It is noteworthy that a similar relationship in carbon–carbon bond distances has been found for the family of ethane derivatives, both experimentally and computationally.[15]

In summary, both experimental and theoretical data indicate that there is a correlation between the pyramidality angle and the metal–metal bond distance. Bonding of axial ligands has several effects: competition with the M–M σ bond to be sure, but also steric repulsion of the M–X bonds, which then induces smaller values of α. The small α values, in turn, weaken the M–M bond. This effect may be enhanced by the steric demands of rigid bridging ligands. The interplay of steric and electronic effects in this system is intricate and intriguing.

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Supplementary Material Available: The references for the 40 structures plotted in Figure 1 (3 pages). Ordering information is given on any current masthead page.

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Boron-Containing Nucleic Acids. 2.[1] Synthesis of Oligodeoxynucleoside Boranophosphates

Anup Sood,*[,†,‡] Barbara Ramsay Shaw,*[,†] and Bernard F. Spielvogel*[,†,‡]

Gross Chemical Laboratory, Duke University Durham, North Carolina 27706
Boron Biologicals, Inc., 2811 O'Berry Street Raleigh, North Carolina 27607

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Synthetic oligonucleotides are currently attracting considerable attention not only as probes for molecular biology[2] but also as potential therapeutics.[3] For example, oligonucleotides with modified backbones[4] may be used as "antisense" agents to inhibit or control growth of viruses as well as to specifically control the expression of oncogenes or other genes associated with various genetic disorders. Several modifications of the phosphate backbone (see, for example, Figure 1c–e) have been carried out[4a–e] and the modified oligonucleotides have been shown[5] to inhibit the growth of viruses (such as HIV, HSV, etc.) and expression of oncogenes (e.g., c-myc, c-mos).

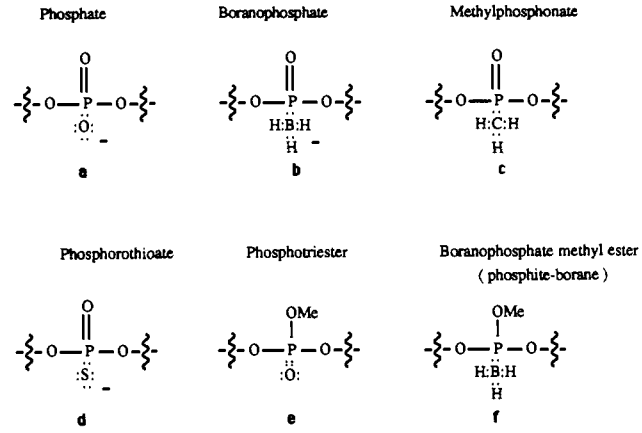
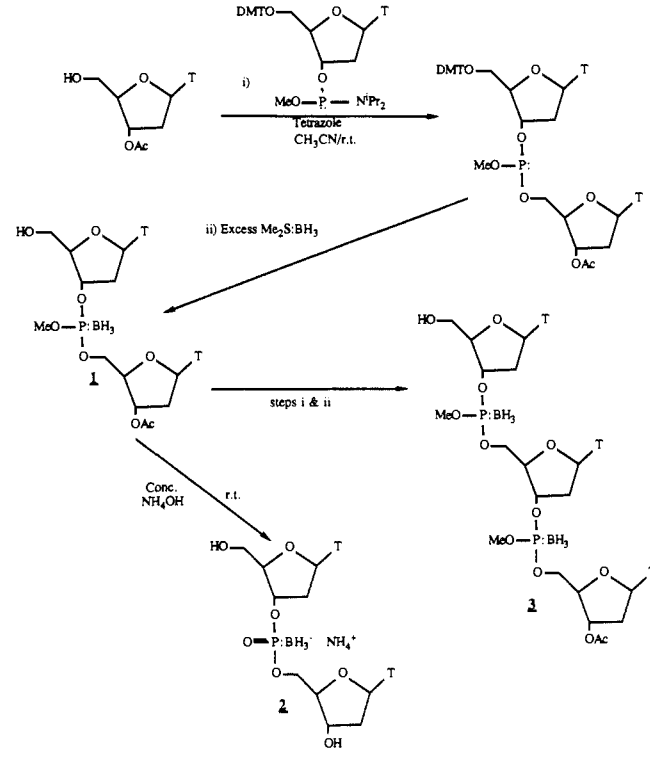


Figure 1. Structurally and/or electronically similar internucleotide linkages: (a) normal phosphate, (b) boranophosphate (borane phosphonate), (c) methylphosphonate, (d) phosphorothioate, (e) phosphotriester, and (f) boranophosphate methyl ester.

Scheme I



We now report the first examples of two types of oligonucleotides with a *boronated* internucleotide backbone: the boranophosphates (Figure 1b) and boranophosphate methyl esters (Figure 1f). The boranophosphate species is very closely related to the normal oxygen oligonucleotides (O-oligos, Figure 1a) and the oligonucleotide methylphosphonates (Figure 1c). The boranophosphate methyl esters on the other hand are closely related

† Duke University.
‡ Boron Biologicals, Inc.

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to oligonucleotide phosphotriesters (Figure 1e).

The borane (BH_3) group is isoelectronic with oxygen and the boranophosphate internucleotide group is negatively charged like the normal O-oligonucleotides. The borane group is also isoelectronic, as well as isostructural, with the oligonucleotide methylphosphonates, which are nuclease resistant. Thus, the boranophosphate linkage may permit the construction of an important and perhaps ideal antisense species in that the nucleotide bases are unaltered (and thus should maintain binding specificity) while the backbone remains negatively charged (and thus should be water soluble) like the O-oligonucleotide. Since BH_3 is much more hydrophobic than oxygen, it may impart a greater membrane permeability than the O-oligonucleotide yet maintain nuclease resistance like the methylphosphonates. Although compounds containing boron–hydride bonds are susceptible to hydrolysis, the B–H bond in boranophosphates possesses unusual hydrolytic stability, as shown below.

The boronated oligonucleotides were prepared according to the method described in Scheme I. Reaction of 5′-DMT-thymidine phosphoramidite with 3′-acetylthymidine in the presence of tetrazole results in the formation of an intermediate phosphite,[6] which is then converted to the dithymidyl boranophosphate methyl ester, **1**, by reaction with dimethyl sulfide–borane (Scheme I). Both reactions can be easily followed by ^{31}P NMR. In the first reaction the amidite peaks at 148.75 and 148.42 ppm were replaced by the new phosphite peaks at 140.41 and 139.80 ppm within the time required for recording the spectrum. In the second reaction the phosphite peaks disappeared within 5–10 min; after a large number of accumulations, a broad peak at 118.0 ppm for boranophosphate phosphorus was observed.

The oxidation step with $Me_2S{\cdot}BH_3$ confers another advantage. In addition to the formation of the desired boranophosphate linkage, it also removes the DMT protecting group from the 5′-hydroxyl position and hence eliminates the extra 5′-deprotection step that is required for chain elongation.

Dimer **1** was purified by flash chromatography followed by reverse-phase HPLC to give an overall yield of 52%. It has been extensively characterized by ^1H NMR (including COSY and HOHAHA techniques), ^{11}B NMR, ^{13}C NMR, ^{31}P NMR, and fast atom bombardment (FAB) mass spectroscopies. Satisfactory elemental analyses for C, H, N, and P (within ±0.4%) have been obtained.

Dimer **1** reacts with concentrated NH_4OH at room temperature, hydrolyzing the POMe and the 3′-acetate groups to give the unprotected dinucleoside boranophosphate **2** (Scheme I), without any detectable degradation of the internucleotide or the glycosidic bonds. The deprotected boronated dimer is very soluble in water as compared to its protected counterpart, which is sparingly soluble. This product has also been characterized by ^1H NMR (including COSY), ^{11}B NMR, ^{31}P NMR, and FAB mass spectroscopies. In the ^1H NMR of **2**, two sets of peaks (for two diastereomers) were observed as opposed to only a single set of peaks (for both diastereomers) observed in the case of **1**.

The internucleotide boranophosphate group is very stable toward basic or acidic hydrolysis. Thus, heating **1** at 55 °C overnight in concentrated NH_4OH (conditions used for deprotection of bases in normal oligonucleotide synthesis) does not result in any change other than the deprotection described above. The boranophosphate group is also remarkably stable under acidic conditions. When shaken at room temperature overnight in a mixture of 1 N HCl and MeOH (1:1 v/v), <10% of the boranophosphate group is converted into phosphate (by ^{11}B and ^{31}P NMR). The 3′-acetate group is hydrolyzed although the POMe group appears to remain intact (by ^1H NMR).

Further, in preliminary studies, the boranophosphate group is also stable under the conditions required for chain elongation. Thus, reaction of **1** with 5′-DMT-thymidine phosphoramidite, followed by $Me_2S{\cdot}BH_3$ results in the formation of trimer **3** (Scheme I), in which both internucleotide linkages are boranophosphate groups.[7]

Finally, the boranophosphate internucleotide linkage in dimer **2** is quite stable toward cleavage by both calf spleen phosphodiesterase and snake venom phosphodiesterase. Thus, under the conditions where normal dithymidylyl phosphate is >97% cleaved, dimer **2** is >92% stable.

In summary, we have prepared two totally new types of modified oligonucleotides in which one of the oxygens in each internucleotide linkage has been replaced with a BH_3 group. The internucleotide linkages in boranophosphates are remarkably stable toward hydrolysis under basic[8] or acidic conditions or by exonucleases. Therefore, these linkages should be stable in vivo.

Thus, these nucleotides with boronated phosphates may represent a new class of potential therapeutic agents. Since these nucleic acids contain boron, the possibility of additional therapy using the unique neutron capturing ability of the nonradioactive ^{10}B isotope[9] (to produce in situ cell killing radiation) also exists.

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(8) The boranophosphate methyl esters on the other hand are base sensitive. Although they are expected to be stable in vivo, a modified method, like the one used by Miller et al.[4a] for the synthesis of phosphotriester, will be required for their synthesis in solid phase.

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Stereocontrolled Total Synthesis of (−)-Anisatin: A Neurotoxic Sesquiterpenoid Possessing a Novel Spiro β-Lactone

Haruki Niwa,* Masanori Nisiwaki, Itaru Tsukada, Takeshi Ishigaki, Shigeki Ito, Kazumasa Wakamatsu, Tatsuya Mori, Megumi Ikagawa, and Kiyoyuki Yamada

Department of Chemistry, Faculty of Science Nagoya University, Chikusa, Nagoya 464, Japan

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Anisatin (**1**) and neoanisatin (**2**), two convulsant principles isolated from the seeds of Japanese star anise (*Illicium anisatum* L.; shikimi in Japanese), are unique, highly oxygenated sesquiterpenoids characterized by a spiro β-lactone.[1,2] The structures of anisatin (**1**) and neoanisatin (**2**), except for the absolute stereochemistry, were based on both chemical and spectral studies.[2] Anisatin (**1**) and neoanisatin (**2**) are the most powerful poisons of plant origin. Recent neurochemical studies have shown **1** to be a picrotoxin-like, noncompetitive GABA antagonist.[3] Several synthetic studies focusing on these challenging molecules have been reported recently.[4] Herein we report the first total synthesis of the natural enantiomer of anisatin (**1**) via a highly stereocontrolled route. We note in advance that the present synthesis of (−)-**1** was achieved starting with bicyclic enone **4**[5] prepared from (*R*)-(+)-pulegone (**3**), and the absolute stereostructure of natural

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