

Boron-Containing Phthalocyanines and Porphyrazines

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Dedicated to A. Yu. Tsivadze on the occasion of his 70th birthday

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The design and synthesis of boron-containing phthalocyanines and porphyrazines is reviewed. Some of the compounds obtained can be used as agents for photodynamic therapy (PDT) and boron neutron capture therapy of cancer (BNCT) as well as dual PDT/BNCT sensitizers.

Keywords: Phthalocyanines, porphyrazines, boron, polyhedral boranes, carboranes, metallacarboranes.

Борсодержащие фталоцианины и порфиразины

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Рассмотрены дизайн и синтез борсодержащих фталоцианинов и порфиразинов, которые могут найти использование в фотодинамической и бор-нейтронозахватной терапии рака.

Ключевые слова: Фталоцианины, порфиразины, бор, многогранные бораны, карбораны, металлокарбораны.

Introduction

Photodynamic therapy (PDT)^[1-7] and boron neutron capture therapy (BNCT)^[8-12] are selective treatment modalities for the local destruction of malignant tumors. The selectivity is based on the ability of a sensitizer molecule to preferentially accumulate in tumor tissue and upon its activation by the application of an external radiation source. In PDT photoactivation of sensitizer causes oxidative damage to a variety of cellular targets and subsequent tumor necrosis. In BNCT irradiation of boron compound with thermal neutron flux results in nuclear fission with localized emission of high

linear energy transfer (LET) particles (⁴He and ⁷Li) having a penetration range of less than 10 μm in biological tissues, which amounts to approximately one cell diameter.

Porphyrins and phthalocyanines employed for PDT demonstrate an improved selective accumulation in tumor tissues and retain there for a long period of time. This observation caused an interest in boron derivatives of porphyrins and phthalocyanines in order to find compounds which can be used as BNCT agents. Due to higher diversity of porphyrine compounds including many naturally occurring, the main attention was paid to synthesis of boron-containing porphyrins and this field has been reviewed several times since 2000.^[13-17]

This review describes the recent development of the chemistry of boron-containing phthalocyanines and porphyrazines excluding chemistry of boron subphthalocyanines^[18] which are intensively studied during the last two decades as precursors for asymmetrically substituted phthalocyanines^[19-21] and components of organic electronic materials.^[22]

Boron-Containing Phthalocyanines

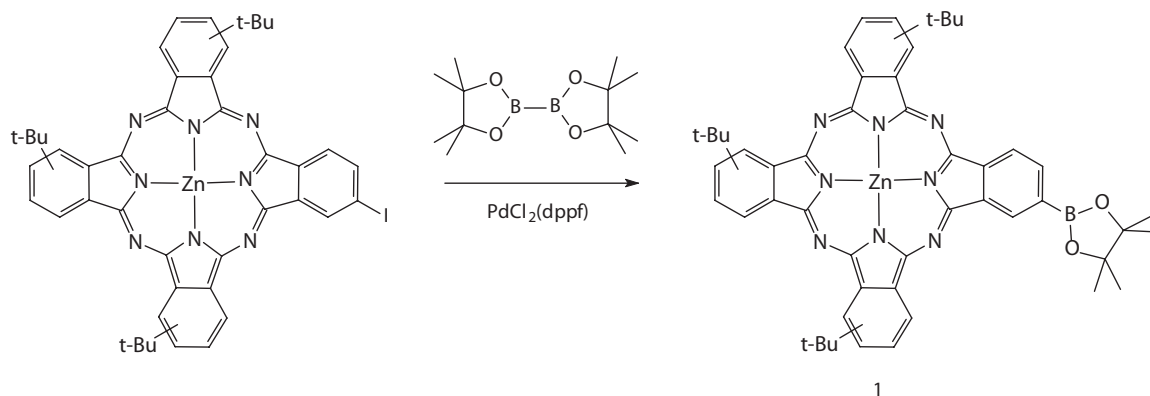
Tri- and Tetra-coordinated Boron Compounds

Since the discovery of phthalocyanines, many efforts are geared towards synthesis of their various derivatives,^[23,24] however only a very limited number of synthesis of boron-containing phthalocyanines has been reported. In general there are two main approaches to synthesis of boronated phthalocyanines. The first one is based on modification of preformed macrocyclic core through the introduction

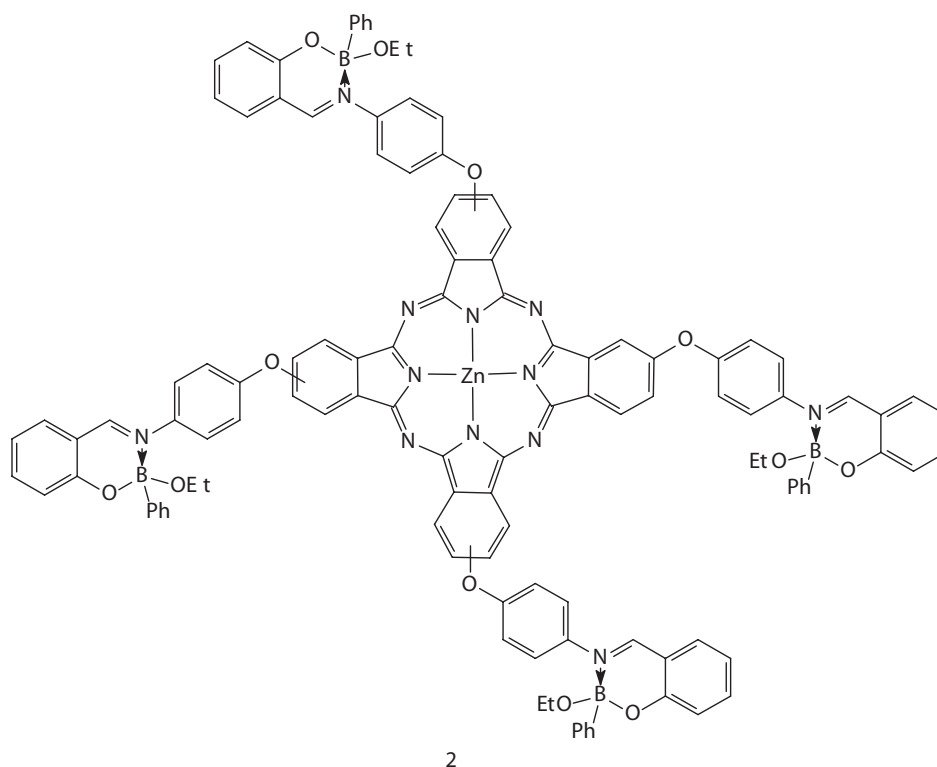
of a boron moiety. The other one includes the template condensation of the corresponding boron-containing phthalonitriles. The synthetic scheme depends strongly on stability of boron fragment used. Low stability of majority of tri- and tetra-coordinated boron compounds under conditions of the template condensation precludes use of this approach.

Synthesis of the first phthalocyanine **1** containing tricoordinated boron atom at the periphery of the phthalocyanine backbone was reported only in 2009 using the Pd-catalyzed cross-coupling reaction of monoiodo tri-*tert*-butyl zinc phthalocyanine with bis(pinalcolato) diboron (Scheme 1).^[25] This Suzuki-phthalocyanine synthon was used for synthesis of various aryl phthalocyanines including covalently linked phthalocyanine-phthalocyanine heterodimers and phthalocyanine-phthalocyanine triads^[25] and phthalocyanine-peptide conjugates.^[26]

Synthesis of the first phthalocyanine **2** containing substituents with tetracoordinated boron atoms by the complexation of zinc phthalocyanine bearing four salicy-



Scheme 1.



Scheme 2.

lideniminophenyloxy substituents with benzenboronic acid has been reported very recently (Scheme 2).^[27]

Polyhedral Boron Compounds

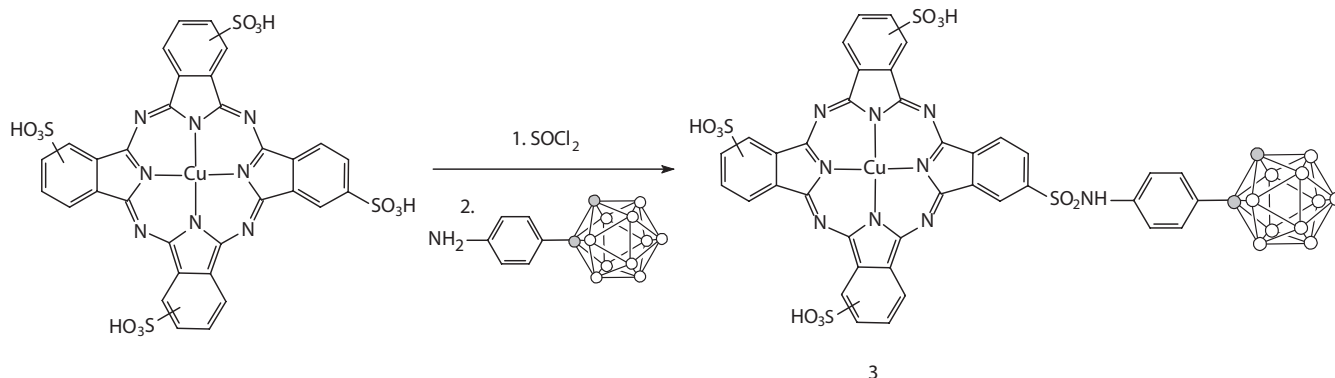
Much more work has been devoted to the synthesis of phthalocyanines containing polyhedral boron clusters (boranes, carboranes and metallacarboranes). The first report on compounds containing both carborane and phthalocyanine fragments was published in 1970 and dealt with thermal stability of polymers containing carborane and phthalocyanine groups.^[28] Later this area was covered by a few patents.^[29-31]

Further development of this field is associated mainly with design and synthesis of new BNCT drugs. The first reported carborane-containing phthalocyanine for BNCT was prepared using the first approach by the reaction of 1-(4-aminophenyl)-*o*-carborane with copper(II) phthalocyanine tetrasulfonylchloride followed by the hydrolysis of unreacted chlorosulfonic acid to sulfonic acid groups (Scheme 3).^[32,33] Unfortunately, no detailed information on synthesis and characterization of phthalocyanine **3** was reported.

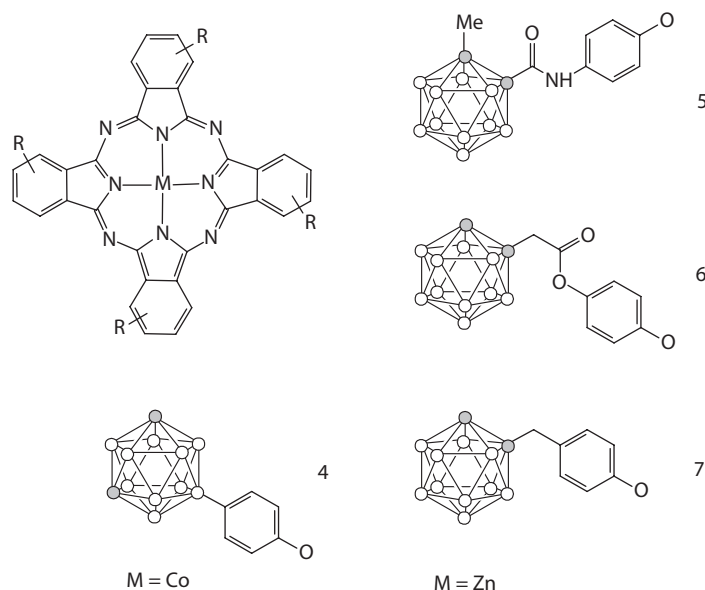
High thermal and chemical stability of the carborane cage allows one to use both approaches to synthesis

of carborane-containing phthalocyanines. A series of carborane-containing phthalocyanines was prepared by the tetramerization of boron-containing phthalocyanine precursors. The cobalt phthalocyanine **4** was prepared in 24 % yield by the reaction of CoCl_2 with 4-[4-(*meta*-carboran-9-yl)phenoxy]phthalonitrile at 200 °C (Scheme 4).^[34] The zinc phthalocyanines **5** and **6** were prepared in 12 and 38 % yields, respectively, by the reaction of zinc acetate with the corresponding phthalonitriles with at 220 °C. An alternative route based on acylation of zinc phthalocyanines bearing aniline and phenol terminal groups with the corresponding *ortho*-carboranyl acylchlorides gave **5** and **6** in 65 and 53 % yields, respectively (Scheme 4).^[35] In a similar way the reaction of zinc acetate with 3-[4-(*ortho*-carboran-1-yl)methylphenoxy]phthalonitrile at 210 °C gave the boronated zinc phthalocyanine **7** in 40 % yield (Scheme 4).^[36,37]

It was demonstrated that boronated phthalocyanine **7** can be efficiently accumulated by B16F1 melanotic melanoma cells *in vitro* and, upon red light irradiation, induced extensive cell mortality. The intravenous injection of **7** to C57BL/6 mice bearing a subcutaneously transplanted pigmented melanoma followed by irradiation with thermal neutrons 24 h after injection led to a 4 day delay in tumor growth as compared with control untreated mice. These



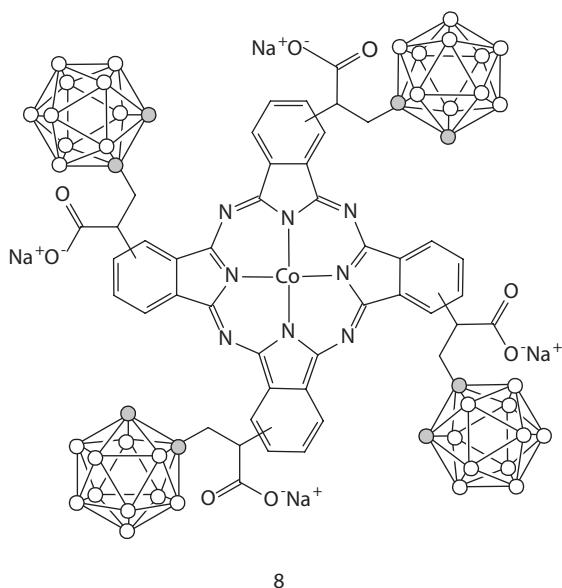
Scheme 3.



Scheme 4.

results open the possibility to use **7** both as a photosensitising and a radiosensitising agent for the treatment of tumors by the combined application of photodynamic therapy and boron neutron capture therapy.^[37]

It should be noted that described above carborane-containing phthalocyanines **4-7** are highly hydrophobic and insoluble in water. Water-soluble cobalt phthalocyanine **8** was prepared in 16 % yield by the condensation of CoCl_2 with dimethyl (3,4-dicyanophenyl)(*ortho*-carboran-1-yl-methyl)malonate at 200 °C followed by ester deprotection and cation exchange (Scheme 5).^[38] Water solubility of **8** is provided by the introduction of four carboxylic groups and their conversion to sodium salts.



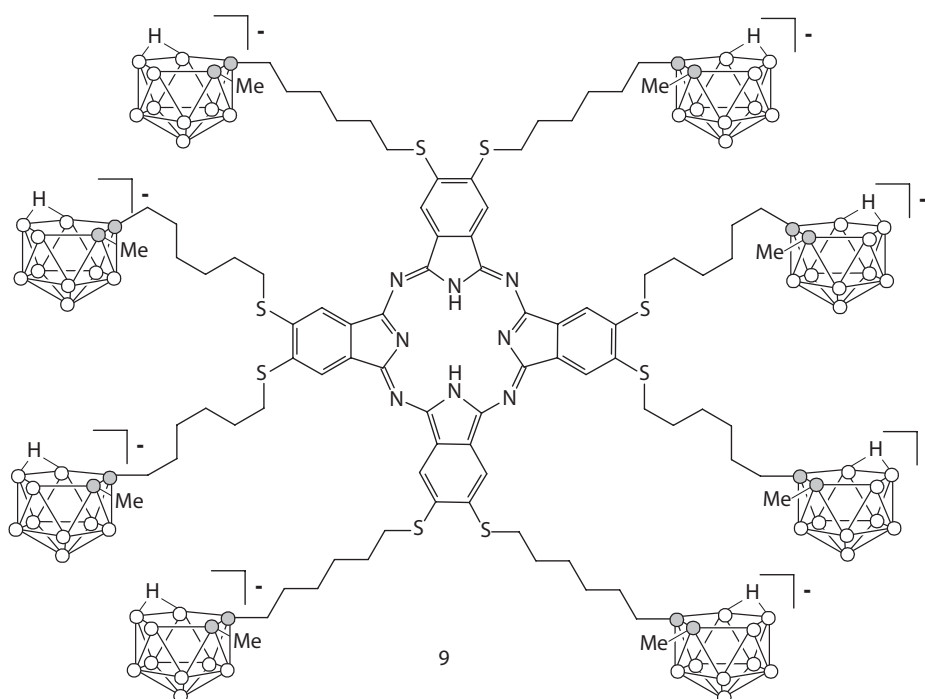
Scheme 5.

Another way to reach water-solubility of carborane derivatives is their transformation from the *closo*- to *nido*- form that can be performed in the presence of strong nucleophiles.^[39] Phthalocyanine **9** bearing eight *nido*-carborane groups was prepared by DBU-promoted cyclotetramerization of 4,5-dithiohexyl-(1-methyl-1,2-*ortho*-carboran-2-yl)-1,2-dicyanobenzene in *n*-butanol at 140 °C. Under these conditions the *ortho*-carborane cage undergoes partial deboronation to the *nido*-form resulting in water-soluble phthalocyanine **9** (Scheme 6).^[40]

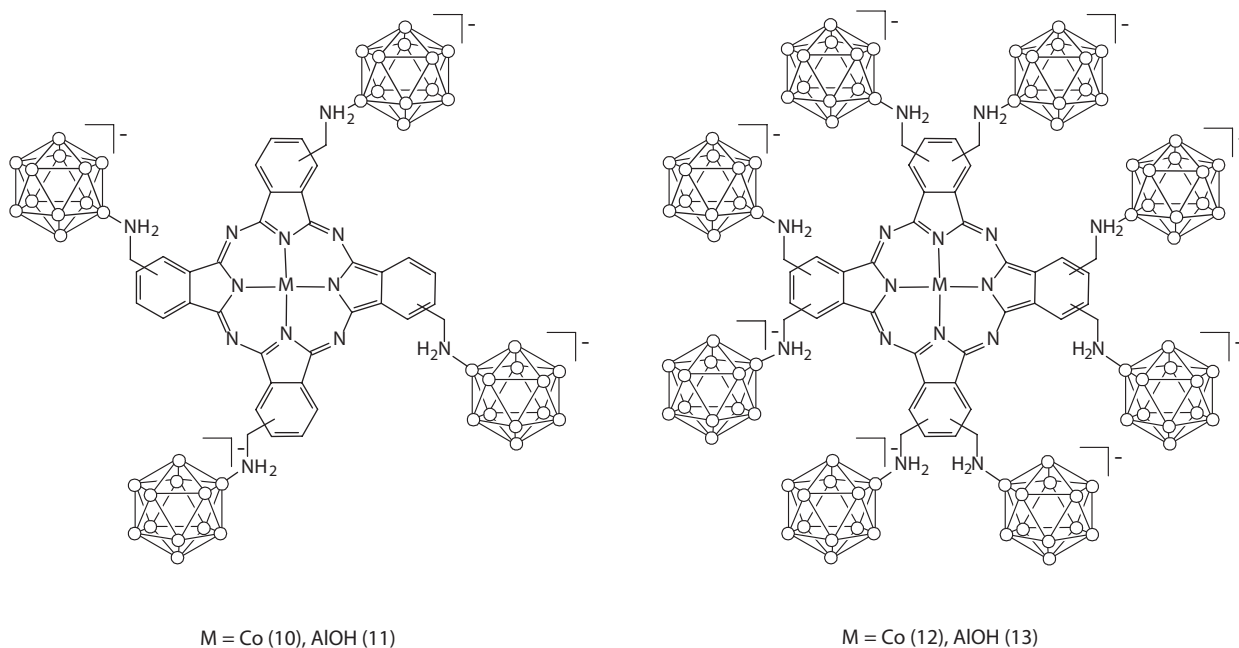
Water solubility of boronated phthalocyanines can be reached by change the carborane cages for the anionic dodecaborate moieties.^[41,42] However, due to higher reactivity of the *closo*-dodecaborate $[\text{B}_{12}\text{H}_{12}]^{2-}$ only the first approach can be used for synthesis of boronated phthalocyanines containing the *closo*-dodecaborate fragments. The first highly-boronated phthalocyanines **10-13** containing the *closo*-dodecaborate cages were prepared by the reaction of the aminododecaborate $[\text{B}_{12}\text{H}_{11}\text{NH}_3]^-$ with chloromethyl derivatives of phthalocyanines (Scheme 7).^[43] *In vivo* studies on B-16 mouse melanoma model demonstrated moderate tumor accumulation and rather high blood/tumor ratio for phthalocyanine **10** and no tumor accumulation for phthalocyanine **11**.^[44]

Boronated zinc phthalocyanine **14** was prepared in 71 % yield by the reaction of zinc 2-(4-carboxyphenoxy) phthalocyanine with sodium mercapto-*closo*-dodecaborate (Scheme 8) and its photosensitizing properties at molecular and cellular level were studied.^[45]

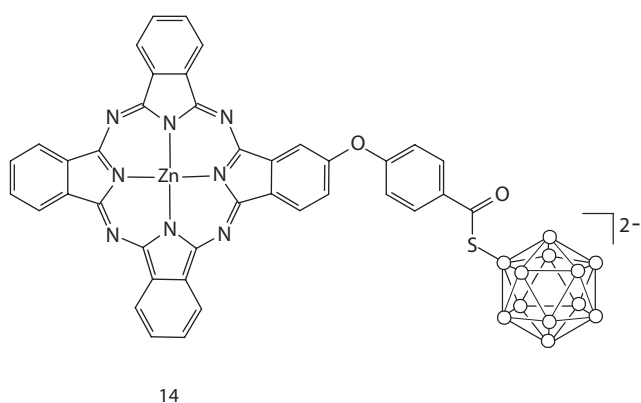
Some later the ring opening of cyclic oxonium derivative of the *closo*-dodecaborate anion^[46] with nucleophiles was used for synthesis of zinc phthalocyanine **15** with four boron fragments connected to the phthalocyanine core through flexible spacers (Scheme 9). The reaction of zinc phthalocyanine containing four 4-hydroxyphenoxy



Scheme 6.



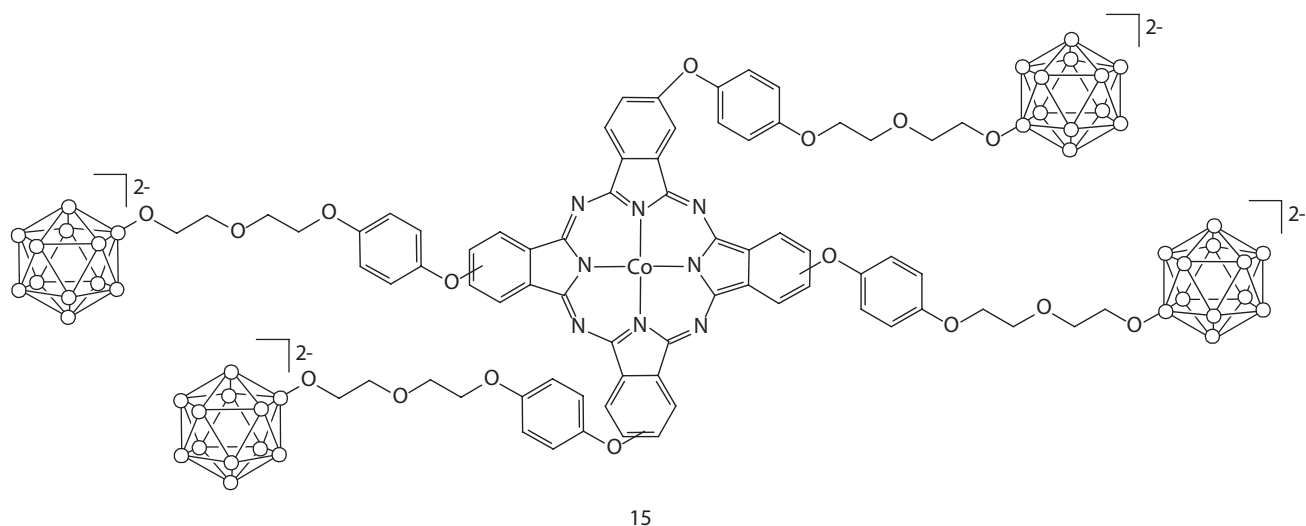
Scheme 7.



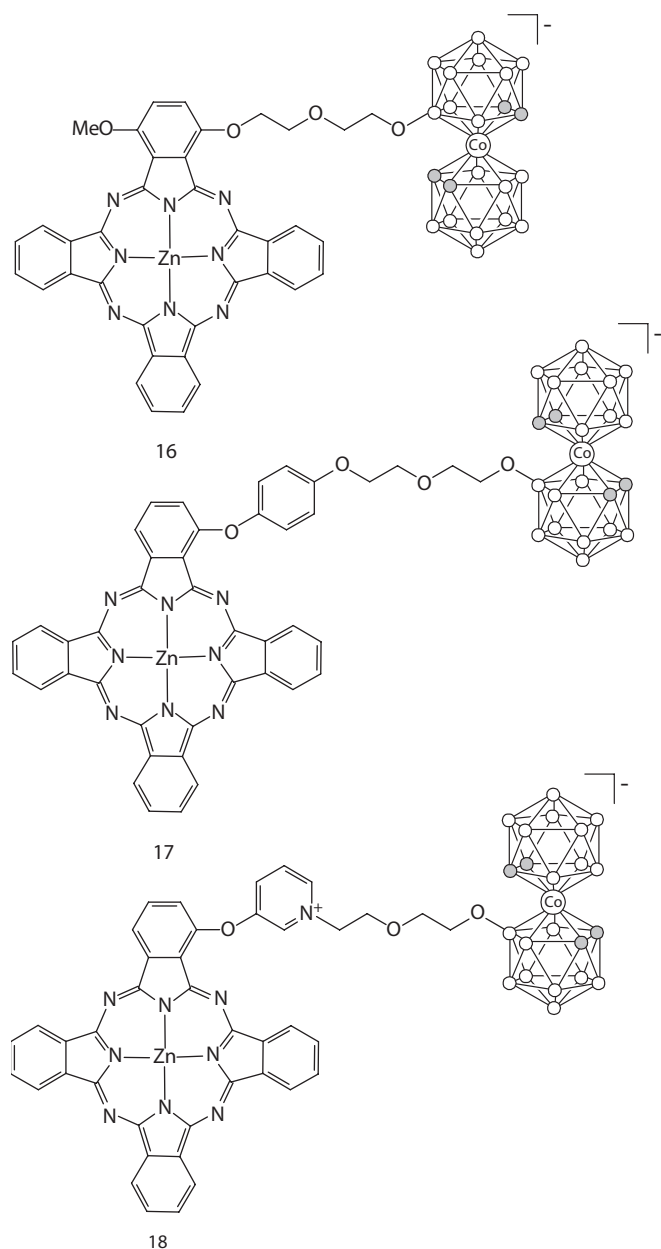
Scheme 8.

substituents with the 1,4-dioxane derivative of *closododecaborate* in the presence of K_2CO_3 gave the desired product in the 66 % yield.^[47]

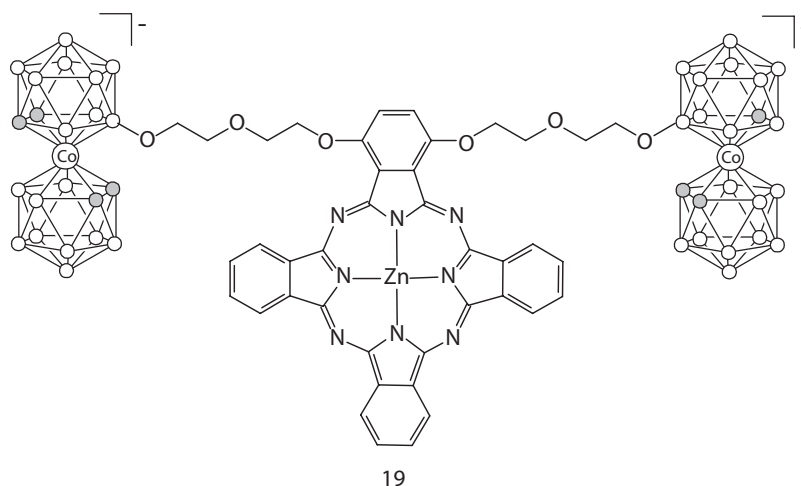
Cobalt bis(dicarbollide) $[3,3'\text{-Co}(1,2\text{-C}_2\text{B}_9\text{H}_{11})_2]^{48]}$ is another boron moiety providing water solubility of boronated phthalocyanines. A series of zinc phthalocyanines **16-19** bearing one or two boron fragments was prepared via cyclotetramerization of the corresponding cobaltacarborane substituted phthalocyanines with excess of phthalonitrile in the presence of $Zn(OAc)_2$ in quinoline at 220 °C (Schemes 10 and 11).^[49,50] The boronated phthalonitriles were synthesized using the 1,4-dioxane derivative of cobalt bis(dicarbollide). The yields of boronated phthalocyanines are low and vary from 1 % for **18** to 15 % for **16**.



Scheme 9.



Scheme 10.



Scheme 11.

The described examples concern introduction of boron fragments on periphery of the phthalocyanine macrocycle. An alternative approach includes attachment of boron fragments to the axial positions of metal phthalocyanines. Synthesis of a series of boron-containing phthalocyanines by the reaction of silicon phthalocyanine dichloride with carborane-containing alcohols was described in patent literature.^[51]

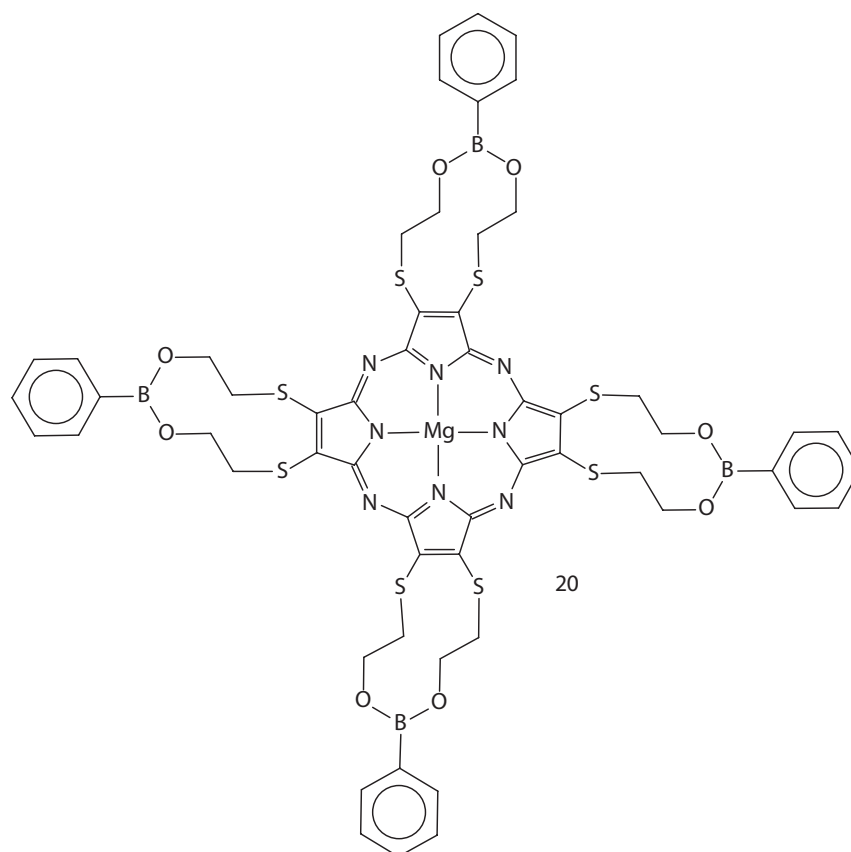
Boron-Containing Porphyrazines

Porphyrazines attract interest of researchers working in the NCT fields in the last five years when the first boron-containing porphyrazines were synthesized. As in the case of phthalocyanines, there are two approaches to synthesis of boronated porphyrazines: 1) the first approach is based on modification of preformed macrocyclic core through the introduction of a boron moiety; 2) the second approach includes the template condensation of the corresponding boron-containing maleonitriles. The first approach was used for synthesis of the first porphyrazine containing tri-coordinated boron by reaction of magnesium octa(2-hydroxyethylthio)porphyrazine with phenylboronic acid (Scheme 12).^[52]

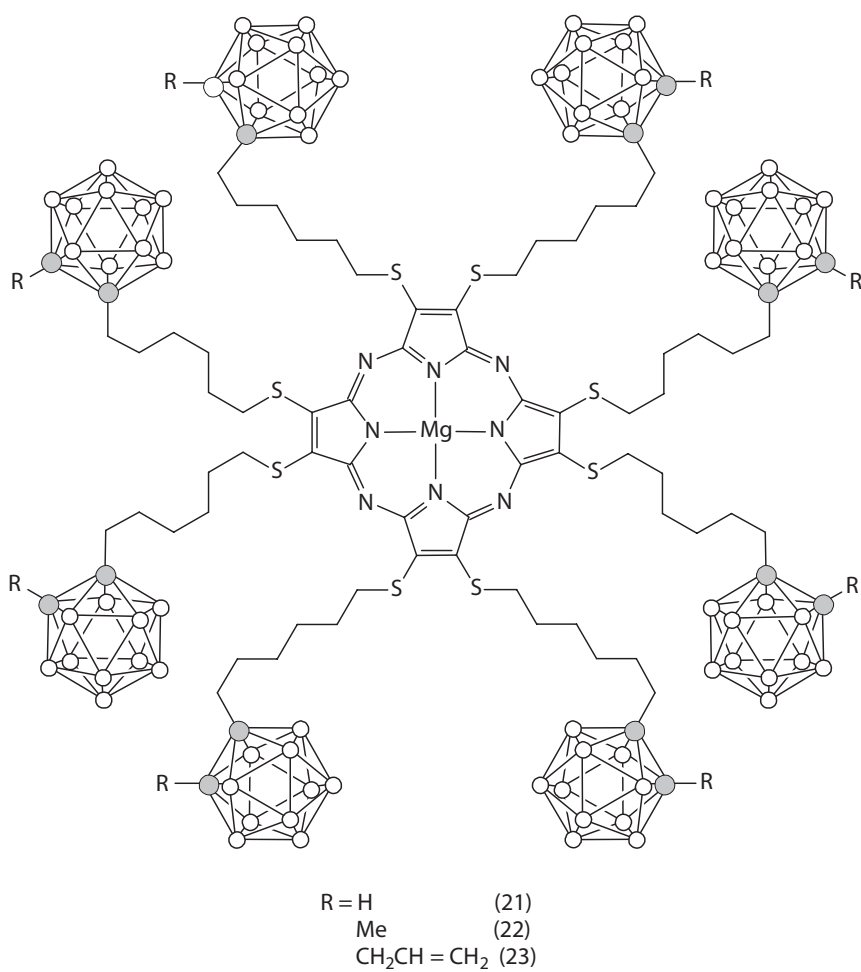
The second approach was used for synthesis of carborane-containing porphyrazines. A series of porphyrazines **21–23** containing eight carborane fragments was prepared by cyclotetramerization of the corresponding carborane-containing maleonitriles in *n*-propanol at 110 °C in the presence of $\text{Mg}(\text{OPr})_2$ (Scheme 13).^[53–56] The synthesized highly hydrophobic porphyrazines were solubilized *via* loading into liposomes of different types and physico-chemical properties of these lipids were studied.^[54–57]

To enhance water-solubility of the prepared porphyrazines the *closo*-carborane groups can be converted to the *nido*-carborane ones by the treatment with CsF followed by the Cs/K exchange to give the corresponding water-soluble boronated porphyrazines (Scheme 14).^[53]

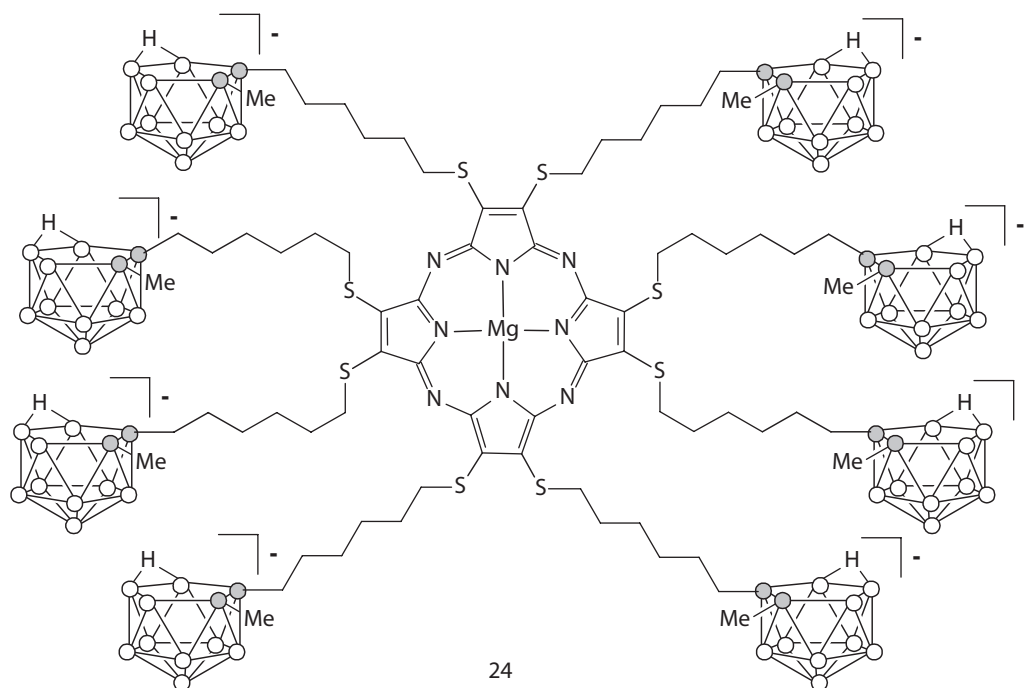
More recently synthesis of the highly boronated porphyrazine **25** containing sixteen carborane fragments has been reported (Scheme 15).^[58]



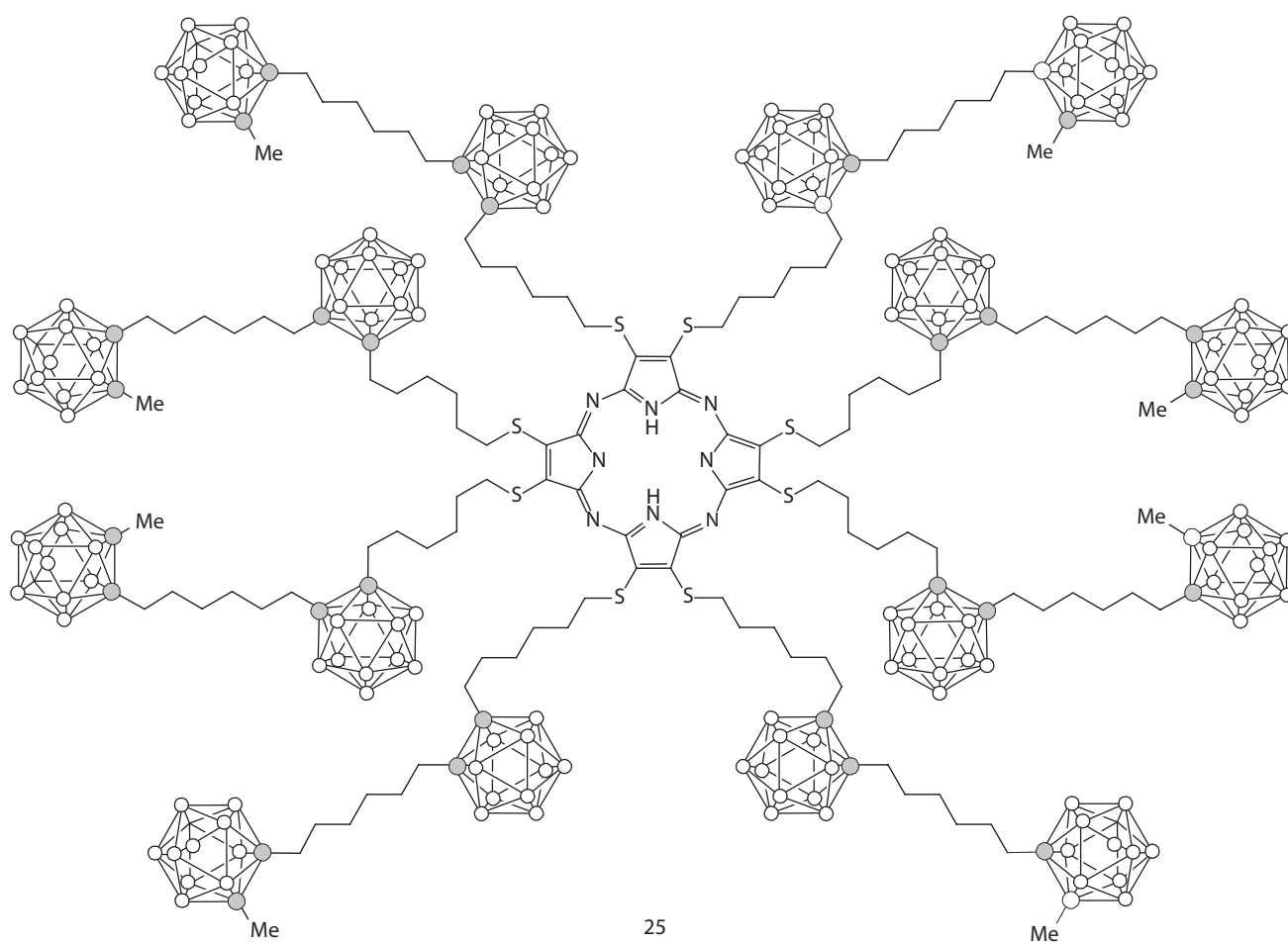
Scheme 12.



Scheme 13.



Scheme 14.



Scheme 15.

Conclusions

Ten years ago we noted in our review^[13] that “chemistry of polyhedral boron derivatives of phthalocyanines is practically non-developed”. The last decade gave a series of new examples of boronated phthalocyanines and porphyrazines bearing from one to sixteen boron fragments of various structure containing from one to eighteen boron atoms. The obtained results open new perspectives for synthesis of new BNCT agents based on tetrapyrrole macrocycles.

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