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Anion-Controlled Assembly of Porphyrin–Bicyclic Guanidine Conjugates

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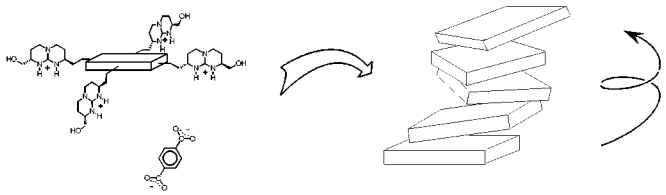
ABSTRACT



Cationic porphyrins 1–3 bearing one, two, and four bicyclic guanidines form highly ordered chiral assemblies in aqueous solutions. The chirality is controlled by the type of the anionic counterpart and results from a spontaneous process. The chiral assemblies of 1–3 relate structurally to the complexes of achiral porphyrins with helical DNA. However, the presence of a chiral template (DNA, poly L-Glu were tested) is not necessary for formation of these specific chiral porphyrin assemblies.

The formation of supramolecular assemblies from well-defined building blocks became the leading area of supramolecular chemistry with a great potential for medicinal applications and for construction of novel materials with interesting properties.[1−3] The covalent or noncovalent binding motifs containing porphyrin moieties have gained importance in view of the crucial role of porphyrin assemblies in biological pigment systems. Aggregation of porphyrins has been reported under various conditions, including self-aggregation, metallocomplexes of pyridinium derivatives, acid-induced aggregation, metal salt-induced aggregation, or acceptor-induced aggregation, and micellar medium influenced aggregation.[4−9] There are numerous reports about porphyrin assemblies on chiral templates such as nucleic acids and peptides.[4,10−13] These aggregates are tightly assembled and stabilized by electrostatic and $\pi-\pi$ interactions. Their formation is well documented by a variety of spectroscopic methods including fluorescence, Raman, UV/vis, and circular dichroism (CD). CD spectroscopy in particular is the method of choice for studying chiral assemblies, largely

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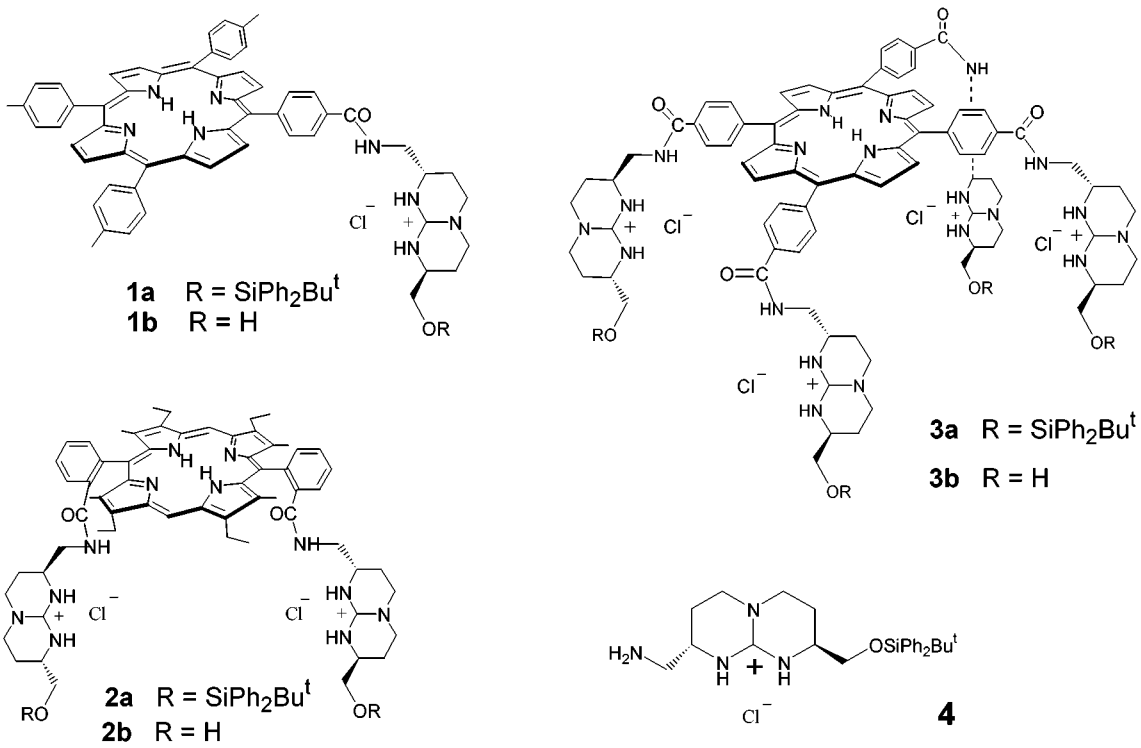

Figure 1. Structures of compounds **1**−**4**.

because the intrinsic circular dichroism of porphyrins is usually very small and a helical arrangement of the porphyrin units on a chiral template can be evidenced by strong exciton coupling in the Soret region.[7,14]

Here we report the synthesis, spectral properties, and anion-controlled assembly of porphyrin−bicyclic guanidine conjugates **1**−**3** (Figure 1) in aqueous solutions. The design of receptors was based on the concept of cooperative interactions of both porphyrin and bicyclic guanidine moieties with an anionic compound of interest. The Coulombic and H-bonding attraction forces are predominantly governed by the peripheral bicyclic guanidines and combine with $\pi-\pi$ stacking of porphyrin units, which additionally impose geometrical restrictions with respect to the mutual distance and orientation of the guanidines. To the best of our knowledge, this is the first porphyrin assembly upon addition of small anions forming chiral structures controlled by the type of the anion used. The synthetic protocol is based on condensation of porphyrin mono-, bis-, and tetracarboxylates with aminomethyl-functionalized bicyclic guanidine derivatives.[15,16,21]

Compounds **1**−**3** were prepared from the respective mono-, di-, or tetracarboxyphenyl porphyrins and the aminomethyl guanidinium salt **4**. The coupling was achieved by the DCC (HOBT) method in dry CH_2Cl_2/MeCN/DMF catalyzed by DMAP (pyridine as a base) or via the acyl chloride method. The protected derivatives (**1a**−**3a**) were isolated by column chromatography on silica gel using CH_2Cl_2/MeOH mixed solvents (from 0 to 10% MeOH). The protecting groups were removed by reaction with about 10 molar equiv of tetrabutylammonium fluoride in dry CH_2Cl_2. After complete deprotection (24−48 h), the products precipitated from solution in high yields (93% for **1**, 91% for **2**, 88% for **3**) upon addition of diethyl ether. The crude compounds were redissolved, crystallized from a mixture of CH_2Cl_2−MeOH−diethyl ether, and identified by ^{1}H NMR and MALDI-TOF (full experimental details are provided as Supporting Information).

Binding of **1**−**3** to dsDNA in acetate buffer (5 mM NaCl, pH 7.1) was indicated by UV/vis, fluorescence, and CD spectroscopy. The CD spectra in the Soret region showed induced positive and negative bands (positive/negative) for **1** (444 nm/463 nm), **2** (435 nm/404 nm), and **3** (400, 445

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nm/424 nm). Such behavior is generally taken as compelling evidence for the presence of organized porphyrin assemblies on the chiral helical backbone of nucleic acids originally proposed by Fiel.[17] This outside binding mode, frequently accompanied with stacking of the porphyrin moiety, was reported for a variety of positively charged porphyrins.[4,11,12]

We are interested in the construction of chiral porphyrin assemblies without the help of polyionic helical templates. Porphyrins **1**−**3** appear to form such chiral arrays. The evidence is based on comparison of UV/vis and CD spectra in methanol and aqueous solutions. Because **1** and **2** have low solubility in water and thus strongly aggregate unspecifically, we focused our attention on the readily soluble tetraguanidine compound **3**.

In methanol, the porphyrin **3** showed a typical spectrum of a monomer displaying the Soret band at 416 nm (Figure 2a) and adhering to the Lambert−Beer law up 15 mM. In

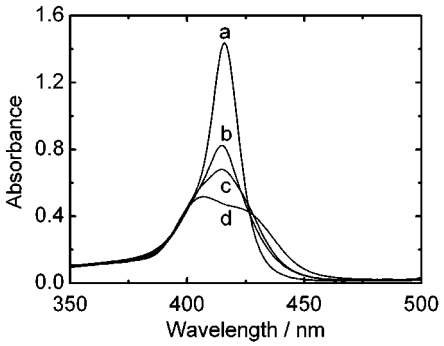

Figure 2. Absorption spectra of **3** in methanol (a), water (b), 10 mM acetate (c), and 0.5 mM anthraquinone-1,5-disulfonate (d).

distilled water the Soret band exhibits a strong hypochromism concomitant with massive broadening (Figure 2b). The bands in the visible region (Q-bands) are red shifted from 514 nm, 548, 590, and 645 nm in methanol to 520, 557, 593, and 649 nm in water. Addition of acetate (Figure 2c), dihydrogenphosphate, terephthalate, or anthraquinone-1,5-disulfonate (Figure 2d) causes an additional decrease and a split of the Soret band of the monomer accompanied by the appearance of two broad maxima at about 405 and 428 nm. According to the exciton theory,[18] these features suggest the presence of porphyrin aggregate structures. The theory predicts that the excited-state energy level of a monomeric dye splits into two upon aggregation and that the shift of the transition to the higher states depends on the structure of aggregated species.[18] Using these arguments, the appearance of a blue-shifted band indicates the formation of a sandwich-type aggregate (H-aggregate). A red shift of the Soret band is attributed to a side-by-side arrangement of the porphyrin units denoted as J-aggregates. Further evidence of large aggregates in aqueous solution can be provided by resonance light-scattering measurements.[19] This is a sensitive method for obtaining detailed information about aggregates including the absorption spectrum and the average size of the scattering species.[12,19] Porphyrin monomers and small oligomers do not show resonance light-scattering profiles. We observed that the decrease of the monomer band (Figure 2a) is connected to the appearance of light-scattering profiles at about 440 nm, confirming extensive aggregation upon the addition of anions. This anion-controlled process was also examined by MALDI-TOF mass spectroscopy. For receptors **1**−**3**, we observed the molecular peaks belonging to 1:1, 2:1, and even higher stoichiometries (3:2, 5:4) in the presence of dianions such as terephthalate and adipate. With proof of higher stoichiometries in the gas phase at hand, we evaluated the anion-driven assembly in aqueous solutions.

CD spectroscopy allowed specification of whether the aggregation of **3** leads to nonordered common aggregates or to well-structured multiporphyrin chiral assemblies. The small intrinsic chirality of **1**−**3** is induced by the chiral bicyclic guanidinium units on the periphery of porphyrin (Table 1). The corresponding CD signals can be measured in methanol where the porphyrins are predominantly monomeric. When **3** is transferred into water, the intensity of the CD signals in the Soret region dramatically increases (Table 1, Figure 3). The strong signals of an induced CD show split Cotton effects centered about 422 nm, proving exciton coupling between the Soret transitions of two or more spatially correlated porphyrin units. The band positions and intensities depend on the type and concentration of anions

Table 1. CD Peaks and Corresponding Molar Ellipticities in Parenthesis for **3** (3 μM) in Water in the Presence of 10 mM Monoanions or 5 mM for Dianions (in order to account for the influence of ionic strength) at Room Temperature

solvent	anion	CD bands/nm ($[\theta] \times 10^{-6}$/deg M^{-1} cm^{-1})
methanol		400 (positive), 430 (negative)
water		410 (0.9), 435 (−1.4), 460 (0.4)
water	acetate	410 (1.8), 430 (−3.2), 460 (0.3)
water	dihydrogenphosphate	412 (1.4), 430 (−2.5), 455 (0.4)
water	tris(hydroxymethylamino)methane hydrochloride, pH 7.4	410 (1.8), 430 (−2.8), 455 (0.4)
water	sulfate	415 (1.8), 430 (−3.6), 455 (0.8)
water	anthraquinone-2,6-disulfonate	420 (0.3), 430 (−0.2), 450 (0.4)
water	anthraquinone-1,5-disulfonate	415 (0.3), 430 (−0.6), 450 (0.4)
water	naphthalene-2,6-dicarboxylate	400 (0.2), 430 (−0.3), 450 (0.5)
water	pyridine-2,6-dicarboxylate	425 (−0.8), 450 (0.8)
water	terephthalate	415 (−1.1), 445 (0.8)

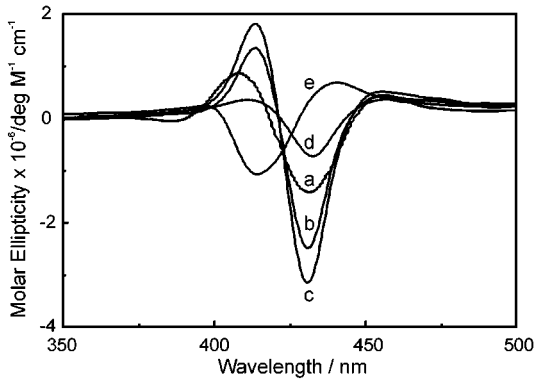

Figure 3. CD spectra of **3** (3 μM) in water (a), the presence of 10 mM hydrogenphosphate (b), 10 mM acetate (c), 5 mM anthraquinone-1,5-disulfonate (d), and 5 mM terephthalate (e) measured in a 10 mm cell at room temperature.

added (Table 1). Dianions have less profound effect on the molar ellipticity than monoanions. Interestingly, addition of terephthalate or pyridine-2,6-dicarboxylate completely reverses the signs of the Cotton effects (Figure 3e).

Exciton splitting in CD spectra is commonly attributed to ordered chiral assemblies. The assembling process is simply achieved by the presence of small achiral anions. Similar anion-controlled helical assembling was recently reported for copper(II)−arginine complexes.[20] Our observations indicate that anions serve as linkers diminishing repulsion forces between porphyrin units. The exact spacing and the chemical nature of the anionic sites interacting with the chiral guanidinium moieties in a well-known host−guest binding motif[15,16] are likely to govern the mutual orientations of the porphyrin components. The CD spectra of **3** in the presence of anions (except terephthalate or pyridine-2,6-dicarboxylate) and dsDNA are similar, indicating that assembling on the DNA surface and in the solution leads to structurally equivalent systems.

In summary, the spontaneous formation of chiral assemblies composed of bicyclic guanidinium porphyrins **1**−**3** is driven by small anions.

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Supporting Information Available: Experimental procedures and characterization for compounds **1a**, **1b**, **2a**, **2b**, **3a**, and **3b** and the conditions for the binding studies in solution and in the gas phase (mass spectroscopy). This material is available free of charge via the Internet at http://pubs.acs.org.

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