Krzysztof Mariusz Borys, M.Sc.
Faculty of Chemistry, Warsaw University of Technology

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Abstract of the PhD Thesis

Synthesis and Investigation of Selected Properties of Oxaboroles

The research presented in the thesis focuses on oxaboroles – organic compounds featuring structural motives of both phenylboronic acids and their esters. Boronic compounds are most commonly associated with the Nobel Prize-winning Suzuki-Miyaura cross-coupling reaction for the formation of carbon-carbon bonds. However, the capacity of oxaboroles and boronic acids to reversibly bind diols has concurrently brought about a wide range of implementations in analytical and materials chemistry.

Among the derivatives of phenylboronic acid, an exceptional place is taken by 1,3-dihydro-1-hydroxy-2,1-benzoxaboroles, often shortly referred to as benzoxaboroles. These compounds can be regarded as the internal, cyclic hemiesters of 2-(hydroxymethyl)-phenylboronic acids. Benzoxaboroles have been found superior to phenylboronic acids in certain applications, mainly those requiring better stability and diols' binding at physiological pH. Another field of extensive studies of benzoxaboroles is their use as microbiologically active compounds, with Tavaborole as the first marketed drug of this class in the USA.

The presented literature review consists of three parts. First, physicochemical properties of benzoxaboroles are highlighted. The diol binding properties, Lewis acidity as well as structural and spectroscopic properties are discussed. Next, the reported methods for the synthesis of benzoxaboroles are shown, distinguishing them with regard to the starting materials used. Finally, the applications of benzoxaboroles are discussed, with the emphasis on their medicinal use and applications based on biomolecules binding.

The aims of the experimental part of the thesis comprised (i) the synthesis of novel benzoxaboroles as potential diol-binding and antifungal agents and (ii) the study of the interactions of oxaboroles and analogous compounds with diols.

The synthesis of hitherto unreported ferrocene derivatives of benzoxaborole has been developed. Two such compounds, including a ferrocene analogue of Tavaborole, have been obtained in a two-step procedure, starting from the commercially available ferrocenecarboxaldehyde. Concurrently, an efficient method for the preparation of the intermediates for their synthesis has been developed. All ferrocene derivatives have been characterized and undergone preliminary electrochemical studies. The obtained ferrocenyl

benzoxaboroles can constitute a novel class of redox-active boronic receptors for electrochemical sensing of diol analytes.

Next, a series of piperazine bis(fluorobenzoxaboroles) have been obtained and characterized. Since the literature method of the synthesis in solution afforded the products in very low to moderate yields, an alternative method for their preparation was sought. A mechanochemical approach have proved successful, delivering piperazine bis(benzoxaboroles) in moderate to good yields. In case of one derivative, the mechanochemical yield was almost 70% higher than the yield in solution.

The obtained bis(benzoxaboroles) along with their phenylboronic analogues have been evaluated in terms of their antifungal activity against seven fungal strains. The preliminary microbiological studies have shown that the antifungal activity in the studied series is affected by the position of the fluorine atoms as well as the presence of the oxaborole rings. Two compounds proved active against the investigated fungi.

Next, the interactions with diols have been investigated. Five benzoxaboroles, together with their 2-formyl analogues and several reference phenylboronic species have been the subject of diol receptor activity studies with the use of UV-Vis-monitored dye displacement assay. The study aimed at the determination of the association constants for the binding with a model dye (Alizarin Red S) and for the displacement with a model diol (ribose). The results implied the tautomerization of 2-formylphenylboronic acids to 3-hydroxybenzoxaboroles to affect the receptor activity of the 2-formyl species in solution.

Finally, the mode of binding of the unsubstituted benzoxaborole and five other structurally relevant boron compounds with β-cyclodextrin has been investigated. The structures of six mechanochemically obtained supramolecular assemblies were studied by means of ^{1}H NMR and ^{1}H-^{1}H ROESY NMR. The employed spectroscopic methods made it possible to distinguish between two possible binding modes and propose their structures. The studied benzoxaborole was found to form non-covalent, hydrogen bonding-based system with β-cyclodextrin. This also proved to be the case for phenylboronic acid and boric acid. Conversely, the catechol and pinacol esters of phenylboronic acid as well as ferroceneboronic acid got complexed inside β-cyclodextrin's cavity, forming host-guest inclusion complexes. The study shows the influence of boron compound structure on the nature of the assembly formed with β-cyclodextrin, laying up the basis for future work with such supramolecular systems.

keywords: oxaboroles, benzoxaboroles, boronic compounds, antifungal activity, diol binding