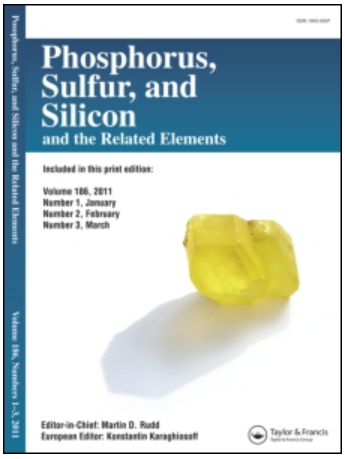

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Boron Analogues of Biomolecules: Biomedical Prospects

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BORON ANALOGUES OF BIOMOLECULES: BIOMEDICAL PROSPECTS

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Boron analogues of a variety of biologically important molecules have been synthesized and characterized. Analogues of amino acids, peptides, phosphonates, nucleosides, nucleic acids, and other derivatives, all containing 4-coordinate boron, possess sufficient hydrolytic and oxidative stability to be useful under physiological conditions. Bearing close structural resemblance to their natural organic counterparts (but different charge), the boron analogues exhibit potent biological activity and possess a wide variety of pharmacological behavior such as hypolipidemic, anticancer, anti-inflammatory, anti-osteoporosis, and other activity in animal model studies. Boron analogues may also be useful in boron neutron capture therapy for the treatment of cancer. Other applications to medical diagnostics exist.

Key Words: Boron, Biomolecules, Pharmacological Activity, BNCT

INTRODUCTION

Life on this planet is based upon the element carbon and organic chemistry. Carbon, combined chemically with nitrogen, hydrogen, oxygen, etc., make up the fundamental molecules of life such as amino acids, proteins, and nucleic acids (DNA). We and our collaborators have been interested in organic-like biomolecules based upon the element boron rather than carbon. Our attention to the element boron and, in particular, to its biomedical applications arises from its fascinating intrinsic chemical, structural, and nuclear properties. Utilizing these properties have enabled us to create many boronated molecules for potential use in therapeutic and diagnostic applications.

CHEMICAL AND STRUCTURAL PROPERTIES OF BORON

Boron is next to carbon on the periodic table of elements, and, structurally, compounds of boron and carbon are very similar. However, boron, atomic number 5, has three electrons in its valence shell while carbon, atomic number 6, has four valence electrons. Both boron and carbon form simple compounds with hydrogen, for example, borohydride, BH_4^- and methane, CH_4. The species are termed isoelectronic and isostructural (both species have their bonds to hydrogen distributed in a tetrahedral

geometry). However, the boron species has an overall negative charge while the carbon species is electrically neutral.

Chemists have long made analogies between boron compounds and carbon compounds. Frequently, though, these analogies have involved typical organic compounds and inorganic compounds based on three-coordinate carbon and boron. While of chemical and theoretical interest, three-coordinate boron compounds are often oxidatively unstable and quite sensitive to water, hydrolyzing rapidly to give boric acid. Therefore, biologically, three-coordinate boron compounds have limited utility.

At BBI, we have advanced and exploited the concept that "molecules of life" built around four-coordinate boron would have considerable biological activity because of their close structural relationship to four-coordinate carbon compounds. Many four-coordinate boron compounds, like their carbon counterparts, are hydrolytically and oxidatively stable which is essential for their survival and utilization in biological systems.

NUCLEAR PROPERTIES OF BORON

The nuclear properties of boron represent a second area of keen interest to BBI. Naturally occurring boron consists of two non-radioactive isotopes, boron-10 and boron-11. The boron-10 isotope makes up about 20% of this mixture. Boron-10 has a profound tendency to "capture" a neutron. This propensity for neutron capture is what makes boron so valuable in the nuclear industry both in nuclear reactors and in nuclear weapons. However, this same neutron-capturing ability of boron-10 can also be applied to the treatment of cancer.[1] Although today's standard treatments - surgery, radiation therapy and chemotherapy - have been successful in curing some kinds of cancers, there are many exceptions. The ideal therapy for cancer would consist of a regimen that kills tumor cells and spares normal tissues. Boron Neutron Capture Therapy (BNCT) appears to represent a significant alternative, and perhaps ideal treatment, for some kinds of cancer. Essentially, BNCT is a twofold treatment that brings together boron-10 and neutrons to create a localized lethal radiation that can attack tumor cells without seriously damaging normal tissues. BNCT has been successfully used in Japan for treatment of brain cancer and malignant melanoma in humans. Clinical trials are currently underway in the United States and are planned in Europe and elsewhere.

SYNTHESIS OF BORON ANALOGUES OF BIOMOLECULES

The following is a brief review of major synthetic routes to boron analogues and some of their chemical properties. Detailed synthetic procedures can be found in the references cited below. Many additional syntheses are also described in the references cited under Pharmacological Behavior.

Amino Acid Analogues

The first amino acid analogue we prepared[2] was borobetaine™ (trimethylamine-carboxyborane), Me_3NBH_2COOH. It was prepared from Me_3NBH_2CN by alkylation of the cyano nitrogen with $Et_3O^+BF_4^-$ followed by hydrolysis. Borobetaine™ is air stable and hydrolytically very stable. Boroglycine™, H_3NBH_2COOH, can be prepared from borobetaine™ by amine exchange.[3]

A variety of N-substituted amine-carboxyboranes[4], their ester[5,6] and amide derivatives[7] as well as boron analogues of common amino acids[8] have been characterized.

An example of the profound effect of replacement of C by B is on the pKa of the free amino acids.[9] For example, the boron analogue of glycine (ammonia-carboxyborane (H_3NBH_2COOH)) has a carboxyl group, pKa of 8.3 compared to 2.4 for glycine. Similarly, the pKa for the ammonia nitrogen deprotonation in $H_3NBH_2CO_2H$ is >11, while for glycine, it is 9.7. Thus, while the boron compounds are similar in size and geometry to their organic counterparts, they have very different electronic and hydrogen bonding properties. Such similarities and differences translate into interesting and significant biological activity.

Boron Containing Peptides

Typical condensation methods can be used to prepare peptides at the carboxy terminus of amine-carboxyboranes. Although condensing agents such as dicyclohexyl-carbodiimide can be used, the yield is quite low and a condensation method using Ph_3P and CCl_4, similar to that used for coupling normal amino acids, produces good yields of di- and tri-peptides.[10] Because of the very high pKa of the NH on boroamino acids, typical peptide bond formation procedures on the amine terminus are unsatisfactory and suitable preparative methods are under development.

Boron analogues of amino acids and peptides are generally stable in water and have amphiphilic character, i.e., they are soluble in water as well as most organic solvents and lipids. This amphiphilic character may be useful for the transport of these compounds across cell membranes. Studies with $Me_3NBH_2C(O)NHCH(Ph)C(O)OMe$, a dipeptide of borobetaine and phenylalanine, indicate that boronated dipeptides can cross cell membranes without hydrolysis of the amide bond as is found with the majority of normal peptides.[11] Such stability may be useful in overcoming problems associated with peptide or protein drug delivery.

Boron Analogues of Phosphonates

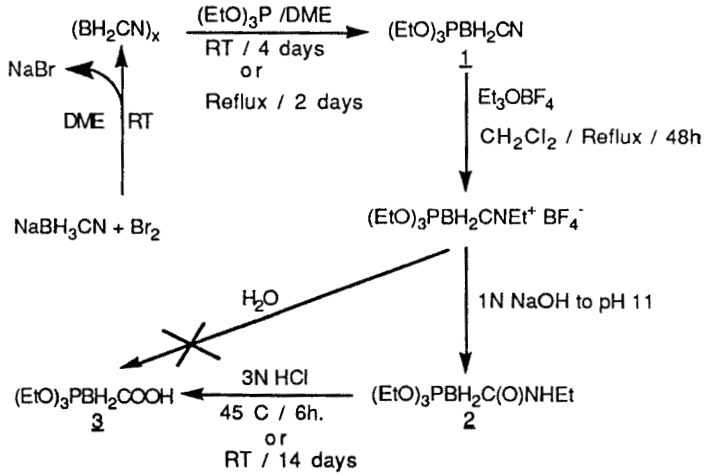
Since phosphate and phosphonate groups are present in a vast variety of biologically important molecules, e.g., DNA, phospholipids, etc., and synthetic phosphonates have been found to possess significant antiviral activity, we set out to prepare a variety of molecules with at lease one P-B bond.[12] Such derivatives may be considered as boron analogues of phosphonates. Scheme 1 presents the overall preparative scheme used to obtain $(EtO)_3PBH_2COOH$, **3** which is a boron analogue of phosphonoacetic acid. The synthesis begins essentially with $(EtO)_3PBHCN$, **1** which is readily prepared as shown.[12] Attempts to prepare **3** directly from the N-ethylated derivative were not successful but it can be readily prepared from the amide **2**.

A variety of derivatives of **3** of both the carboxylic acid and the PO group have been prepared and characterized[12] as shown in Scheme 2.

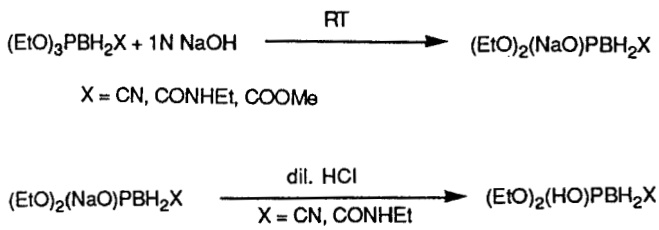
Heterocyclic Amine Derivatives

To carry out structure activity relationships, we have prepared and characterized a large variety of heterocyclic amine adducts of BH_2CN, $BH_2C(O)NEtH$, BH_2COOH, and BH_2COOR.[13,14] Two methods were used (Scheme 3). The heterocyclic amine (saturated and unsaturated) derivatives included imidazoles, piperazines, pyridines, etc.

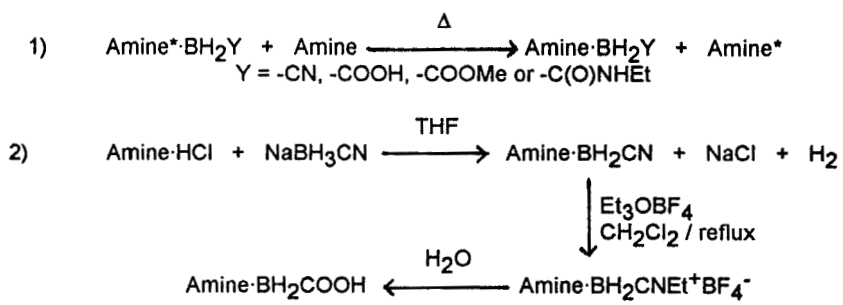
Scheme 1



Scheme 2



Scheme 3



Nucleoside and Nucleic Acid Derivatives

With experience gained in the preparation of boron analogues of phosphonates and heterocyclic amines, attention was focused on related very biologically relevant species, nucleosides, and nucleic acids.

The boronated (BH_2CN) nucleosides were prepared by an exchange reaction of silylated nucleosides with triphenylphosphine-cyanoborane followed by deprotection of the silylated products.(15) The compounds prepared and characterized are shown in Figure 1.

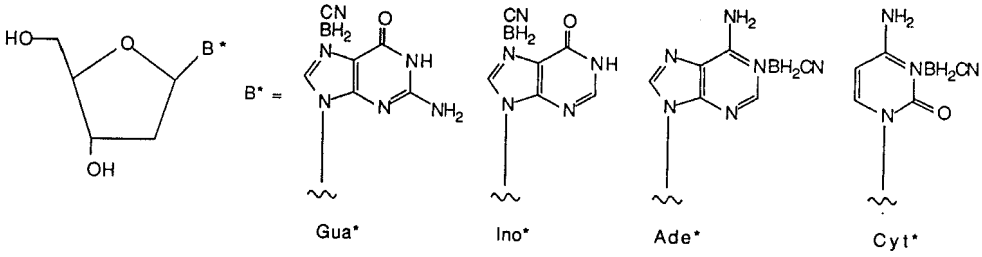
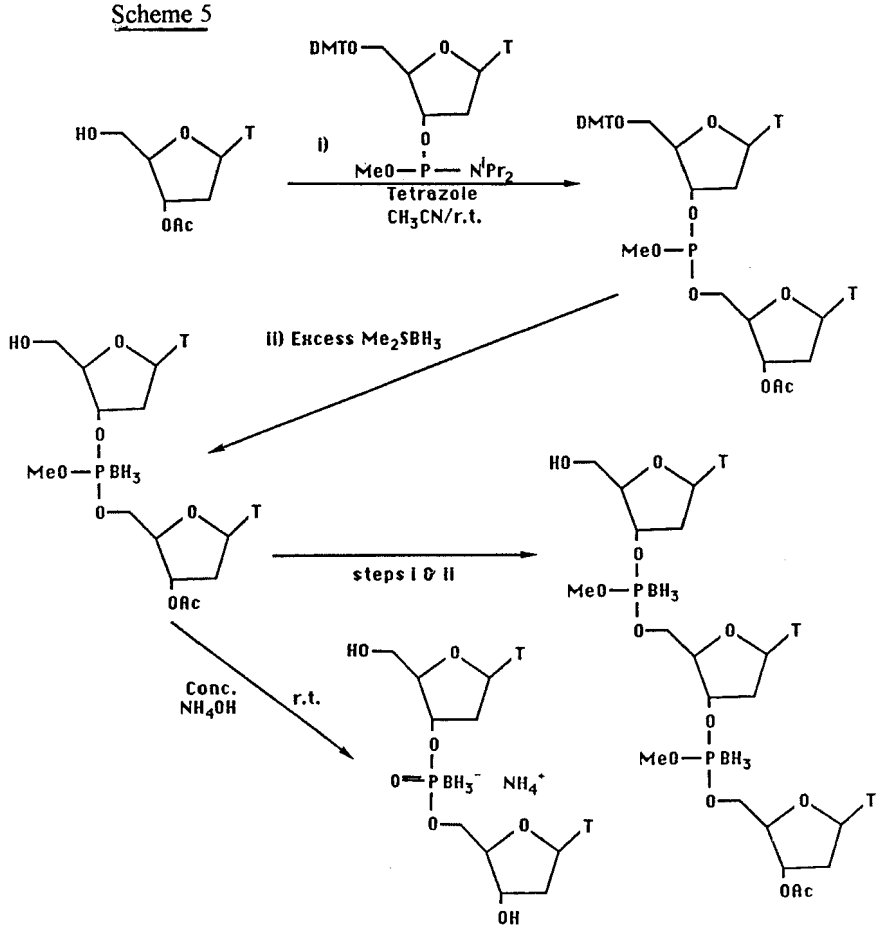


FIGURE 1. Nucleoside Cyanoboranes

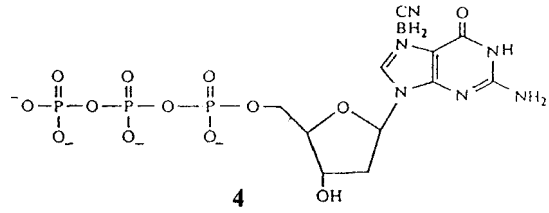
The "boronophosphate" oligonucleotides (Scheme 5) are prepared by formation of an intermediate phosphite which is then converted into the phosphite-borane by reaction with Me_2SBH_3.[16] Treatment with base gives the boranophosphate.

Scheme 5

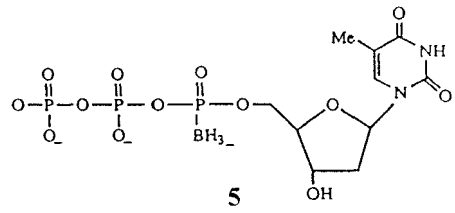


The hydrolytic and nuclease stability is of considerable importance for use of these species in antisense therapy and for BNCT. We have found that the internucleotide boranophosphate group is remarkably stable to basic and acidic hydrolysis and is also quite stable to nucleases.[16,17]

Related to the species in Schemes 4 and 5 are nucleoside triphosphates that have been recently prepared[18,19] and are shown in Figure 2.



4



5

FIGURE 2. N^7-Cyanoborano-2'-deoxyguanosine 5'-triphosphate (**4**), 5'-αP-borane thymidine triphosphate (**5**)

Both **4** and **5** are substrates for DNA polymerases and can be enzymatically incorporated into DNA. Indeed, 5'-αP-borane triphosphate of all four nucleoside bases T, A, C, G, have been prepared and can be incorporated, base specifically, into DNA during the polymerase chain reaction (PCR) and may simplify PCR sequencing.[20]

PHARMACOLOGICAL BEHAVIOR

Hypolipidemic Activity

Boron analogues of selected biomolecules and their derivatives cause significant reduction of serum cholesterol and triglyceride levels in rodents.[14,21-27] These compounds reduce LDL and VLDL cholesterol levels while elevating HDL cholesterol. This type of cholesterol modulation has been shown to protect humans against myocardial infarctions. Based on animal studies, these compounds are very promising hypolipidemic agents, comparable or superior to currently available drugs. For example, in rats, trimethylamine-boranecarboxylic acid methyl ester reduces serum cholesterol by 37% (as compared to control) and serum triglycerides by 34%. In contrast, lovastatin, a drug used clinically, reduces cholesterol by only 18% and triglycerides by 14%. Additionally, the effect on high density lipoproteins (HDL, "good cholesterol") is also markedly different. Trimethylamine-boranecarboxylic acid methyl ester increases HDL to 195% of control while lovastatin increases HDL to only 127%.

These dramatic effects on reduction of lipids appear to be via inhibition of Acyl CoA cholesterol acyl transferase, sn-glycerol-3-phosphate acyl transferase, and stimulation of neutral cholesterol ester hydrolase.[23,27] Thus, less cholesterol ester is stored in the aorta wall.

Anti-inflammatory Activity

With activities similar to the commercial drug indomethacin, select boron analogues are potent inhibitors of induced edema in mice and rats.[28] These compounds, however, have a much larger therapeutic index than indomethacin. For example, methylamine-boranecarboxylic acid (borosarcosine™) at 8 mg/kg (x2) results in 46% inhibition of the carrageenan-induced edema in mice and has an LD_{50} of >1000 mg/kg. Indomethacin, on the other hand, although somewhat better in inhibiting induced edema (78% inhibition) at 10 mg/kg (x2), has an LD_{50} of only 28 mg/kg in mice. Additionally, select boron analogues possess antiarthritic, antipleurisy, and analgesic properties.[10,26,28] They also inhibit prostaglandin synthesis and lysosomal enzyme activities in PMNs, macrophages, and fibroblasts.

Antineoplastic Activity

Boron analogues of amino acids and peptides have shown significant cytotoxic activity against a number of murine and human tumor cell lines, and additionally, in vivo antitumor activity has been demonstrated in a variety of tumors.[10,12-13,28-37] Activities observed include inhibition of nuclear DNA polymerase, 5-phosphoriboxyl-l-pyrophosphate (PRPP) amidotransferase, dihydrofolate reductase, and Topo II isomerase.

Osteoporosis

Osteoporosis is associated with reduced bone volume leading to increased frequency of bone fractures. This process is due to a metabolic imbalance between rates of new bone formation and bone resorption. The process of bone resorption is divided into two concurrent processes. Phase I involves inorganic mineral metabolism conducted by osteoclasts, macrophages, monocytes, PMNs, and fibroblasts. Phase II involves organic metabolism where proteolytic destruction of the bone matrix collagen releases hydroxyproline to the extracellular compartment.

Evidence that boron, as inorganic borate, at 3 mg/kg/day in humans may prevent osteoporosis has been presented.[38] We have found evidence that select boron analogues of biomolecules increases the rate of bone formation and decreases bone resorption.[40] Incorporation of B into biomolecules improves solubility, bioavailability, and transport into the cell or across natural barriers in the body.

Boron Neutron Capture Therapy (BNCT)

The destruction of cells in BNCT is a result of the nuclear reaction between thermal neutrons and the ^{10}B nucleus:

$$^{10}B + {}^{1}n \rightarrow {}^{7}Li + {}^{4}He + 2.4\ MeV$$

This reaction thus releases large amounts of ionizing energy (largely by the α particle, ^{4}He), and is confined mostly to the cells containing boron. Provided sufficient ^{10}B atoms can be made to selectively accumulate in tumor cells, this method can theoretically

kill tumor cells, sparing normal cells. One of the prime targets of BNCT is malignant brain tumors. The proceedings of the Fifth International Symposium on Neutron Capture Therapy, held in September, 1993 in Columbus, Ohio, has now been published and contains a thorough overview of the progress and rapidly increasing interest in this area.[1] Several chapters are devoted to compound development, many of which involve boronated biomolecules such as amino acids, nucleosides, nucleotides, etc. One compound, B-10 enriched p-boronophenylalanine (BPA), is entering clinical trials in the U.S.

A number of our boron amino acids, peptides, and nucleic acid compounds have been screened for use in BNCT,[18,32,40-42] with some showing uptake equivalent to BPA.[43] We have demonstrated, using molecular biology techniques, that boronated nucleoside triphosphates can serve as substrates for DNA polymerases and can be incorporated into DNA.[17-20] Since the boron neutron capture event has its highest lethality when it occurs in the nucleases, appropriate delivery to tumor cells and uptake may result in enhanced tumor cell kill. Such studies are underway in our laboratories.

Toxicology

Recently, the first International Symposium on Health Effects of Boron and Its Compounds was held and the proceedings published.[38] More data is available on inorganic borate, and it appears that there is a wide safety margin for inorganic boron for humans. Indeed, it is now clear that very small amounts of boron have primarily beneficial effects.

Acute toxicology studies on boron analogues we have prepared[35,43] have generally shown no or very little toxicity at 1, 3, 5 times the therapeutic dose. Thus, the boron agents tested are safe in their therapeutic range based on organ weights, histological tissue sections, clinical chemistry, and hematopoietic parameters. Additional studies at much higher doses are underway to uncover possible toxic effects.

In general, simply on the basis of LD_{50} values in mice, toxicity varies with the substituents attached to boron and for BH containing compounds, with the reducing power. The LD50 (mice) for the following series illustrates this.

Compound	**H_3BCN^-**	**BH_4^-**	**Me_3NBH_2CN**	**$Me_3NBH_2C(O)NEtH$**	**Me_3NBH_2COOH**
LD_{50} (mg/kg)	<1	~50	70	320	>1800

Conclusions

The results presented above and given in detail in the cited references shows that four-coordinate boron analogues of biomolecules and other small boron compounds possess sufficient hydrolytic and oxidative stability under physiological conditions and effect powerful biological effects and potent pharmacological activity in a variety of disease states. For the beneficial pharmacological effect, a high therapeutic index is observed for the boron analogues. Although more extensive toxicological studies are required, the pharmacological activity of these boron analogues is a rich area to explore. Furthermore, boron analogues of biomolecules show considerable promise for BNCT for cancer. Lastly, there are many opportunities for boron analogues in the medical diagnostic area including DNA sequencing and diagnostics.

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