might occur.

Hydroboration reactions of organic groups attached to the cluster were found to proceed without problems [5]. The cluster itself has no potential for hydroboration.

The exo amine ligand can be replaced readily with other primary or secondary amines. Aliphatic amines can be replaced with pyridine derivatives [7,8]. When compounds containing two pyridine units are used, it is possible to isolate singly and doubly substituted products. The exchange reactions limit, to some extent, the possible reactions of these cluster compounds, when the original amino substituent is to be retained while reactions with other amines are intended.

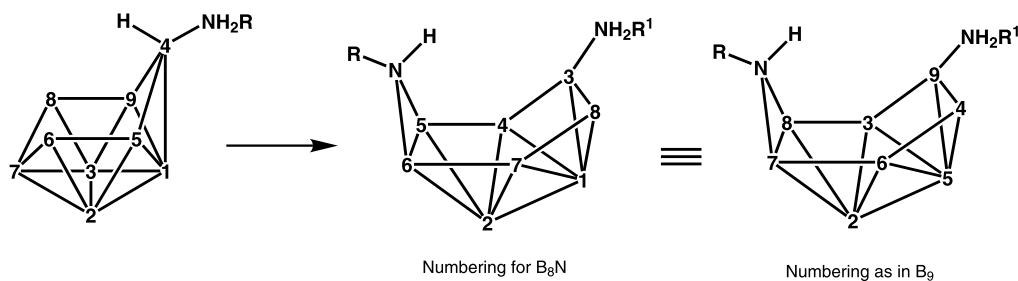The cluster can be halogenated at B^8 with elemental chlorine, bromine, or iodine [9]. Whereas the starting

Fig. 2. Rearrangement of the nonaborane cluster to the azanonaborane cluster. Only one of the two possible enantiomers of the azanonaborane cluster is shown. The numbering of the left and center structures is according to the IUPAC rules; the structure on the right is numbered according to the numbers the boron atoms had in the nonaborane structure.
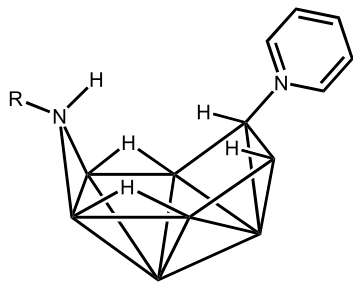
Fig. 3. Pyridine adducts of the $B_8H_{11}NH-R$ cluster.

Table 2
Solubility of hydroxypropyl derivatives in water [5]

R	R^1	R^2	Solubility in water
$-(CH_2)_3OH$	H	$-(CH_2)_3OH$	RT
$-(CH_2)_3OH$	$-(CH_2)_3OH$	$-(CH_2)_3OH$	RT
$-CH_3$	$-(CH_2)_3OH$	$-(CH_2)_3OH$	RT
$-(CH_2)_3OCH_3$	$-(CH_2)_3OH$	$-(CH_2)_3OH$	at 60 °C
$-CH_3$	H	$-(CH_2)_3OH$	No

For the position of the substituents, refer to Fig. 1.

compound is stable toward water, the presence of water leads to degradation of the halogenated cluster to a hypho–pentaborane system [9].

4. Electronic properties

The pyridine adducts of the cluster (see Fig. 3) are all colored compounds [7,8], in accord with similar observations with other substituted cluster compounds. The difference between the HOMO and LUMO energies, calculated with AM-1, agree well with the observed spectra.

When using *trans*-1,2-di-(4-pyridyl)-ethene, the resulting product containing only one cluster is a mixture of 30% cis and 70% trans, when the *trans*-ethene is used as starting material. This conversion occurred in the dark. Assuming that the mixture reflects the thermodynamic equilibrium, a considerable decrease of the difference in free energy between trans and cis must have occurred. When two clusters are attached to the ethene derivative, only trans is found.

The electronic interaction between the cluster and the pyridine unit might also be the reason why the reaction between *meso*-tetrakis-(3-pyridyl)-porphyrin and the cluster stops after one cluster is attached to the porphyrin [10].

5. Applications of the cluster

One obvious application for compounds containing the $RNH_2-B_8H_{11}NH-R$ cluster is boron neutron capture therapy, BNCT. For a review of the chemistry of BNCT, see Ref. [11]. For this application, the compounds must be sufficiently soluble in water to be transported with the blood stream to the target cells. As the cluster itself is hydrophilic, but not yet completely soluble in water, a systematic study was undertaken to determine the additional degree of hydrophilicity which must be introduced. It was found that two hydroxypropyl groups are sufficient for water solubility, when no other hydrophobic groups are present [5]. Equally, the presence of amino groups suffices for full water solubility at neutral pH values [12] (Table 2).

The toxicity of the cluster in vitro and in vivo is low, and the toxicity of a compound is governed mostly by its side chains [5,12].

The hydrophilic properties of the cluster, together with the electrical neutrality, distinguishes the RNH_2- $B_8H_{11}NH-R$ cluster from *o*-carboranes (which are neutral, but extremely hydrophobic) and from nido-*o*-carborane, $B_{12}H_{12}^{2-}$ [13] and $SnB_{11}H_{11}^{2-}$ [14], which are charged. It offers therefore an additional approach to the synthesis of water-soluble compounds for BNCT.

The strong electronic interaction of the cluster with N-heterocycles, together with the ease with which these compounds can be prepared, could make the cluster also a candidate for applications in, e.g. non-linear optics. For this application, the dicarba-*closo*-dodecaborane cluster has already been proposed [15].

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