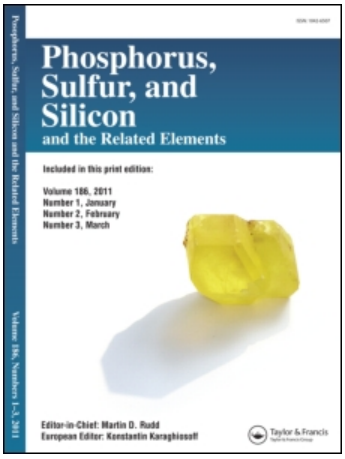

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A NEW APPLICATION OF INORGANIC CLUSTER, CARBORANES FOR MEDICINAL DRUG DESIGN AND MOLECULAR CONSTRUCTION

Yasuyuki Endo,[a] *Kiminori Ohta,*[a] *Tomohiro Yoshimi,*[a] *and Kentaro Yamaguchi*[b]
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*The inorganic cage compounds, dicarba-*closo*-dodecaboranes (carboranes), are chemical building blocks of remarkable thermal and chemical stability, with spherical geometry and exceptional hydrophobic character. We have focused on medicinal drug design using carboranes as a hydrophobic pharmacophore and have developed a potent estrogen agonist, BE120. We also have applied carboranes for structural chemistry, utilizing their specific three-dimensional character to obtain multilayer aromatic structures.*

Keywords: Carborane drugs; diranbadodecaboranes

The icosahedral carboranes have characteristic properties, such as high boron content, remarkable thermal and chemical stability, spherical geometry and hydrophobicity.[1] The high boron content and chemical stability are utilized in materials chemistry and in the specific field of boron neutron capture therapy (BNCT).[2] However, we have focused on the possibility of using carboranes as a hydrophobic component in biologically active molecules, which interact hydrophobically with receptors,[3] and on the potential of carboranes as components or building blocks in supramolecular systems, based on their characteristic shape.

The carboranes have several desirable features for application in molecular design. The rigid and bulky cage structures hold substituents in well-defined spatial relationships. The two carbon atoms of carboranes bear relatively acidic protons that can readily be substituted with metal and organic groups. Substituents also can be introduced

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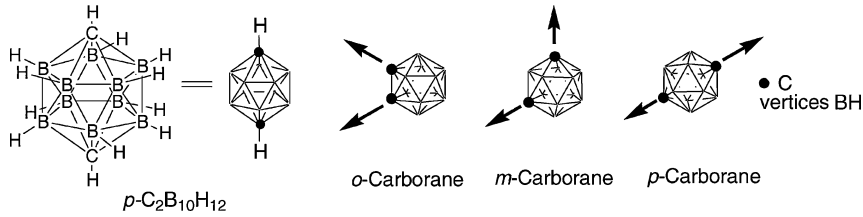

FIGURE 1 Cage structure of carborane (left) and directions of substituents of 3 isomers of carboranes (right).

at certain boron vertices (Figure 1). The B—B and C—B bond lengths of 12-vertex carboranes are approximately 1.8 A, and the molecular size of carboranes is somewhat larger than that of adamantane or a rotated benzene ring.

RESULTS AND DISCUSSION

Estrogen is an important hormone that mediates a wide variety of cellular responses through its binding to a specific estrogen receptor (ER). High binding affinity for estrogen receptor and the appearance of estrogenic activity require a phenolic ring, an appropriate hydrophobic group adjacent to the phenolic ring, and another hydroxyl group located at a suitable position on the molecule, as in 17β-estradiol (**1**). Therefore, we designed a simple compound having a 4-phenolic residue and a hydroxymethyl group on the *p*-carborane (Figure 2). The structure of the designed compound resembles that of estradiol. The estrogenic activities of the synthesized compounds were examined by means of luciferase

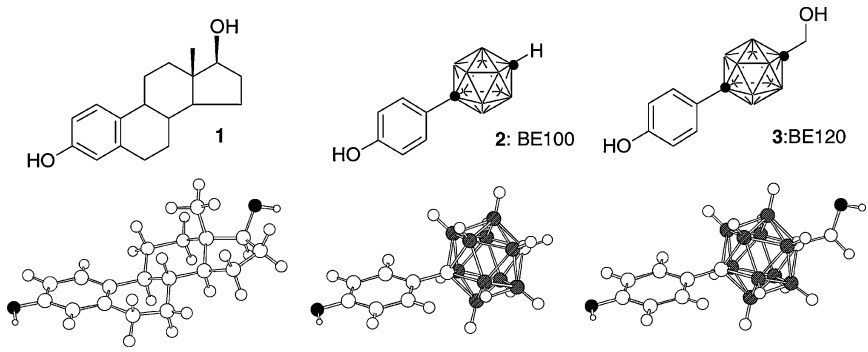

FIGURE 2 Designed estrogen agonist bearing carborane (**2** and **3**) based on the structure of β-estradiol (**1**).

reporter gene assay and receptor binding assays. Surprisingly, the simple 4-(*p*-carboranyl)phenol (BE100, **2**) exhibited potent binding affinity to ERα. Its potency is comparable to that of estradiol. The activity was increased by the introduction of a hydroxymethyl group onto carbon of the carborane cage. The most potent compound, BE120 (**3**), was several times more active than estradiol. BE120 (100 ng/day) also showed potent in vivo activity to restore the uterine weight of ovariectomized mice.[4]

We also have aimed to apply carborane geometry for the design and synthesis of three-dimensional structures. It has been reported that *N*-methylation of aromatic amides and ureas causes conformational alteration.[5] The secondary ureas exist in *trans,trans*-conformation, and the *N*,*N*′-methylated ureas prefer *cis,cis*-orientation, both in the crystal and in solution. To evaluate the possibility of employing carboranes containing aromatic urea structure to construct more complex molecules, we first synthesized compounds in which extremely bulky carborane units were attached at 3-, 4- and 3,5-positions, and investigated whether the *cis*-preference of the aromatic ureas is retained

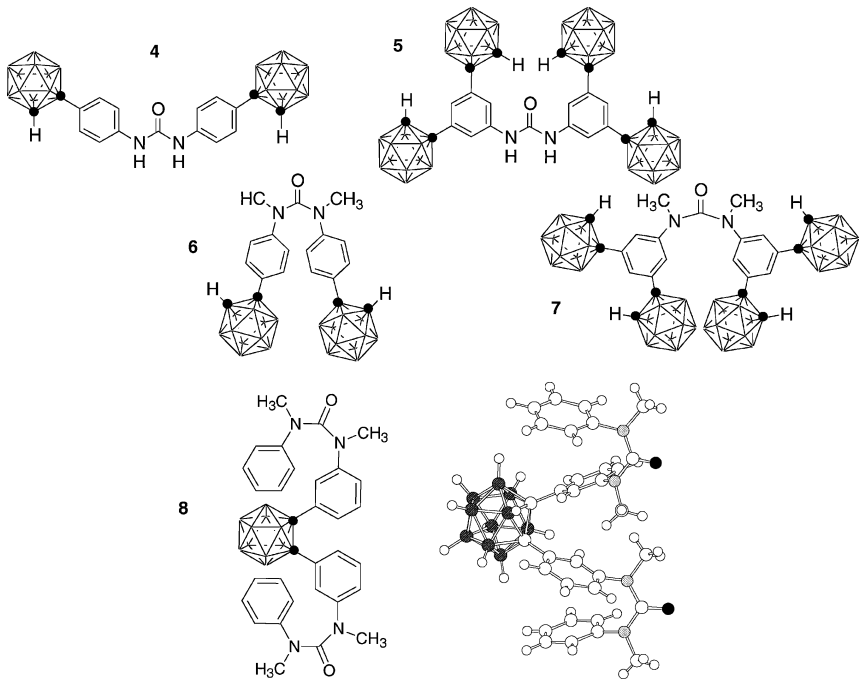

FIGURE 3 Structures of aromatic ureas (**4–7**) and aromatic multi-layered molecules **8**.

or not. The secondary ureas exist in *trans*-conformation, for example, **4** and **5** (Figure 3). On the other hand, in spite of the bulkiness of the carborane cage, the *N*-methylated ureas exist in *cis*-conformation, both in solution and in the solid state (**6** and **7**) (Figure 3). These results should make it possible to construct complex molecules.[6] The face-to-face geometry of aromatic rings on a carboranylphenylurea scaffold was applied to prepare aromatic multi-layered molecules.[7] Among the synthesized four-decker aromatic ureas, recrystallization of several compounds afforded single crystals suitable for x-ray crystallography. The compounds with the 1,3-disubstituted benzene moiety with two *o*-carboranyl units and one urea unit, and the compound with one *o*-carboranyl and two urea units (**8**), formed multilayer aromatic structures with *W*-shaped conformation.

Further development should make it possible to synthesize a range of carborane-containing functionalized molecules that would be useful in the fields of medicinal chemistry, materials science, and supramolecular chemistry.

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