FEATURE ARTICLE

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The versatile chemistry of the $[B_{20}H_{18}]^{2-}$ ions: novel reactions and structural motifs

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Among the polyhedral [*closo*-B_nH_n]$^{2-}$ ion series (n = 5–12 inclusive) the aromatic [*closo*-$B_{10}H_{10}$]$^{2-}$ ion is both readily available and quite reactive. Among its many reactions which retain its cage structure one finds the oxidative dimerization reaction in which two [*closo*-$B_{10}H_{12}$]$^{2-}$ ions each formally lose a hydride ion and undergo dimerization of the resulting [*closo*-$B_{10}H_9$]$^-$ ions to produce the [*trans*-$B_{20}H_{18}$]$^{2-}$ ion. The two-component [*closo*-$B_{10}H_9$]$^-$ ions of the latter are linked together by a pair of unique B–B–B bonds which provide unprecedented reactivity to the structure. Among these reactions are the two-electron reduction to a set of three interconvertible [$B_{20}H_{18}$]$^{4-}$ ions having intercage B–B bonds and the related reductive substitution reaction in which [*trans*-$B_{20}H_{18}$]$^{2-}$ undergoes attack by nucleophile, L, to produce [$B_{20}H_{18}L$]$^{2-}$. The latter species is formally a substituted [$B_{20}H_{19}$]$^{3-}$ (L = H) ion formed by B–B bond protonation of one of the isomeric [$B_{20}H_{18}$]$^{4-}$ ions. These and a variety of novel reactions are described here along with interrelated reaction mechanisms considered for the first time.

1 Introduction

The chemistry of boron resembles that of carbon as does no other element. Both boron and carbon possess the ability to bond with themselves (catenate) and to form families of binary hydrides (boranes and hydrocarbons, respectively). Hydrocarbons are broadly classified as aliphatic or, if stabilized by extensive electron delocalization, aromatic. Aliphatic and aromatic hydrocarbons display characteristic chemical properties and reactions such as free-radical and electrophilic substitution of hydrogen, respectively. Similarly, borane structures may be broadly classified as analogs of these two hydrocarbon types. The only boranes reported as late as 1959 were relatively unstable and they may now be retrospectively classified as 'aliphatic boranes'. Such species, originally discovered by Alfred Stock,[1] have hydrogen-rich, open and reactive structures exemplified by B_2H_6, B_4H_{10}, B_5H_9, B_6H_{10}, B_9H_{15}, $B_{10}H_{14}$, *etc*. These boranes are members of the nido and arachno structural categories.[2]

2 Aromatic polyhedral borane dianions and the discovery of [*trans*-$B_{20}H_{18}$]$^{2-}$(*trans*-1)

The discovery of the [*closo*-$B_{10}H_{10}$]$^{2-}$ ion[3,4] and the [*closo*-$B_{12}H_{12}$]$^{2-}$ ion[5] (Fig. 1) in 1959 and 1960, respectively, combined with theoretical investigations by Hoffman and Lipscomb[6] established aromatic polyhedral borane chemistry as a new field of chemistry.[7,8] Such species as these are now classified as *closo* based upon their n + 1 pairs of delocalized

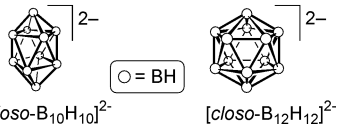

Fig. 1 Structures of aromatic polyhedral borane dianions.

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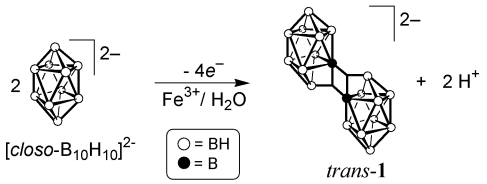
cage-bonding electrons, where n is the number of polyhedral vertices.[2] The [*closo*-$B_{10}H_{10}$]$^{2-}$ ion has the D_{4d} structure of a bicapped square antiprism. While the bonding in this closo dianion is delocalized and aromatic, [*closo*-$B_{10}H_{10}$]$^{2-}$ is more reactive than the icosahedral [*closo*-$B_{12}H_{12}$]$^{2-}$ in electrophilic substitution reactions[8] due to its reduced symmetry relative to that of the latter. This same difference in reactivities prevails when these two dianions are subjected to oxidation reactions with simple reagents such as Ce^{4+} or Fe^{3+} in aqueous acid solution; [*closo*-$B_{12}H_{12}$]$^{2-}$ is unreactive[9] while [*closo*-$B_{10}H_{10}$]$^{2-}$ undergoes[10–12] smooth oxidative conversion to [*trans*-$B_{20}H_{18}$]$^{2-}$, *trans*-**1**. This oxidative dimerization reaction proceeds in virtually quantitative yield with Fe^{3+} as the oxidant [Scheme 1 and eqn. (1)]. Note that it is the equatorial (*e*) boron



Scheme 1

$$2[\textit{closo}\text{-}B_{10}H_{10}]^{2-} \rightarrow [\textit{trans}\text{-}B_{20}H_{18}]^{2-} + 2H^+ + 4e^- \quad (1)$$

atom, shown by the filled circle in Scheme 1, that loses its terminal (exo) hydrogen atom during the oxidation, rather than the apical (*a*) boron atom. Electrochemical oxidation is facile and the mechanism of this coupling reaction has been studied by this means.[13]

The *trans*-**1** ion was discovered simultaneously at the Redstone Arsenal Research Division of the Rohm and Haas Company,[14] the Central Research Laboratory of E.I. du Pont Company[11] and by W. N. Lipscomb and coworkers in 1961.[10] This initial work was rapidly published and plagued by errors in structural assignments based upon limited information. The correct rationalization[15] of this early work was assisted by the correct structure of *trans*-**1** determined from ^{11}B NMR data and later confirmed by X-ray diffraction.[16] As required by considerations of electron and orbital balance, *trans*-**1** may be assembled by joining two [$B_{10}H_9$]$^-$ cage fragments with a pair of three-center bond interactions. These interactions proved to be of the B–B–B type,[15] although B–H–B could not be ruled out *a priori*.[10] The unique chemical and physical properties of [*trans*-$B_{20}H_{18}$]$^{2-}$ are explained by its very electron-deficient double three-center bond array.

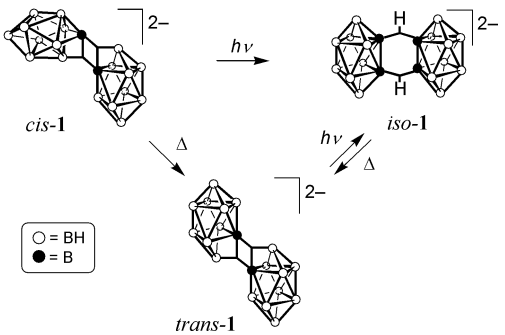
The oxidation of [*closo*-$B_{10}H_9L$]$^-$ derivatives [L = neutral two-electron donor such as $(CH_3)_2S$] was reported in 1964[11] to provide neutral [*trans*-$B_{20}H_{16}L_2$] species isoelectronic with *trans*-**1**. These reactions extend the scope of *trans*-**1** chemistry by eliminating net ionic charge and supplying a new route to substituted *trans*-**1** derivatives.

Following its initial characterization and several preliminary investigations of its reactivity, the elaboration of *trans*-**1** and its derivatives languished for some time despite its unique position in the active field of polyhedral borane chemistry.[7] However, as part of an ongoing investigation of new boron-rich target species for application in boron neutron capture therapy,[17,18] we began to exploit the then known reactions of *trans*-**1**. The results of these studies provided new approaches for targeting boron to tumor cells in therapeutic amounts involving unilamellar liposomes[17] and also revealed unexpected and intriguing chemical results. This extension of the chemistry of *trans*-**1** and related B_{20}-species revealed novel reaction modes, uncovered new structural principles and provided fresh insight into the versatile reactivity of these polyhedral borane derivatives. This article presents a correlated survey of the new reactions and structures that have resulted from these investigations. In some instances these new data have provided new mechanistic insights regarding B_{20}-chemistry which are presented here for the first time. In general, mechanistic conclusions are limited by the absence of information regarding the energetics of reactants, intermediates and products as well as the timing (or sequence) of events. What has emerged are patterns of reactivity (roadmaps) which suggest definitive processes. Thus, nearly all mechanistic opinions expressed here are shadows of more explicit information which is hopefully yet to come.

3 Isomers of [$B_{20}H_{18}$]$^{2-}$ (1)

The centrosymmetric structure of *trans*-**1** has proven to be only one of three known structures for ions having the [$B_{20}H_{18}$]$^{2-}$ formulation.

The pale yellow color of *trans*-**1** is due to a pair of strong electronic absorptions at 2320 and 2920 Å.[19] Irradiation of *trans*-**1** with ultraviolet light (in CH_3CN solution) results in its complete conversion to a new isomer of **1**, the *iso*-**1** ion[20] (also known as the *hν*- or *photo*-**1** ion). The structure of the *iso*-**1** ion is, as in the case of *trans*-**1,** unprecedented. The two [$B_{10}H_9$]$^-$ cages are still connected in *iso*-**1** by a pair of three-center two-electron bonds, but here these bonds are of the B–H–B variety and similar to the bonds originally proposed for the ion now known to have the *trans*-**1** structure.[10] Thus, *iso*-**1** retains the electrophilic nature of the *trans*-**1** precursor and exhibits chemical reactivity similar to that of *trans*-**1**. Although the chemistry of *iso*-**1** has not been extensively studied, it appears to be slightly more reactive than *trans*-**1** with nucleophiles. Heating *iso*-**1** in acetonitrile regenerates the original *trans*-**1** ion (Scheme 2).



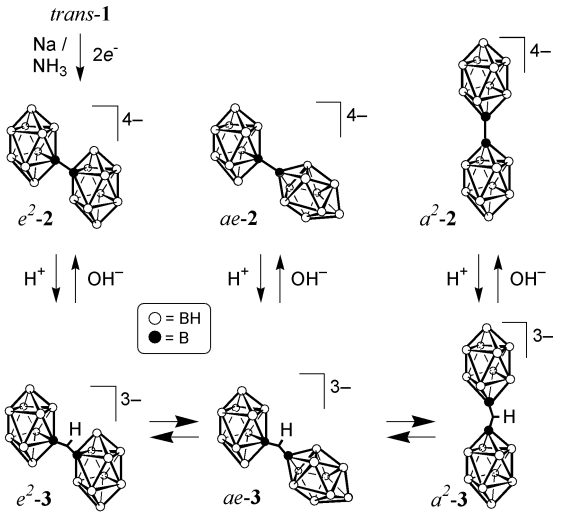
Scheme 2

A third isomer of **1**, *cis*-**1**, was recently produced[21] from the low temperature (0 °C) oxidation of [*ae*-$B_{20}H_{18}$]$^{4-}$ with Fe^{3+} (*vide infra*). As in *trans*-**1**, the two [$B_{10}H_9$]$^-$ cages of *cis*-**1** are connected by a pair of three-center two-electron B–B–B bonds, but using different boron vertices such that the [$B_{10}H_9$]$^-$ components are nonequivalent and arranged in a cisoid configuration (Scheme 2). Like *trans*-**1**, *cis*-**1** absorbs strongly in the near ultraviolet giving transitions at 2290 and 2770 Å. Solutions of *cis*-**1** slowly rearrange to *trans*-**1** at room temperature. Photolysis of *cis*-**1** (CH_3CN solution) with ultraviolet light produces the known photoisomer, *iso*-**1**. The relative thermodynamic stabilities of the three known isomers of **1** appear to decrease in the order *trans*-**1** > *cis*-**1** > *iso*-**1**. The three isomers of **1** undergo similar reactions with simple reagents. However, the reductive substitution reaction of each isomer with a given nucleophile yields a characteristic isomer of the product (*vide infra*).

4 Reduced derivatives of 1: isomeric [$B_{20}H_{18}$]$^{4-}$ (2) and [$B_{20}H_{19}$]$^{3-}$ (3) ions

The electron-deficient *trans*-**1** ion readily accepts electrons from active metals[22] and other sources. This reaction, com-

monly carried out with sodium in liquid ammonia solution, is not the reverse of eqn. (1), but a two-electron reduction to produce the e^2-isomer of $[B_{20}H_{18}]^{4-}$ ion (e^2-**2**, Scheme 3). Each



Scheme 3

of the various isomers of the **2** ion formally consists of two $[B_{10}H_9]^{2-}$ radical dianions joined by a B–B covalent bond.[22] Thus, the **2** isomers are analogous to biphenyl if one were to consider [*closo*-$B_{10}H_{10}]^{2-}$ analogous to benzene.

A protonated derivative of **2**, $[B_{20}H_{19}]^{3-}$ (**3**, *vide infra*), has also been observed as an intermediate during the ceric ion oxidation of [*closo*-$B_{10}H_{10}]^{2-}$ under mild conditions.[23]

A Rearrangements leading to linkage isomers of 2

The formal linkage of two [*closo*-$B_{10}H_9]^{2-}$ radical dianions, each of which presents two types of boron sites (apical or equatorial), produces three possible isomers of **2**, all of which are known (Scheme 3). Rearrangements interconverting these isomers are facilitated by protic solvents and acid-catalysis. The initial (kinetic) product of the sodium reduction of *trans*-**1** is the e^2-isomer of $[B_{20}H_{18}]^{4-}$, e^2-**2**.[22] In protic solvents, and more rapidly with acid-catalysis, the e^2-**2** ion rearranges to the *ae*- and subsequently to the a^2-**2** isomer. For the majority of known derivatives of **2** the a^2-isomers have been found to be the most thermodynamically stable species,[22] but substituent effects may influence the order of stability. In one recent example, the [e^2-$B_{20}H_{16}(CO)_2]^{2-}$ ion was the only isomer observed[24] under conditions conducive to acid-catalyzed rearrangement.

B The chemistry of isomers of 3 and their rearrangement

The proton-assisted rearrangement of the isomeric **2** ions and the isolation of an isomer of **3** from syntheses of **1** using [*closo*-$B_{10}H_{10}]^{2-}$ as a precursor suggested the existence of a set of isomeric **3** ions resulting from the reversible protonation of the corresponding e^2-, *ae*- and a^2-**2** isomers. These species have been observed and the pK_a of the labile proton estimated to be in the 6–7 range by potentiometric titrations.[11,23] The ^{11}B NMR spectra of these protonated species usually display complexity which has been attributed to facile proton exchange and isomer interconversion in polar or protic solvents, and the fluxionality of the bridging proton as it tautomerizes between the intercage B–B σ bond and adjacent sites having high electron density.[25] Although protonation is a common occurrence for derivatives of **2**, the potential formation and rapid equilibration of isomers, as well as the higher solubility of species of type **3** compared to those of type **2**, has made the isomeric **3** ions difficult to isolate and characterize in stereochemically pure form. The only available structural data are provided by the single crystal X-ray diffraction study of the (bis-pyridinium) (triethylammonium) salt of a^2-**3**[25] whose structure is presented in Fig. 2. The

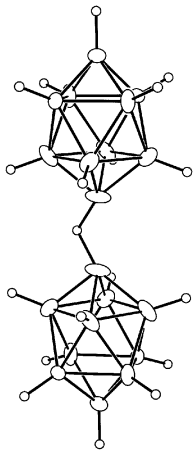


Fig. 2 Single crystal X-ray structure of the $[a^2$-$B_{20}H_{19}]^{3-}$ anion (a^2-**3**). The anion has approximate C_{2v} symmetry, with a mirror plane passing through the atoms of the central B–H–B bridge, and is centrosymmetric. The bridging hydrogen atom shown is at half-occupancy.

structure of the a^2-**3** ion is similar to that of linear a^2-**2**,[26] but the presence of a bridging proton between the two cages results in a B–B intercage distance that is approximately 0.25 Å longer than that observed in the former ion. The proton is not found on the long axis of a^2-**3**, but slightly displaced in such a way as to produce a 'side-bonded' B–H–B three-center bond while maintaining linearity of the a^2-**2** boron framework.

The observed rearrangements of e^2-**2** to *ae*-**2** and then a^2-**2** catalyzed by protons most likely proceed through the formation of the isomeric **3** ions as intermediates. A mechanism which explains this series of transformations is proposed (Scheme 3 and Fig. 3) in which intercage B–H–B bridge bonds are broken

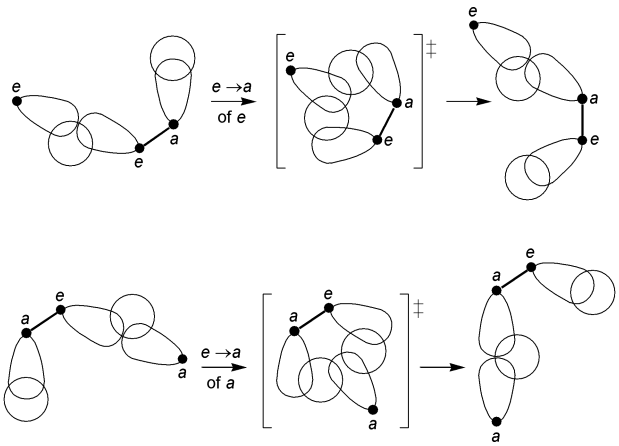


Fig. 3 Depiction of proposed B–H bonding orbital motion during the isomerization of e^2-**3** to *ae*-**3** ($e \rightarrow a$ migration of an *e*-vertex) and the similar rearrangement of *ae*-**3** to a^2-**3** ($e \rightarrow a$ migration of an *a*-vertex) employed in Scheme 3.

and new ones established by nucleophilic displacement of a two-center B–H bond (leaving group) by an entering two-center B–H bond (nucleophile) originating at a vertex neighboring that of the leaving B–H vertex. A related disruption of a central B–B–B three-center bond by a neighboring B–H vertex is proposed below (Fig. 4).

C Oxidation of isomers of 2

The reduction of **1** to isomers of **2** is reversible with a variety of oxidizing agents. This type of oxidation reaction is more facile

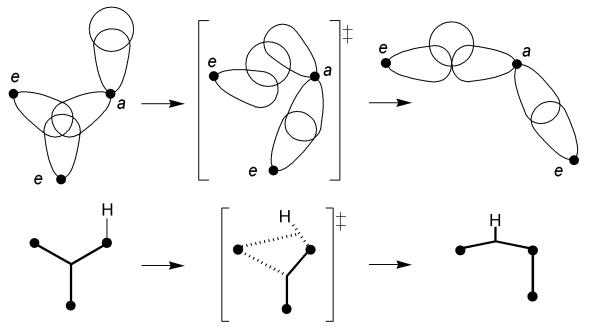


Fig. 4 Mechanism proposed in Scheme 4 for the displacement of a two-center, two-electron bond from a three-center, two-electron bond by a flanking nucleophilic B–H bond.

than the oxidative coupling of [*closo*-$B_{10}H_{10}$]$^{2-}$ which produces *trans*-**1**; 1,4-benzoquinone will oxidize either e^2- or a^2-**2**, but the oxidative coupling of [*closo*-$B_{10}H_{10}$]$^{2-}$ to *trans*-**1** requires the more energetic 2,3,5,6-tetrachloro-1,4-benzoquinone.[27] The particular isomer of **1** that results form the oxidation will depend upon the reaction conditions, the isomer and the degree of substitution of the **2** precursor. As an example, all three isomers of **2** will produce thermodynamically preferred *trans*-**1** when oxidized with hot aqueous ferric ion, but the *cis*-**1** isomer is obtained as a kinetically controlled product when the oxidation of *ae*-**2** is performed at 0 °C in the presence of a precipitating counter ion (such as Me_4N^+) that removes the product from solution before further reaction or rearrangement occurs.[21] The mechanisms of these facile oxidations have not been investigated. Rapid rearrangement of the **3**-isomers prior to oxidation is a complicating factor. However, modern electrochemical techniques would appear to be useful in such a study.

5 Reductive substitution reactions of *trans*-1

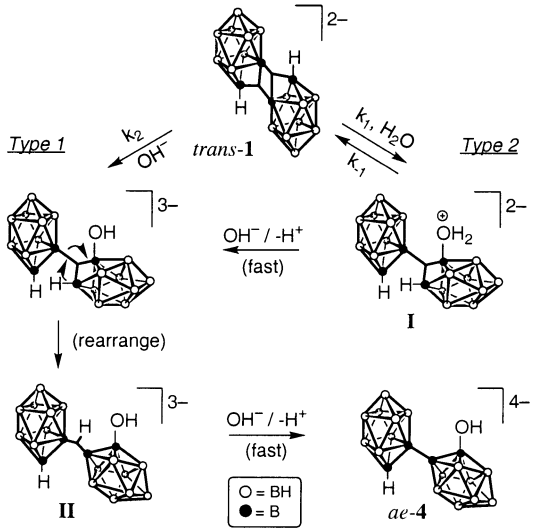
Both of the two equatorial boron vertices lacking a bond to a terminal hydrogen atom in *trans*-**1** support three-center two-electron bonds and provide electrophilic centers for nucleophilic attack. Such reactions lead to ligand coordination accompanied by two-electron reduction yielding a substituted isomer of **3**. Proton loss from the B–H–B bridge of the latter species to produce a two-center, two-electron bond provides the substituted **2** isomer commonly observed. These so-called reductive substitution reactions were immediately recognized[10,12] following the discovery of *trans*-**1**.

The prototypical example of this reaction, the reductive substitution of *trans*-**1** with aqueous hydroxide ion[28] was thoroughly studied. A detailed kinetic study of this reaction (Scheme 4) proved the rate equation to be composed of two kinetic terms as shown in eqn. (2).

$$-\mathrm{d}/\mathrm{d}t[\textit{trans}\text{-}\mathbf{1}] = k_1[\textit{trans}\text{-}\mathbf{1}] + k_2[\textit{trans}\text{-}\mathbf{1}]\,[OH^-] \qquad (2)$$

At 29.9 °C, $k_1 = 0.7 \times 10^{-4}\ s^{-1}$ and $k_2 = 0.60 \times 10^{-2}$ L mol^{-1} s^{-1}. The k_1 term, in view of newly acquired results, represents a reaction involving nucleophilic attack by water upon *trans*-**1** while the k_2 term denotes the corresponding hydroxide ion reaction. As expected, the k_1 term displayed no dependence upon the ionic strength of the media while the observed dependence of the k_2 term was in agreement with the attack of a −1 ion (hydroxide) upon a −2 ion (*trans*-**1**). Thermodynamic activation parameters are also in agreement with these assignments. The products of these reactions were identical; the same isomer of [$B_{20}H_{17}OH$]$^{4-}$ (*ae*-**4** in Scheme 4). Acid-catalyzed isomerization of *ae*-**4** produces a quantitative yield of the thermodynamically more stable a^2-**4**.

At the outset of *trans*-**1** chemistry the hydroxide ion/water reaction stood out as an important example of reductive



Scheme 4

substitution. Little progress was made with alternative nucleophiles although it seemed logical that many types of nucleophilic reagents might be adopted. Later, our interest in the boron neutron capture therapy of cancer[18]suggested the reductive substitution reaction as a possible pathway to born-rich species suitable as target compounds for neutron capture.[17] This synthetic effort revealed the hidden subtleties of these reactions and allowed the formulation of a provisional mechanism for the reductive substitution reaction, presented here, which extends beyond that originally proposed.[28] In each example denoted below, the exclusive reaction product was an analog of *ae*-**4** (the OH^-/H_2O product) with the entering ligand formally replacing the −OH. The collected data are presented in Table 1.

The reactions shown in Table 1 are seen to fall into three categories depending upon the charge and secondary reactivity of the attacking nucleophile. Type 1 reactions (A, D and E of Table 1) involve the irreversible attack of a strongly nucleophilic anion (HO^- or CH_3O^-) upon an electrophilic vertex of *trans*-**1** (Scheme 4).

The proposed rearrangement of species **I** to the B–H–B bridged species **II** involves the nucleophilic attack of the indicated B–H bond upon the remaining B–B–B three-center bond which connects the two cages. The electron pair in the latter bond returns to the domain of the indicated decaborate cage and the *ae*-B–H–B bridge bond is established. Abstraction of the bridging hydrogen atom from **II** as a proton produces the B–B σ bond in *ae*-**4**. The decaborate cage which is attacked by the anionic nucleophile also provides the nucleophilic apical B–H bond employed in the rearrangement of **I** to **II** and the ionic charge associated with both **I** and **II** is 3−. The latter point will reemerge below. Fig. 4 depicts the orbital motion required to accommodate the proposed rearrangement of **I** to **II**.

Type 2 reactions (C and F in Table 1) involve nucleophilic attack by the conjugate acid of the ligand observed in the product, $–NH_2$ (actually observed as $–NH_3^+$ due to its basicity) and –OH. The solvent H_2O or $NH_{3(l)}$ supplies the entering ligand (Scheme 4). The initial complexation of the solvent with *trans*-**1** must be reversible since the magnitude of the limiting first-order water term [eqn. (2), measured in the presence of hydroxide ion to assure irreversibility] gives *trans*-**1** a half-life of about 2.8 hours at 29.9 °C. Since *trans*-**1** is routinely purified without loss by recrystallization from hot water and aqueous solutions of *trans*-**1** in water are stable indefinitely at room temperature, reversibilility is clearly indicated.

In example F of Table 1, sodium acetylide was employed as the base in a Type 2 reaction carried out in liquid ammonia. The

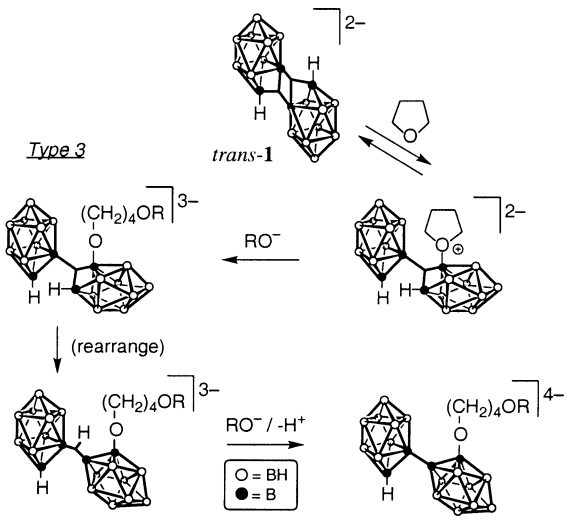
Table 1 Reductive substitution reactions and products derived from *trans*-**1**

Entry	Solvent	Base	Entering ligand	Product ligand	Reaction type	Reference
A	H_2O	OH^-	HO^-	HO^-	1	28
B	H_2O	H_2O	None	None	—	28
C	H_2O	OH^-	H_2O	HO^-	2	28
D	CH_3OH	CH_3O^-	CH_3O^-	CH_3O^-	1	28
E	$(C_2H_5)_2O$	$CH_3CH_2O^-$	$CH_3CH_2O^-$	$CH_3CH_2O^-$	1	29
F	$NH_{3(l)}$	$HC{\equiv}C^-$	NH_3	NH_3	2	30
G	$NH_{3(l)}$	NH_3	None	None	—	30
H	CH_3CN	$CH_3CH_2O^-$	CH_3CN	NH_3	3	31
I	CH_3CN	$H_2NCH_2CH_2NH^-$	CH_3CN	NH_3	3	31
J	THF	CH_3O^-	THF	$CH_3O(CH_2)_4O^-$	3	32
K	THF	i-$C_5H_{11}O^-$	THF	i-$C_5H_{11}O(CH_2)_4O^-$	3	32

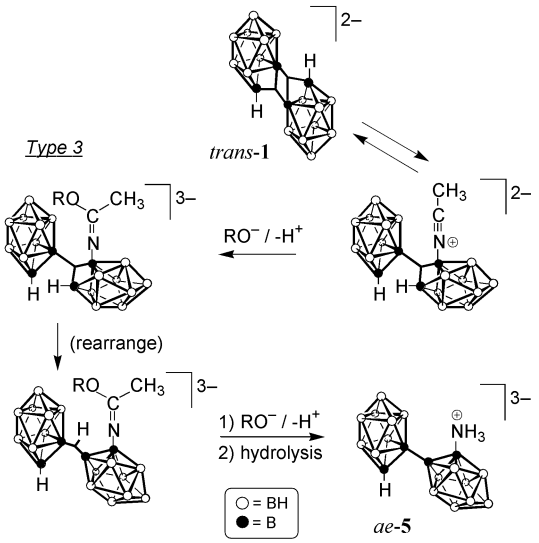
sole product of these reactions was [*ae*-$B_{20}H_{17}NH_3]^{3-}$ (*ae*-**5**, analogous to *ae*-**4**). No reaction occurred when *trans*-**1** was simply dissolved in liquid ammonia. It is highly unlikely that acetylide ion could generate sufficient amide ion *in situ* to account for the direct formation of *ae*-**5** (Type 1 reaction) since the acidity of acetylene exceeds that of ammonia by 10 p*K* units. Consequently, NH_3 must coordinate with an electron-deficient vertex of *trans*-**1** and proceed to *ae*-**5** using a Type 2 mechanism analogous to the water reaction shown in Scheme 4.

Only in the presence of an added base (OH^- in H_2O and $HC{\equiv}C^-$ in $NH_{3(l)}$) are Type 2 processes productive. As proposed here, the initial solvent adduct (**I**, Scheme 4) preferentially returns to reactants rather than undergo three-center bond rearrangement. However, once the coordinated solvent molecule donates its proton to base, the resulting 3− ion is sufficiently nucleophilic at the apical B–H vertex of the substituted decaborate cage to initiate rearrangement to the B–H–B isomer. The bridge hydrogen atom is subsequently lost as a proton.

Reactions of Type 3 (H, I and J of Table 1) involve the reversible coordination of a nucleophilic solvent molecule with *trans*-**1**. In these reactions the coordinated solvent molecule (THF or CH_3CN) is activated for nucleophilic attack by an anionic nucleophile present in solution. This attack by an anion produces an intermediate of the familiar type having a 3− charge. This species is postulated to be capable of the three-center bond rearrangement shown in Schemes 5 and 6. The initial acetonitrile product, an imine derivative, is easily converted to the $-NH_3$ ligand by hydrolysis and protonation during product isolation.



Scheme 5

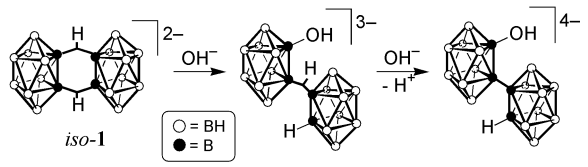


Scheme 6

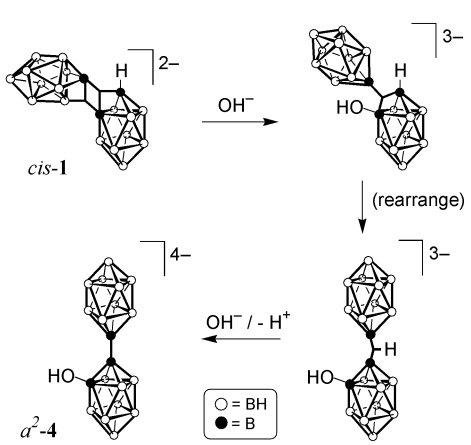
The course of the reductive substitution reactions described above appears to be strongly influenced by the presence of ionic charges among the reactants. The general predominance of solvolytic attack in reactions of Types 2 and 3 as opposed to direct attack by added bases [OH^-, CH_3O^-, $C_2H_5O^-$, $HC{\equiv}C^-$ and $H_2N(CH_2)_2NH^-$] suggests that the direct attack pathway is retarded by anion–anion repulsion in the transition state with *trans*-**1** and that neutral molecule *trans*-**1** reactions are coulombically most favorable and enhanced by the high concentration of nucleophile. Secondly, the three-center bond rearrangement, which is postulated to follow the initial nucleophilic attack, appears to require the intermediate to bear a 3− charge. Of these three negative charges, two are associated with the decaborate cage not attacked by nucleophile while one negative charge is associated with the other. This charge distribution is thought to be required to attain sufficient nucleophilicity at the apical B–H vertex to achieve rearrangement.

The *iso*- and *cis*-**1** isomers are also subject to nucleophilic attack and they form products similar to those obtained from *trans*-**1**. However, in each case a different isomer of the product is obtained. Reductive substitution of *cis*-**1** produces substituted a^2-isomers directly[21] while the reactions observed with *iso*-**1** result in the formation of an e^2-isomer.[33] The proposed mechanism for the reaction of *iso*-**1** with an anionic nucleophile such as OH^- is shown in Scheme 7.

The two decaborate cages present in *cis*-**1** are not equivalent and the reaction product suggests that the simple mechanism shown in Scheme 8 prevails. In the latter process the decaborate cage having the apical B–H vertex and its neighboring hydrogen-less equatorial vertex undergoes nucleophilic attack

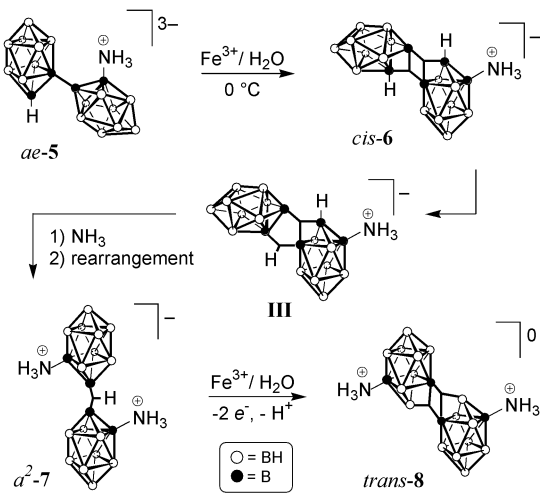


Scheme 7



Scheme 8

at the latter position. This simple mechanism cannot be generally correct when this same decaborate cage carries a substituent as shown with *cis*-**6** (*vide infra*) in Scheme 9. In the

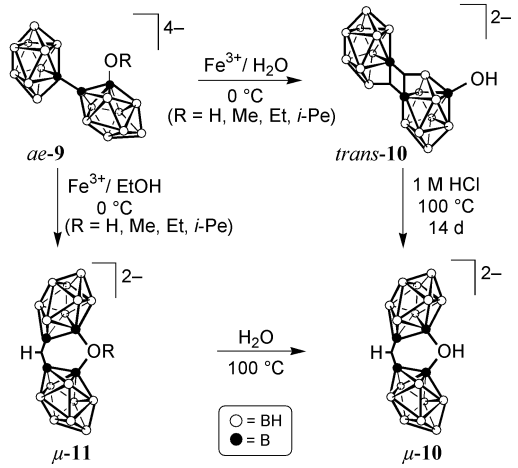


Scheme 9

latter case the entering nucleophile attacks the unsubstituted decaborate cage.[34] To explain the latter course, one may assume the appearance of B–H–B intermediate **III** which undergoes attack at the equatorial vertex required to rationalize the reaction product, a^2-**7**. Further oxidation of a^2-**7** yields the symmetrically neutral and disubstituted *trans*-**1** derivative *trans*-**8**.

6 Neighboring group participation accompanying the oxidation of substituted derivatives of [*ae*-$B_{20}H_{18}$]$^{4-}$

The availability of a variety of substituted derivatives of *ae*-**2**, most notably the [*ae*-$B_{20}H_{17}OH]^{4-}$(*ae*-**4**) and the corresponding ammonio derivative [*ae*-$B_{20}H_{17}NH_3]^{3-}$ (*ae*-**5**) led to an investigation of the fate of these ions when subjected to oxidizing conditions. For example, the low temperature (0 °C) oxidation of *ae*-**4** with aqueous ferric ion produced the [*trans*-$B_{20}H_{17}OH]^{2-}$ ion (*trans*-**10**, Scheme 10).[28] Under similar conditions the [*cis*-$B_{20}H_{17}NH_3]^-$ ion (*cis*-**6**, Scheme 9) was obtained from the oxidation of [*ae*-$B_{20}H_{17}NH_3]^{3-}$ (*ae*-**5**).[34] However, under non-aqueous conditions these oxidation reactions produced strikingly different results which revealed a new pathway for such oxidation reactions.



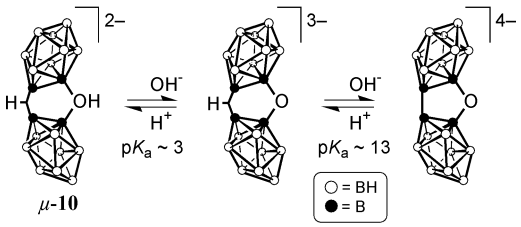
Scheme 10

The reaction of [*ae*-$B_{20}H_{12}OR]^{4-}$ (*ae*-**9**) with ferric chloride in anhydrous ethanol provided the unusual [μ-$B_{20}H_{17}OR]^{2-}$ (μ-**11**, Scheme 10) in good yield.[35] During the course of this oxidation reaction, the normally expected fusion of the two decaborate cages has been intercepted by the neighboring alkoxide substituent. Consequently, the structure of the product incorporates a pair of decaborate cages linked by two bridge arrays of different types [B–H–B and B–O(R)–B] forming an essentially planar, six-membered BHBBOB ring.

The planar, tricoordinate oxygen atom of μ-**11** is quite robust and its alkyl substituent groups, R, may be removed by reaction with water at 100°C to produce [μ-$B_{20}H_{17}OH]^{2-}$ (μ-**10**, Scheme 10). The bridging oxygen atom in μ-**10** may be alkylated by reaction with alkyl halides in acetonitrile solution.

As expected, the μ-**10** ion was also obtained directly by the oxidation of *ae*-**4** under the anhydrous conditions described above. Also, as suggested by its numerical designation, μ-**10** is actually an isomer of *trans*-**10** and, indeed, heating *trans*-**10** in 1 M HCl resulted in the slow, but irreversible formation of μ-**10** thus providing a third route to this novel anion.

Both the hydroxyl and the hydrogen bridging groups of μ-**10** are proton donors. Aqueous solutions of μ-**10** are acidic due to the ionization of the oxygen-bound proton (estimated K_a of 10^{-3}) and the formation of [μ-$B_{20}H_{17}O)^{3-}$ (Scheme 11).[35] The

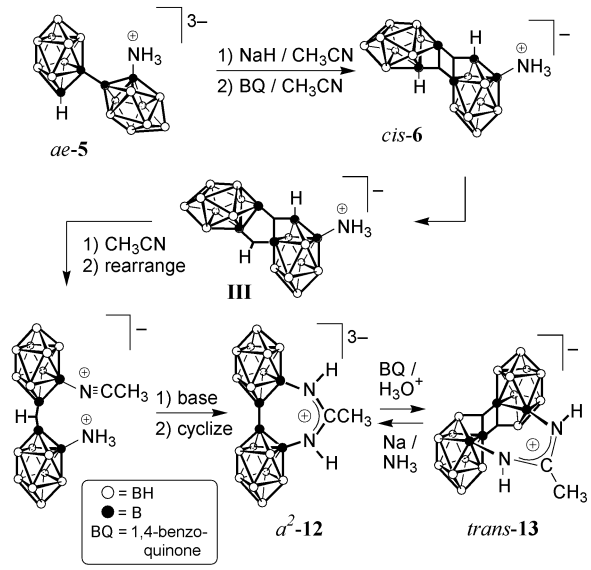


Scheme 11

latter species may be alkylated with alkyl halides in acetonitrile to regenerate O-alkyl derivatives such as μ-**11**. Deprotonation of the B–H–B bridge of [μ-$B_{20}H_{17}O]^{3-}$, forming [μ-$B_{20}H_{16}O]^{4-}$, occurs only in strongly basic solution. The estimated K_a of this proton is approximately 13. The reduced

acidity of this bridging hydrogen atom compared to the similar bridge hydrogen atom found in a^2-**3** (pK_a = 7.3) has been attributed to the introduction of ring strain and loss of net orbital overlap caused by the removal of the bridging hydrogen atom from the ring structure of μ-**10**.[35] Both a^2-**3** and $[\mu\text{-}B_{20}H_{17}O]^{3-}$ are comparable trinegative anions.

Investigation of the oxidation of the ammonio-substituted derivative *ae*-**5** also produced novel results. The reaction of *ae*-**5** with benzoquinone in anhydrous acetonitrile resulted in the amidinium-bridged structure $[\mu\text{-}\{CH_3C(NH)_2\}B_{20}H_{16}]^{3-}$ (a^2-**12**, Scheme 12).[21] This product results from the intervention of



Scheme 12

both the ammonio neighboring group and the acetonitrile solvent in the oxidation process. Further two-electron oxidation of a^2-**12** forms the unusual sterically constrained *trans*-**1** derivative (*trans*-**13**, Scheme 12). The mechanism leading to a^2-**12** from *ae*-**5** is proposed to proceed using *cis*-**6** (Scheme 12) as an intermediate.

7 Boron neutron capture therapy and B_{20}-chemistry

The thermal neutron capture cross-section of the ^{10}B nucleus (approximately 3800 Barns) is several orders of magnitude greater than that of the elements which comprise the bulk of mammalian tissues (C, H, N, O, P, Na, Ca, Cl, *etc*.). The ^{10}B neutron capture reaction [eqn. (3)] provides approximately 2.4

$$^{10}_{5}B + ^{1}_{0}n \rightarrow ^{4}_{2}He^{2+} + ^{7}_{3}Li^{3+} + \gamma \qquad (3)$$

MeV of energy and two heavy ions which are lethal to cells at the point of their creation and for a distance of about one cell diameter along their track lengths. The gamma photon (0.5 MeV) is less useful since its energy is dissipated isotropically. The ^{11}B nucleus is essentially inert.

Thus, the selective placement of ^{10}B nuclei in, or very near, critical regions of a cancer cell (DNA, organelles, or less effectively, the cytoplasm) followed by irradiation with relatively non-injurious and capturable low-energy neutrons provides a selective binary radiation therapy. The chemist's challenge is the design and synthesis of boron-rich compounds which are relatively non-toxic, selectively delivered to tumor cells and retained sufficiently long to allow effective neutron irradiation.[18,36] One method we have developed for the delivery of therapeutic quantities of ^{10}B to tumor cells (> 30 ppm ^{10}B) involves the fabrication of small (30–120 nm) unilamellar liposomes having water-soluble B_{20}-anions (with sodium cations) in their aqueous core.[17,30]

Liposomes of this type are self-targeting and Fig. 5 is a cross-sectional view of such a liposome. The bilayer may carry hydrophobic carborane derivatives to further enhance the boron

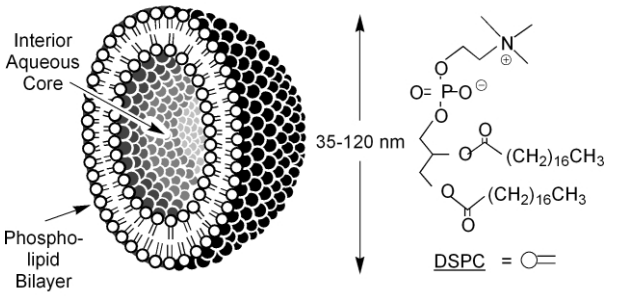


Fig. 5 A cross-sectional view of a small unilamellar vesicle, and the structure of distearoylphosphatidyl choline, which together with cholesterol makes up the phospholipid bilayer.

content of the liposome.[37] Species which have proved most effective as solutes in the aqueous core of liposomes are the amine derivative $[ae\text{-}B_{20}H_{17}NH_2R]^{3-}$ where R = –H or $–CH_2CH_2NH_2$.[30] These derivatives will be recognized from the discussion above as substituted **2** ions. Many other B_{20}-derivatives were evaluated in the aqueous core of unilamellar liposomes, but only a few were sufficiently non-toxic and retained by tumor cells in sufficiently high concentration for therapeutic purposes. Experiments with disodium *trans*-**1** as the liposome solute proved this species to be effective, but surpassed in performance by the amine-substituted **2** ions. The effective amine derivatives proved to be easily oxidized[30] to the corresponding *trans*-**1** ions (established by cyclic voltammetry), an important facet of the argument presented below. It is presently postulated that the small liposomes employed are capable of leaking through the immature cell walls of rapidly growing tumor vasculature. This places the liposomes uniquely within the tumor mass. Endocytosis by the tumor cells in that mass provides internalization of the intact liposome[30] and subsequent endosomal digestion of the liposome releases the B_{20}-derivative into the cytoplasm. A two-electron biological oxidation of the **2** derivative (−3 charge) to the corresponding **1** derivative (−1 charge) is postulated. The latter species would be expected to be exceptionally electrophilic, due to its uninegative charge (compared to dinegative *trans*-**1**) and react rapidly with endogenous amino groups in the cytoplasm (Fig. 6). This would explain the high uptake and retention of boron

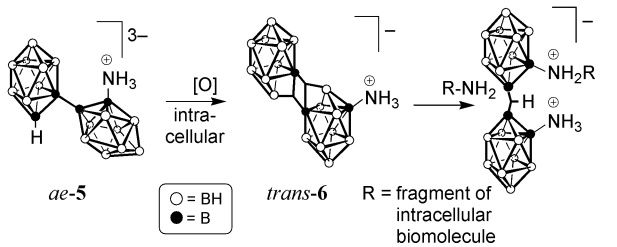


Fig. 6 Proposd mechanism for the intracellular immobilization of a substituted *trans*-**1** molecule following its delivery within a liposome.

accumulated over a thirty-hour period following the injection of the liposomes in tumor-bearing mice[30] and rats.[33]

Thus, the understanding of B_{20}-chemistry gained from the fundamental studies presented in this article has allowed the creation of a family of relatively simple borane derivatives whose effective targeting with liposomes and tumor cell retention may be developed for cancer therapy in humans. Much remains to be done in the biological area related to the

mechanisms regulating B_{20}-agent performance and the associated design of new agents. The B_{20}-family of polyhedral borane anion derivatives remains as a singularly attractive group of relatively non-toxic, boron-rich and structurally versatile building blocks for pharmacology and material science applications.

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