SYNTHESIS OF NEW BORON POLYMERS

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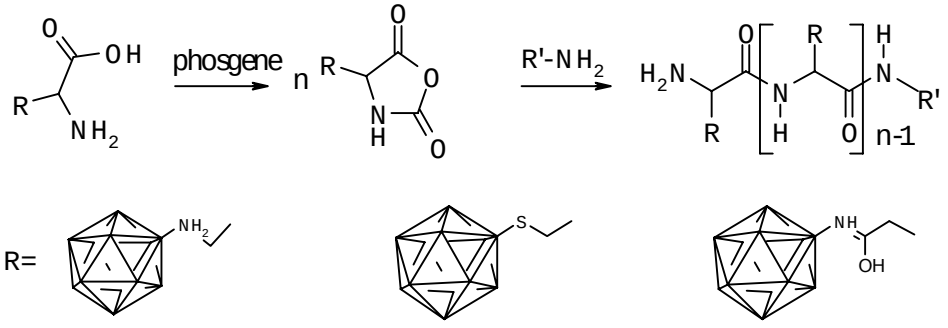
The principle for boron neutron therapy for treatment of cancer is the nuclear reaction that occurs when ^{10}B is irradiated with thermal neutrons. This reaction yields an unstable intermediate , ^{11}B, which undergoes fission, yielding ^{7}Li and ^{4}He. One of the conditions for this therapy to be successful depends on the ability to transport sufficient concentrations of boron to the tumor tissue and preferably localize the boron into the cell.

Criteria for BNCT Agents

In the early years of BNCT (1940-1961), agents were considered that were either readily available commercially or easily synthesized. They were evaluated exclusively for the treatment of brain tumors. Since that time, other tumors have been considered and the design of new tumor-targeting entities has not focused solely on malignant brain tumors.
The three most important parameters for compound development have essentially not changed since the early days of BNCT: (1) achieving tumor concentrations in the range of 20-35 µg ^{10}B/g; (2) a tumor: normal tissue differential greater than 1 and preferably 3-5; (3) sufficiently low toxicity so that the dose administered would be well tolerated first in animals and subsequently in patients. An added requirement was that the concentration differential would obviously persist during the entire neutron irradiation period[1].
Many workers are involved in the construction of carrier systems with capacity for enhanced loads of boron. Holmberg and co-workers[2] carried out the synthesis for polymers for BNCT using dextran and BSH. In principle, this approach seems to be useful. They observed, however, problems with low degree of substitution or the polymer units by the boron-containing compound. Also, in this approach there is much organic matter for each boron unit, and the attachment of targeting units and the transport to the tumor tissue is difficult. The same problems were met in the work of research group of Soloway[3]. They synthesized boronated starburst dendrimers and tried to boronate antibodies. The boronated antibodies did not show all necessary properties.

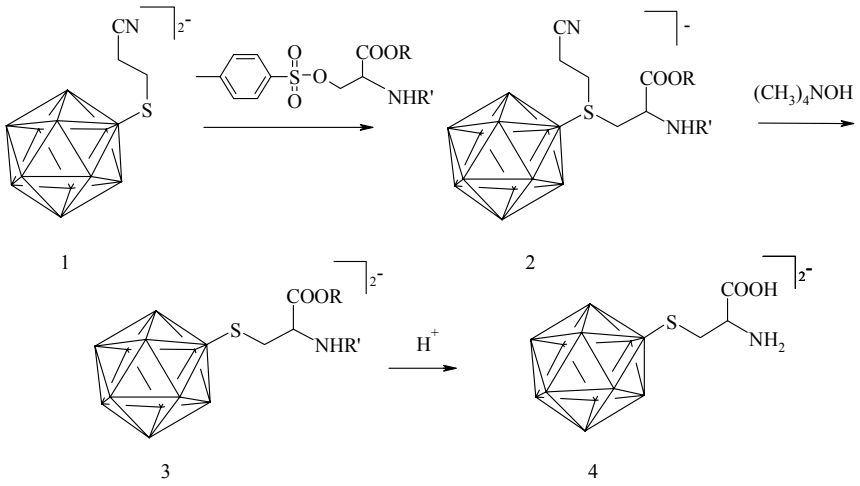


Our Ideas

After studying the work of our colleagues we are planning to synthesize boronated amino acids, which are water-soluble. After converting them to Leuchs anhydride by phosgene, they are polymerized by the addition of an amine. The advantage of our ideas is to produce polymers which carry boron in each monomer unit. There is only a single amino group and a single carboxyl group, at each end of the polymer. Polymerization can be started with an amino group of either the targeting unit or of a unit suitable for detection (fluorescent groups) inside the tumor tissue.

Results

We carried out a chain of reactions for preparation subunits for polymerization. First, cyanoethyl-$B_{12}H_{11}S$ is alkylated with a tosylated serine derivative, to give a sulfonium ion. The cyanoethyl group is removed by strong base, and the protecting groups of the serine are removed by acid. The amino acid will be reacted with phosgene to the Leuchs anhydride, which then is polymerized by the addition of an amine.
Alternatively, in order to reduce the net charge of the polymer, amino acids will be prepared which carry only a single negative charge per monomer.



All the synthesized compounds were characterized by NMR, IR and mass spectra.

Acknowledgment

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References

1. A.H. Soloway, W. Tjarks, B.A. Barnum, F-G. Rong, R.F. Barth, I.M. Codogni, and J.G. Wilson, The Chemistry of Neutron Capture Therapy, *Chem. Rev*., 98, 1998, 1515-1562.
2. A. Holmberg, L. Meurling, Preparation of Sulfhydrylborane-Dextran Conjugates for Boron Neutron Capture Therapy, *Bioconjugate Chem*., 4, 1993, 570-573.
3. L. Liu, R.F. Barth, D.M. Adams, A.H. Soloway, R.A. Reisfeld, Critical Evaluation of Bispecific Antibodies as Targeting Agents for Boron Neutron Capture Therapy of Brain Tumors, *Anticancer Research*, 16, 1996, 2581-2588.