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# Utility of Boron Clusters for Drug Design. Hansch–Fujita Hydrophobic Parameters π of Dicarba-*closo*-dodecaboranyl Groups

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**Abstract**—The spherical boron clusters, dicarba-*closo*-dodecaboranes (carboranes) are new hydrophobic pharmacophores, which interact hydrophobically with receptors. We have experimentally measured the partition coefficients log *P* for carboranylphenols employing an HPLC method, and determined the Hansch–Fujita hydrophobic parameters π of various carboranyl groups. The values (π = 2.69–4.44) vary depending on the position of substitution on the carborane cage and the isomeric form (*o*-, *m*-, *p*-carboranes). These values lie within the range of those of hydrocarbons. 

The icosahedral carboranes (dicarba-*closo*-dodecaboranes) have characteristic properties, such as high boron content, remarkable thermal and chemical stability, spherical geometry and exceptional hydrophobic character. Their unusual properties have been utilized in materials chemistry in the preparation of materials for liquid crystals[1] and non-linear optics[2] and in medicinal chemistry in the field of boron neutron capture therapy (BNCT).[3] We have focused on the possibility of using carboranes as a hydrophobic component in biologically active molecules which interact hydrophobically with receptors. This concept has been realized by the synthesis of several biologically active peptides, in which phenylalanine residues were replaced with (*o*-carboranyl)alanine.[4] However, this concept has not been extended to the possible use of carborane as a hydrophobic skeletal structure, in the field of drug design. Recently, we have reported examples of the design, synthesis and biological evaluation of nuclear receptor ligands (estrogens[5,6] and retinoids[7]) and other biologically active molecules[8] containing a carborane cage as a hydrophobic pharmacophore. These drug designs are based on the hydrophobic nature of carboranes. However, there is only one report on the hydrophobic parameter of one carborane-containing group, *o*-carboranylmethyl, evaluated by considering the side chains of glycine[9] and this has been the basis for the putative hyperhydrophobicity of carboranes. In the framework of studies for application of carboranes on medicinal chemistry, we have designed and synthesized nuclear receptor ligands bearing a variety of carborane-containing substituents, and found that alteration of the position of substitution on the carborane cage affected the biological activities. Therefore, quantitative evaluation of the hydrophobic character of various types of carboranes is important if carboranes are to be widely utilized in drug design. We describe here measurement of the partition coefficients log *P* for eight carboranylphenols (**1**–**8**) by employing an HPLC method and we present the Hansch–Fujita hydrophobic parameters π of the various carboranyl groups.

We selected carboranylphenols for the determination of the hydrophobic parameters π of the carboranyl group, because determination of partition coefficients of phenol derivatives is one of the fundamental methods for determination of 'aromatic' substituent constants,[10] and some of these carboranylphenols exhibited potent binding affinity to estrogen receptor.[5] We designed eight 4-(*o*-, *m*- and *p*-carboranyl)phenols (**1**–**8**). The syntheses of the molecules are summarized in Fig. 1. The three C-substituted carboranylphenols, 4-(*o*-, *m*-, *p*-carboran-1-yl)phenols (**1**–**3**) were prepared by coupling of the C-copper(I) derivative of the corresponding carborane with 4-iodoanisole in dimethoxyethane in the presence of pyridine,[11] followed by demethylation with boron

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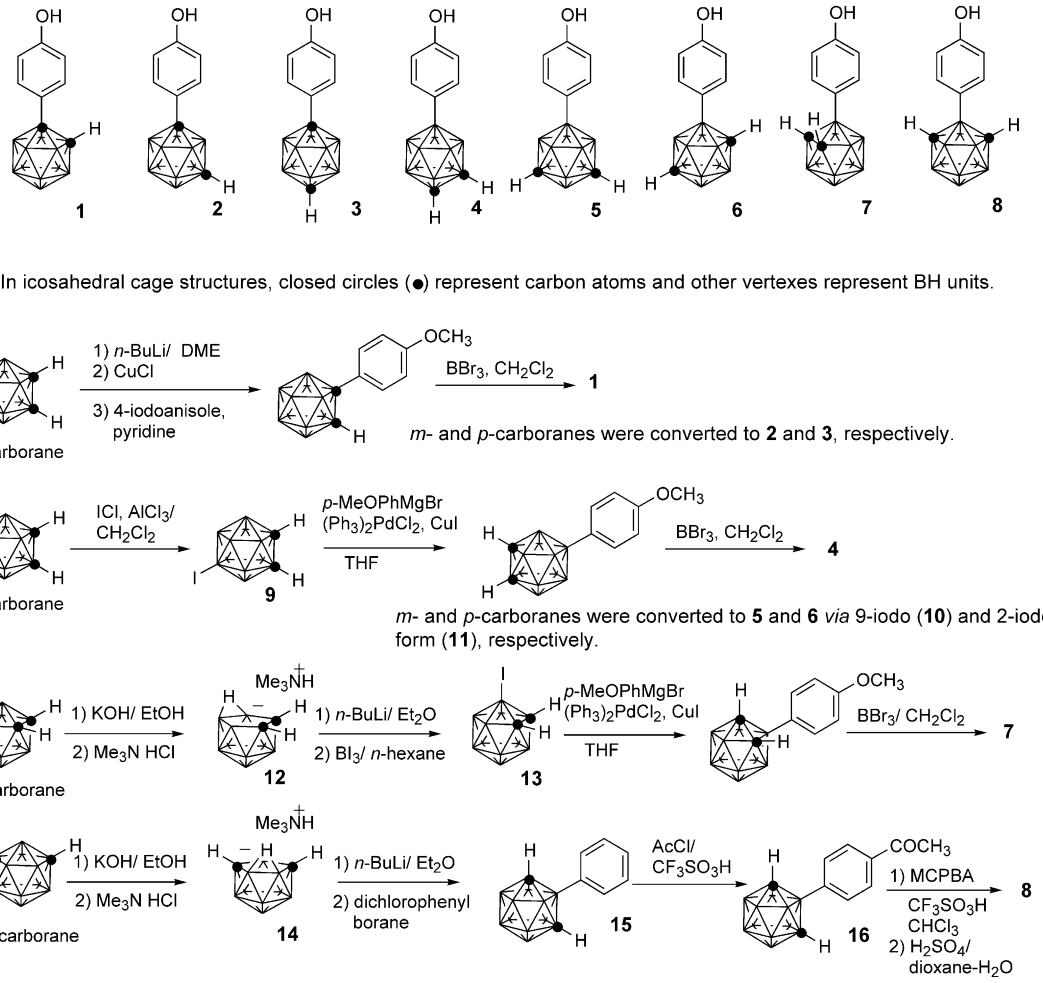


**Figure 1.** Design and preparation of carboranylphenols (**1**–**8**).

tribromide[5] in 27–56% yield (two steps). Substituents can be also introduced selectively at some boron vertices. Friedel–Crafts mono-halogenation of *o*-, *m*-, *p*-carborane proceeds on the most electron-rich boron atom[12,13] to give 9-iodo-*o*-carborane (**9**), 9-iodo-*m*-carborane (**10**) and 2-iodo-*p*-carborane (**11**), respectively (63–91%). Coupling reaction of the *B*-iodocarboranes with Grignard reagent in the presence of dichlorobis(triphenylphosphine)palladium,[13] followed by demethylation with boron tribromide afforded 4-(*o*-carboran-9-yl)phenol (**4**), 4-(*m*-carboran-9-yl)phenol (**5**) and 4-(*p*-carboran-2-yl)phenol (**6**), respectively (72–89%). On the other hand, nucleophilic attack occurs at the most electron-deficient boron atom of *o*-carborane, and a strong nucleophile such as alkoxide affords deboronated *nido*-7,8-$C_2B_9H_{12}^-$(**12**).[14] Boron-insertion reaction of the *nido*-anion with boron triiodide[15] gave 3-iodo-*o*-carborane (**13**), which was converted to 4-(*o*-carboran-3-yl)phenol (**7**) in 15% yield (three steps) using the same procedure described for **4**–**6**. Deboronation of *m*-carborane by alkoxide proceeds under more drastic conditions to give *nido*-7,9-$C_2B_9H_{12}^-$(**14**).[14] The boron-insertion of the *nido*-anion with dichlorophenylborane[16] afforded 2-phenyl-*m*-carborane (**15**), which was converted to 4-(*m*-carboran-2-yl) acetophenone (**16**) using Friedel–Crafts acylation as previously reported.[17] The Baeyer–Villiger oxidation of **16** with *m*-chloroperbenzoic acid[18] in the presence of triflic acid followed by acid-hydrolysis gave 4-(*m*-carboran-2-yl)phenol (**8**) in 82% yield.

The determination of the partition coefficient, log *P*, by an HPLC method has the advantage of speed of determination, and applicability to highly hydrophobic compounds in the range of log *P* above 4. We performed the measurement according to the OECD Guideline for Testing of Chemicals 117.[19] The measurements were performed on a Hypersil ODS 5 μm, 250×4.6 mm (GL Science Inc., Japan), by using an LC6AD HPLC instrument (Shimadzu, Japan). The injection volume was 20 μL (concentration 15–35 μM) in all cases. The flow-rate was 1.0 mL/min [71(±2)kgf/cm$^2$] in all cases, and detection was done by measuring UV absorption at 240 nm (carboranylphenols) or 230 nm (others). The temperature was kept at 40.0 (±0.1)°C. The measurements were performed in methanol–aqueous 0.1 M phosphoric acid as the mobile phase, starting with 80% (v/v) organic modifier and decreasing it in 5% (v/v) concentration steps. Examples of elution profiles in methanol (70%)–aqueous 0.1 M phosphoric acid (30%) as the mobile phase are shown in Figure 2. Each measurement was performed in triplicate and the mean was used in further calculations. The dead time $t_0$ was measured with thiourea as the unretained compound. The retention times were determined for seven reference

phenols (except for diphenylether) in the range of log *P* between 1.46 and 5.12, which we selected from among recommended reference compounds in the OECD guidelines.[20,21] In the preliminary measurement and calculation, we found an exactly linear correlation between the retention parameters and the concentration of organic modifier in the mobile phase in the cases of both carboranylphenols and the other phenols, though the slopes were different for these two groups. Therefore, we performed the measurements with 80–60% (v/v) methanol in 5% concentration steps, and plotted percentage methanol against the corresponding logarithms of the capacity factor, log $k'$ ($R^2 > 0.9983$). The capacity factor, log $k'_W$, with 100% aqueous eluent was estimated by extrapolation of the line in the graphs.[22,23] The log $k'_W$ values were plotted as a function of log *P*.

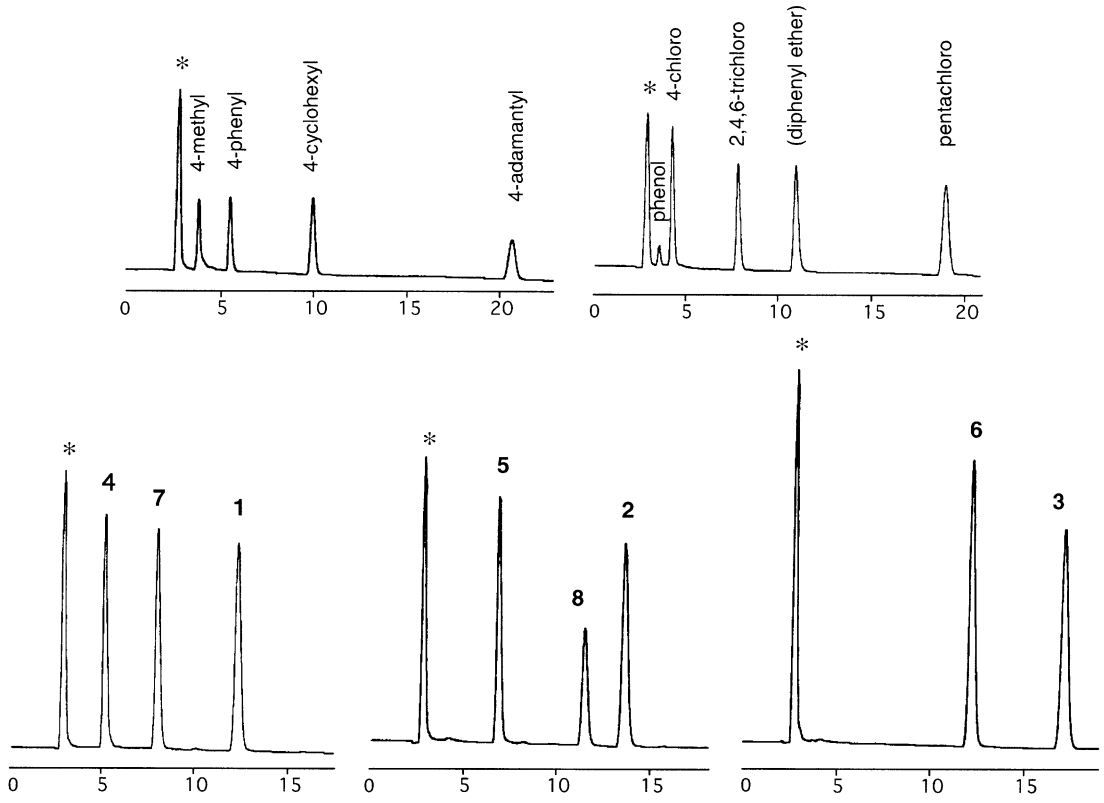


**Figure 2.** Elution profiles in methanol (70%)–aqueous 0.1 M phosphoric acid (30%) as mobile phase. Asterisks show peaks of thiourea, which is the unretained compound for measurement of deadtime $t_0$.

**Table 1.** Retention data and calculated log *P* values of reference compounds and carboranylphenols

| Compound | log *P* (standard)[a] | log $k'$[b] | | | | | log $k'_w$ | log *P* (calcd) |
|---|---|---|---|---|---|---|---|---|
| | | Organic modifier (%) | | | | | | |
| | | 80 | 75 | 70 | 65 | 60 | | |
| Phenol | 1.46 | −0.869 | 0.761 | −0.644 | −0.541 | −0.411 | 0.956 | 1.42 |
| 4-Cresol | 1.94 | −0.696 | −0.574 | −0.435 | −0.316 | −0.171 | 1.393 | 1.97 |
| 4-Chlorophenol | 2.39 | −0.611 | −0.473 | −0.329 | −0.198 | −0.029 | 1.686 | 2.34 |
| 4-Phenylphenol | 3.20 | −0.363 | −0.197 | −0.014 | 0.148 | 0.355 | 2.480 | 3.33 |
| 2,4,6-Trichlorophenol | 3.69 | −0.111 | 0.057 | 0.239 | 0.397 | 0.605 | 2.718 | 3.63 |
| Diphenylether | 4.20 | 0.060 | 0.244 | 0.452 | 0.629 | 0.867 | 3.250 | 4.29 |
| Pentachlorophenol | 5.12 | 0.322 | 0.527 | 0.755 | 0.952 | 1.211 | 3.837 | 5.03 |
| 4-Cyclohexylphenol | | −0.020 | 0.177 | 0.405 | 0.586 | 0.825 | 3.333 | 4.40 |
| 4-(1-Adamantyl)phenol | | 0.313 | 0.538 | 0.802 | 1.010 | 1.287 | 4.180 | 5.46 |
| 4-(*o*-Carboran-9-yl)phenol (**4**) | | −0.541 | −0.326 | −0.115 | 0.113 | 0.382 | 3.102 | 4.11 |
| 4-(*m*-Carboran-9-yl)phenol (**5**) | | −0.313 | −0.090 | 0.152 | 0.373 | 0.647 | 3.488 | 4.59 |
| 4-(*o*-Carboran-3-yl)phenol (**7**) | | −0.265 | −0.018 | 0.249 | 0.489 | 0.793 | 3.921 | 5.13 |
| 4-(*p*-Carboran-2-yl)phenol (**6**) | | 0.005 | 0.248 | 0.522 | 0.756 | 1.051 | 4.157 | 5.43 |
| 4-(*m*-Carboran-2-yl)phenol (**8**) | | −0.044 | 0.207 | 0.485 | 0.727 | 1.030 | 4.216 | 5.50 |
| 4-(*m*-Carboran-1-yl)phenol (**2**) | | 0.054 | 0.304 | 0.581 | 0.829 | 1.141 | 4.360 | 5.68 |
| 4-(*o*-Carboran-1-yl)phenol (**1**) | | −0.021 | 0.236 | 0.519 | 0.772 | 1.093 | 4.389 | 5.72 |
| 4-(*p*-Carboran-1-yl)phenol (**3**) | | 0.174 | 0.425 | 0.706 | 0.955 | 1.266 | 4.504 | 5.86 |

[a]Values cited in the OECD guideline for the testing of chemicals.[20,21]
[b]The capacity factor $k$ is given by $k = (t_R - t_0)/t_0$.

**Table 2.** Calculated log *P* values of carboranylphenols and hydrophobic parameter π values of carboranyl groups

| Compound | log *P* | π |
|---|---|---|
| 4-Cyclohexylphenol | 4.40 | +2.97 (+2.51)[a] |
| 4-(1-Adamantyl)phenol | 5.46 | +4.04 (+3.30)[b] |
| 4-(*o*-Carboran-9-yl)phenol (**4**) | 4.11 | +2.69 |
| 4-(*m*-Carboran-9-yl)phenol (**5**) | 4.59 | +3.17 |
| 4-(*o*-Carboran-3-yl)phenol (**7**) | 5.13 | +3.71 |
| 4-(*p*-Carboran-2-yl)phenol (**6**) | 5.43 | +4.01 |
| 4-(*m*-Carboran-2-yl)phenol (**8**) | 5.50 | +4.08 |
| 4-(*m*-Carboran-1-yl)phenol (**2**) | 5.68 | +4.26 |
| 4-(*o*-Carboran-1-yl)phenol (**1**) | 5.72 | +4.30 |
| 4-(*p*-Carboran-1-yl)phenol (**3**) | 5.86 | +4.44 |

[a]Literature value[25] (from substituted phenoxyacetic acid solutes by shaking flask method).
[b]Literature value[25] (calculated from –OH derivative).

The retention data and literature log *P* values for the reference compounds are shown in Table 1. The log *P* values of the carboranylphenols (**1**–**8**) were obtained by interpolation of the calculated capacity factors on the calibration graph ($\log P = 1.2515 \times (\log k'_w) + 0.2250$, $R^2 = 0.9958$). The log *P* values and the aromatic hydrophobic parameters π of carboranylphenols are shown in Table 2. It is apparent that C-substituted carboranyl groups (*p*-carboran-1-yl, *m*-carboran-1-yl, *o*-carboran-1-yl) are more hydrophobic than the adamantyl group. The hydrophobicity of *m*-carboran-2-yl and *p*-carboran-2-yl groups are comparable to that of the adamantyl group. The hydrophobicity of other phenols decreases in the order of *o*-carboran-3-yl > *m*-carboran-9-yl > *o*-carboran-9-yl. The *o*-carboran-9-yl group is less hydrophobic than a cyclohexyl group. The π values of the test compounds were in the range of 2.69–4.44. The values correspond to those of various types of hydrocarbon groups (*n*-alkyl, cycloalkyl, etc.), even though all the carboranyl groups have the same molecular shape. Recent studies of carboranes in the field of supramolecular chemistry have dealt with the effects of hydrogen-bonding interactions between cage CH of *o*-carborane and aza-crownether.[24] The CH on the carborane cage outside the molecule (*m*-carboran-9-yl and *o*-carboran-9-yl) seems to have a weak hydrophilic interaction with water.

The unique character of biologically active molecules containing a carborane skeleton may give rise to unusual membrane transport characteristics and metabolism, compared with conventional active molecules. Now, we have experimentally measured the partition coefficients log *P* for carboranylphenols, employing an HPLC method, and determined the Hansch–Fujita hydrophobic parameters π of various carboranyl groups. These results should be useful for application of carboranes in the design of a wide range of drugs.

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