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Symmetrically Substituted *nido*-Carboranylphthalocyanines: Facile Synthesis, Characterization, and Solution Properties. Evidence for Intra- and Intermolecular H^+/K^+ Exchange

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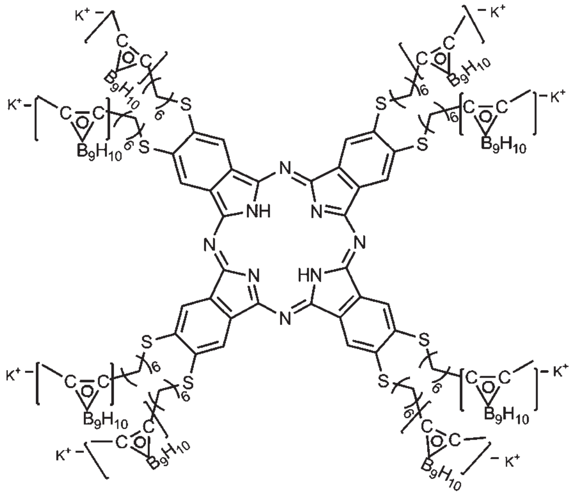
S *Supporting Information*

ABSTRACT: The direct, non ex post synthesis of a novel phthalocyanine decorated with eight thiohexyl-*nido*-carborane functions, *nido*-[H_2MCHESPc]K_8, where the anionic polyhedra are in the form of K^+ salt, is reported and discussed. The solution properties of this compound, including the unprecedented exchange between the pyrrolic protons and the peripheral alkali-metal ions, are also analyzed.

The versatile spectroscopic and electrochemical properties of phthalocyanines (Pcs) have attracted the interest of researchers in a variety of leading edge fields, such as nonlinear optics, optical data storage molecular electronics, solar energy conversion, catalysis, and gas sensing.[1] Moreover, owing to the intense absorption in the near-IR region, which coincides with the therapeutic window in which tissue absorption and scattering is minimal, Pcs have been proposed as photosensitizers in photodynamic therapy and other medical applications.[2] Cyclotetramerization of a phthalic acid or phthalonitrile derivative bearing appropriate chemical functions has provided synthetic access to peripherally and nonperipherally substituted Pcs. Although much success has been achieved over time in attenuating the harsh cyclization conditions, which are detrimental to chemically delicate substituents, or in using ex post synthetic methods, examples of complexly decorated Pcs are still scarce and their structural diversity is severely restricted. Thus, the discovery of new synthetic routes to functionalized Pcs has been the focus of research in recent years, particularly of water-soluble derivatives.[3]

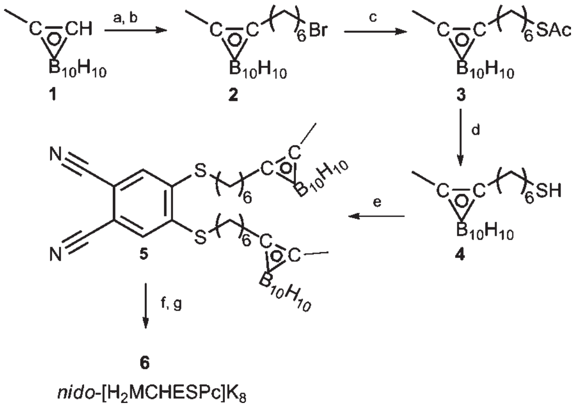
In continuing our search for new molecules for application in boron neutron capture therapy,[2d] we report herein the synthesis of the first Pc bearing eight *nido*-carborane units, the octaanionic 2,3,9,10,16,17,23,24-octakis(7-methyl-7,8-dicarba-*nido*-undecaboran-8-yl)hexylthio-6,13,20,27-(29*H*,31*H*)phthalocyanine in the form of potassium salt (hereafter abbreviated *nido*-[H_2MCHESPc]K_8). A schematic representation of the molecular structure of this compound is shown in Figure 1. The *nido*-[H_2MCHESPc]K_8 salt was synthesized through direct cyclization of the dicyano derivative **5** (see Scheme 1) in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in a 1:7 molar ratio. The well-known tendency of carboranes to undergo extensive decomposition at high temperatures and in the presence of DBU[2c] was substantially prevented by setting the temperature of the cyclization reaction in *n*-BuOH at 140 °C. Under these conditions, the effective cyclization



nido-[H_2MCHESPc]K_8

Figure 1. Molecular structure of *nido*-[H_2MCHESPc]K_8.

Scheme 1. Synthetic Pathway to *nido*-[H_2MCHESPc]K_8[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, Ar, −50 °C to room temperature, 2 h, yield 90%; (b) 1,6-dibromohexane, −78 °C to room temperature, 2 h, yield 95%; (c) AcSK, 2:1 EtOH/THF, room temperature, 4 h, yield >95%; (d) HCl_{aq} (35%), MeOH, room temperature, 3 h; (e) 4,5-dichloro-1,2-dicyanobenzene, K_2CO_3, DMSO, 45 °C, 3 h; (f) DBU, *n*-BuOH, 140 °C, 24 h; (g) DOWEX resin in K^+ form, yield 30%.

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of **5** and concomitant closo → nido conversion of the carborane polyhedra occurred. Evidently, DBU, which is normally regarded as a hindered and non-nucleophilic base, in the employed conditions is a sufficiently effective catalyst to guarantee cyclization of **5** and a sufficiently weak nucleophile to limit deboronation to the closo → nido conversion. That the peripheral heteroatoms may contribute, owing to their electron-withdrawing capability, to facilitate the cyclization reaction, should be taken into account, however.

The synthetic route to the *nido*-[H_2MCHESPc]K_8 salt is illustrated in Scheme 1. The synthesis of (bromohexyl)carborane (**2**) from the commercially available methyl-*o*-carborane (**1**) was readily accomplished by literature techniques.[4] Conversion of **2** to (thiohexyl)carborane (**4**) was readily carried out in 95% yield through conversion to (thioacetylhexyl)carborane (**3**), followed by deacetylation. The phthalonitrile derivative, **5**, was obtained by quantitative base-catalyzed aromatic nucleophilic substitution of **4** on 4,5-dichloro-1,2-dicyanobenzene. Finally, the *nido*-[H_2MCHESPc]K_8 salt was obtained from **5** (after passing through the Na^+ parent; see the Supporting Information) in 30% yield. Complete closo → nido conversion of the carborane cages in the formed Pc was primarily assessed by the IR spectrum, showing the typical absorption of the B−H stretching occurring in *nido*-carboranes at 2516 cm^{-1}.[5]

A complete NMR spectral characterization of *nido*-[H_2MCHESPc]K_8 was achieved through two-dimensional homo- and heterocorrelated spectroscopy experiments in acetone-d_6. The resulting spectral data are listed in Table S1 in the Supporting Information. The phthalocyanine NH protons showed a sharp resonance at δ −3.0, while the endo protons of the *nido*-carborane polyhedra exhibited a broad signal at δ −2.45 to −2.80 due to tautomerism. The signals of the hexylthio tail protons and of some of the B−H protons overlapped in the δ region between 1.0 and 3.8 ppm of the ^{1}H NMR spectrum. Two peaks were observed for the aromatic protons, suggesting the coexistence of aggregated species, as confirmed by the spectra recorded at different concentrations (1−7 mM). A sharp peak at 9.43 ppm was assigned to the monomer, while a broader peak at 8.65 ppm, whose intensity increased with the concentration, was assigned to aggregated species. The ^{11}B NMR spectrum recorded in acetone-d_6 showed signals associated with the anionic *nido*-carborane structure[6] (Figure 2a).

The ^{11}B chemical shifts observed at δ −38 and −35 were assigned to B1 and B10, respectively, while the signals belonging to the other boron atoms resonated at δ −18 (B2, B4, B5, and B6) and δ −10 (B3, B9, and B11) (for numbering of the boron atoms, see Figure S1 in the Supporting Information).

The compound proved to be electrospray ionization mass spectrometry silent. Quite surprisingly, however, time-of-flight matrix-assisted laser desorption ionization (MALDI-ToF) spectra showed, instead of the expected molecular peak at *m/z* 2920.540, a rather weak cluster centered at *m/z* 2600.202, suggesting that the compound undergoes relevant fragmentation processes during MALDI analysis. These may be related to the acidity of the matrix and local heating upon laser-induced matrix desorption. It is well-known, indeed, that the acidification of *nido*-carboranes results in protonation to generate neutral *nido*-carboranes (*nido*-7,8-$C_2B_9H_{13}$), which may convert, after relatively mild heating and release of molecular hydrogen, into 11-vertex *closo*-carboranes.[7] That *nido*-[H_2MCHESPc]K_8 may undergo protonation and dehydrogenation during MALDI analysis, as indicated in eqs 1 and 2,

$$(C_{104}H_{210}B_{72}N_8S_8)^{8-}(K^+)_8 + 8H^+ \rightarrow C_{104}H_{218}B_{72}N_8S_8 + 8K^+ \qquad (1)$$

$$C_{104}H_{218}B_{72}N_8S_8 \rightarrow C_{104}H_{202}B_{72}N_8S_8 + 8H_2 \qquad (2)$$

is strongly supported by the evidence that the molecular peak predicted for [$C_{104}H_{202}B_{72}N_8S_8$], i.e., the species derived by the octaanionic Pc upon sequential protonation and release of hydrogen, is *m/z* 2600.318, in close agreement with the experiment.

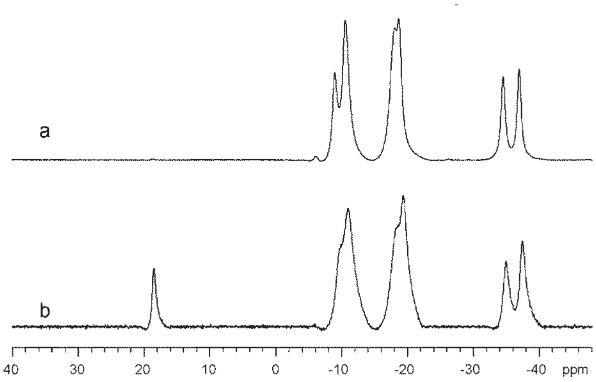

Figure 2. ^{11}B NMR spectra recorded in (a) acetone-d_6, showing the typical peak pattern of *nido*-carboranes, and (b) MeOH-d_4, showing, besides the resonances due to the anionic *nido*-carboranes, the peak associated with the (protonated) neutral *nido*-carborane cage.

As inferred from Figure S2 in the Supporting Information, *nido*-[H_2MCHESPc]K_8 does not aggregate in acetone in the concentration range 10^{-7}−4×10^{-6} M. Consistently, the UV−vis spectrum of a 5×10^{-7} M solution of the complex in this solvent was characteristic of nonaggregated metal-free Pcs, with Q_y(0,0) and Q_x(0,0) bands at 699 and 726 nm, respectively, and a Soret band near 335 nm (Figure 3 in the Supporting Information), and the fluorescence spectrum displayed a strong emission band at 731 nm.

The electronic spectrum of the compound in water showed, in the concentration range 10^{-6}−10^{-8} M, a rather broad absorption in the Q-band region with a maximum at around 657 nm and a shoulder in the red tail, tentatively located at 710 nm (inset of Figure S3). The blue shift of the absorption intensity relative to the mononuclear species, the broadening, and the hypochromism seem to be spectral signatures of molecular aggregation.[8] Water solutions of *nido*-[H_2MCHESPc]K_8 deviated appreciably from the Beer law in the concentration range 10^{-6}−10^{-8} M and were not emissive.

As inferred from the time evolution of the UV−vis spectrum of *nido*-[H_2MCHESPc]K_8 in MeOH reported in Figure S4 in the Supporting Information, deprotonation of the Pc ring slowly occurred in this solvent. This is most likely because the sulfur-induced enhancement of the acidity of the pyrrolic protons and the well-known basicity of the *nido*-carborane cages[9] cooperate in inducing the observed proton abstraction. Obviously, (solvated) potassium ions should move from the protonated (neutral) *nido*-carboranes toward the tetrapyrrolic cavity to balance the charge of the Pc dianion. Apart from a thiohexyl-group-induced red shift,[10] the MeOH spectrum of the compound exhibited indeed the single MPc-like Q band associated with the nominal D_{4h} symmetry of the Pc ring already observed for deprotonated Pcs and alkali-metal Pc complexes, such as K_2Pc$(DMF)_4$[11] and

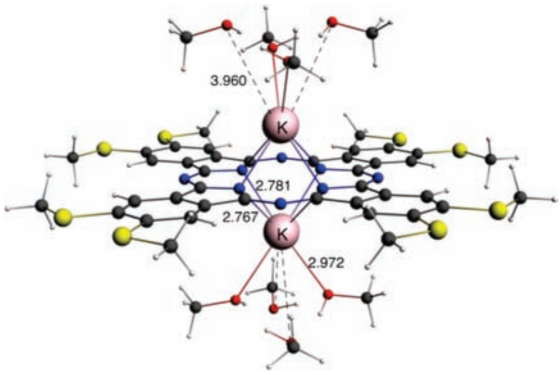

Figure 3. DFT-optimized structure of the model complex $K_2Pc(SMe)_8(MeOH)_8$ in MeOH indicating the relevant bond lengths (Å).

$K_2Pc(18\text{-crown-}6)_4$.[12] This suggests that, just as for these compounds, in a MeOH solution the K^+ ions are bound to the tetrapyrrolic $(N_p)_4$ cavity, with their actual location resulting from competitive coordination between the Pc dianion and the solvent molecules.

To confirm proton exchange among the indolic protons and two out of the eight potassium ions belonging to the *nido*-carborane polyhedra, *nido*-$[H_2MCHESPc]K_8$ was further analyzed by NMR spectroscopy in MeOH-d_4, by recording a ^1H NMR spectrum every 1 h. The disappearance of the NH indolic signal was complete after ca. 4 h. The ^{11}B NMR spectrum recorded after proton exchange showed a *new* sharp peak at $\delta + 18.6$, to be assigned to the B2 and B4 atoms in the neutral *nido*-carborane structures[7] (Figure 2b). The protonation-induced changes in the chemical shifts of the other boron atoms were pretty exiguous to be visible in the spectrum of Figure 2b, as expected on the basis of previous evidence.[7]

Structural information on the complex formed upon the interaction of deprotonated Pc and K^+ in MeOH was obtained by density functional theory (DFT) calculations on a "monomeric" model system, $K_2Pc(SMe)_8(MeOH)_8$, where the thiohexylcarboranyl tails were replaced by methylthio groups and the potassium ions were capped by four MeOH molecules. Unconstrained geometry optimization of the model led to a structure of S_4 symmetry, with a substantially planar $Pc(SMe)_8$ ring (Figure 3). The bond lengths computed for the inner coordination sphere of the complex compared well with the literature X-ray data.[11,12] For instance, the distance between potassium and the $(N_p)_4$ plane was only slightly shorter than that observed in $K_2Pc(DMF)_4$[11] (1.924 vs 1.967 Å). The K–O distances reported in Figure 3 show that only two out of the four MeOH molecules capping the potassium ions set up effective interaction with the alkali metal, leading substantially to hexacoordinated potassium ions. Time-dependent DFT (TDDFT) calculations of the lowest optically allowed excited states in MeOH predicted an intense absorption ($f = 0.750$) at 673 nm, in close agreement with the experimentally observed Q band, suggesting that $K_2Pc(SMe)_8(MeOH)_8$ is a realistic model for the title complex.

In summary, we have reported the first direct synthesis of a Pc ring decorated with eight thioalkyl-*nido*-carborane units. Because of its chemical constitution and solution properties the molecule has potential in biomedicine and related fields.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Synthetic and computational details, spectroscopic data (Table S1 and Figures S1–S4). This material is available free of charge via the Internet at http://pubs.acs.org.

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