Medical applications of boron compounds

Boron Targets Cancer

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Modifying chemical compounds found in living cells is one of the methods for developing potential new medications. Boron atoms included into multimolecular complexes, for example, can be used as precision targeting mechanisms for destroying diseased cells

Molecules containing boron have found a wide range of applications, including as insecticides, bactericidal agents, reducing reagents in organic chemistry, catalysts, materials for producing certain types of ceramics, components of liquid crystals and temperature-resistant polymers, plus many others. They have also long been an object of study as potential medications. Boron-modified amino acid analogs and their derivatives have recently been discovered to demonstrate anti-inflammatory, anti-arthritic, analgesic, and other properties.

In the 1970s, much interest was piqued by attempts at cancer treatment using what is called boron neutron capture therapy (BNCT). Such therapy introduces molecules containing the boron isotope ^{10}B into cancerous cells, and then the tissue is placed under a neutron beam. When such boron absorbs neutrons it immediately breaks down, emitting high-energy particles that destroy the cancerous cells. Researchers are therefore striving to create boron-bearing molecules that can be introduced into cancer cells in a special way.

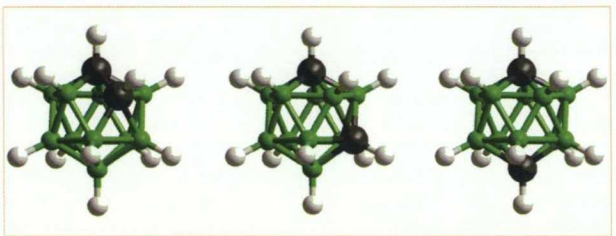
Cluster structures

More or less at the same time, attention shifted from molecules containing a single boron atom in their structure to more complex arrangements within a lattice structure, called carboranes and metallacarboranes.

Most simply speaking, carboranes are boron clusters in which one or more boron atoms are replaced by carbon atoms. Rapid advances in research on such compounds have been driven by the search for new boron carriers for use in BNCT. Derivatives of nucleosides (a composite element of nucleic acids) and oligonucleotides (short chains of nucleic acids) seem particularly attractive here: such molecules accumulate in cells, become built into DNA (nucleosides), and undergo accumulation in cell nuclei (oligonucleotides). Importantly, they are potentially specific and can be designed to "fit" certain cellular types of DNA and RNA.

A new generation of boron carriers for use in BNCT consists of biopolymers containing one or more carboranyl units. These are modified proteins, oligophosphates, and nucleic acids. Although BNCT treatment experiences periodic rises and falls (being used experimentally only in Japan, the United States, the Netherlands, and Sweden), information about the toxicity and pharmacokinetics of carboranes obtained from BNCT research is useful in studying compounds containing them with potential medicinal properties. For example, boron clusters' activity in inhibiting HIV virus replication and their anticancer action have recently been studied. The nucleosides bonded to boron clusters may also modulate the action of purinergic receptors.

Carboranes are precursors of metallacarboranes, which additionally include a metal ion (magnesium, iron, cobalt, nickel, molybdenum, rhodium, lead, platinum, palladium and many others). Metallacarboranes also have many applications. They can serve as homogenic catalysts, they can be used to extract metal ions from diluted water solutions, and they can act as cytostatic agents. In 1981, for example, the metallacarborane $[CpFe(III)(MeC_3B_7H_9)]^+$ and the unreactive $CpFe(II)(MeC_3B_7H_9)$ were shown to be effective cytostatic agents for many types of cancer, including lymphoid leukemia L-1210, cervical cancer Hela-S3, and lung bronchogenic cancer MB-9812. Large metallacarboranes may also form the basis for constructing "nano-machines." This process utilizes the fact that a change in the oxidation level of the metal ion within



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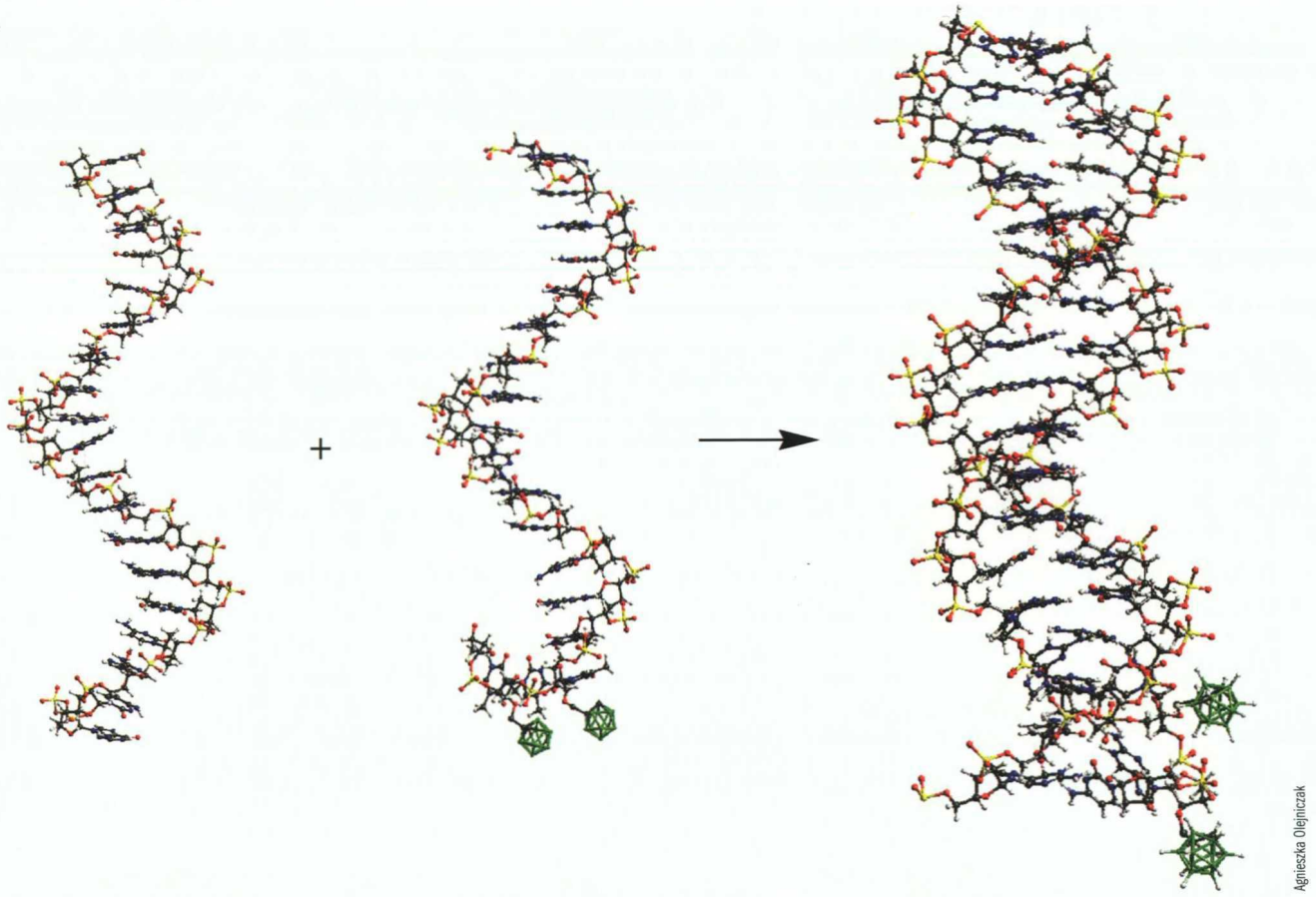
Clusters of boron atoms (green spheres) which also contain carbon atoms (black) are called carobranes. They can be attached to biologically active molecules and then tested for use in the therapy of many diseases



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One idea for precisely "targeting" a pathological factor is to utilize short DNA fragments (oligonucleotides) bonded with carboranes (green), which have a sequence corresponding to the target nucleic acids. Such carborane-modified oligonucleotides are being tested, for example, for their viability in cytomegalovirus therapy

the structure causes a shift in the configuration of the metallacarborane molecule.

First in Poland

The Laboratory of Molecular Virology and Biological Chemistry, at the Center for Medical Biology in Łódź, is Poland's only laboratory pursuing research on nucleic acids modified with boron clusters. Such research is interdisciplinary, standing at the crossroads of organic and inorganic chemistry, biology, and medicine. In recent years our work has concentrated on deriving methods of synthesizing new combinations between nucleosides and the carboranyl and metallacarboranyl groups. We have developed the first method for synthesizing purine nucleosides modified with the carbonyl group - here the model nucleoside was adenosine, as it is an important component of nucleic acids and coenzymes, and also a precursor of the biologically important compound adenosine phosphate.

Our laboratory's other notable achievements include work on a purine nucleoside derivative containing a hydrophobic carboranyl group bonded to the base, opening up the prospect of synthesizing a completely new sort of biologically important derivatives. Moreover, our work on methods of synthesizing the four basic nucleosides (T, dC, dA, dG) modified with the carboranyl group containing a cobalt ion (demonstrating diamagnetic properties) has led to two domestic patent requests filed in 2003 and an international patent filed in 2004.

Our research has also enabled the toxicity of metallacarborane conjugates and nucleosides to be evaluated in vitro, on the U118MG line of glioma cells - a model of human brain cancer. Their toxicity has been shown to be low, making them good candidates for further research as boron carriers in BNCT.

Over the past two years we have developed methods for synthesizing not only low-molecular conjugates of nucleosides containing boron, but also the corresponding modified nucleic acids. We have obtained a new class of antisense DNA-oligonucleotides containing a carboranyl group, which are complementary to the genome of the cytomegalovirus (HCMV), as well as DNA-oligomers modified with a metallocarboranyl group, which are complementary to a fragment of the gene encoding the insulin receptor substrate (IRS-1), whose over-expression is observed in certain types of cancer. It is our hope that these methods will contribute significantly to the development of new therapies for the diseases mentioned here. ■

Further reading:

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