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Strategies toward the synthesis of amphiphilic porphyrins

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1. Introduction

Heme, an important molecule for life, is an amphiphilic porphyrin possessing both hydrophilic and lipophilic groups at the opposite ends of the macrocycle, a typical architecture for

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amphiphilic molecules. Amphiphiles are defined as molecules possessing both hydrophilic (*water-loving*, polar) and lipophilic (*fat-loving*, non-polar) properties, which stem from the presence of polar and non-polar residues in the molecule's structure.[1] Polar head groups can be either uncharged (hydroxy, thiol, carbohydrate, oligo- and poly(ethylene)glycol) or charged (carboxylate, sulfate, phosphate, ammonium, pyridinium, phosphonium, amino acid, peptide, etc.) while the lipophilic tail is usually represented by a hydrocarbon chain (Fig. 1).

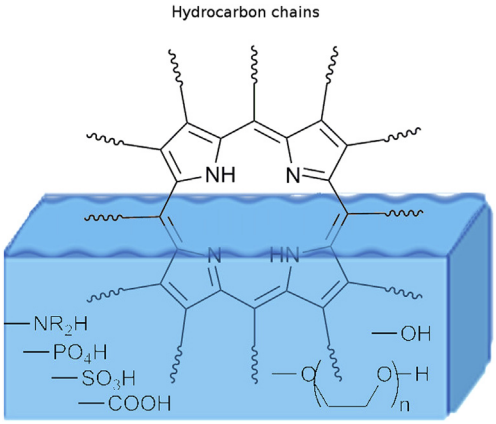

Fig. 1. Structure of facial amphiphiles based on porphyrins.

The porphyrin skeleton is essentially hydrophobic therefore its transformation to an amphiphile requires introduction of hydrophilic head groups. The properties of a molecule are determined by the equilibrium between hydrophilic and hydrophobic moieties and amphiphilic porphyrins frequently possess both head and tail groups. However, the amphiphilic properties are not solely defined by the exact number of hydrophilic and hydrophobic substituents present at the periphery of the porphyrin macrocycle. Other factors such as inductive and resonance effects, steric effects, branching, and conformation contribute to their amphiphilic character. Therefore, it is almost impossible to predict what type and how many head and tail groups should be attached to the macrocyclic core, especially in the case of substituents of variable sizes. Based on the number and type of head/tail connections, Sorrenti classified porphyrin-based amphiphiles as *bolaamphiphiles*,[1] molecules comprised of two hydrophilic heads connected by a hydrophobic skeleton (e.g., one or two alkyl chains, a steroid, or a porphyrin). Such simple examples are rare among amphiphilic porphyrins; usually they belong to a class of 'facial amphiphiles' having hydrophobic and hydrophilic moieties on the opposite poles of the porphyrin core.

The character of porphyrins is often assessed with respect to partitioning of the compound between the aqueous and organic phases. The partition ratio (Eq. 1) is the ratio of the concentration of a single definite form (A) of a substance in the extract to the concentration of A in the other phase at equilibrium.[2a] Although IUPAC recommends the use of partition ratio values, herein the partition coefficients $(P_O)_A$[2b] will be discussed, as it is commonly used function for describing various porphyrins.

$$(P_O)_A = [A]_{org}/[A]_{aq} \quad (1)$$

It is widely accepted that a porphyrin has an amphiphilic character if the logarithm of partition coefficient ($P=c_{oct}/c_{aq}$) is $-0.1<\log P<0.4$. Lindsey and co-workers stressed that for a true partition coefficient to be measured, one must assume that the same species is present in both phases, but this is not often the case.[3a] Additionally, over simplification of calculations precludes a definitive prediction of molecular partitioning between an aqueous phase and lipid membranes.[3] Therefore, log *P* values cited in this review will be only used to compare amphiphilic properties of porphyrins.

Amphiphilic porphyrins have been studied in a range of various applications including catalysis,[4] P_{450} mimics,[5] decomposition of $ONOO^-$ and $O_2^{\cdot-}$ dismutation,[6] semiconductors, and electronic materials,[7] anti-cancer drugs,[8,9] etc. Amphiphilic porphyrins, due to their unique tendency to form aggregates, are good synthetic model systems for studies of natural and artificial photosynthetic systems.[10,11] In such systems, porphyrins interact with the membrane bilayer and/or form various aggregates in aqueous solutions. Sorrenti emphasized that both the molecular structure of the amphiphile (nature of the hydrophobic and hydrophilic groups) and the experimental conditions played a role in the aggregation process.[1] Micelles, vesicles, liquid crystals, and Langmuir monolayers are the most commonly observed self-assemblies, which influence the aggregation photophysical properties of the porphyrin.[12] Monomeric porphyrins can form highly ordered J-aggregates—formed by side-by-side arrangement of porphyrin or H-aggregates—formed by face-to-face non-covalent interactions.[12a]

The literature on amphiphilic porphyrins demonstrate their rich potential in various applications. To this end, various approaches toward the synthesis of such compounds have been reported. In this review, we only highlight methods leading toward amphiphilic porphyrins rather than reporting all data on these types of compounds. Synthetic methodologies leading to such porphyrins do not differ from standard procedures used in tetrapyrrole chemistry,[13,14] however, this review is entirely concentrated on porphyrins with head and tail groups attached to the macrocyclic core. These structures can be obtained by direct synthesis from adequate precursors or by transformations of pre-prepared or natural porphyrins (Fig. 2). The synthesis of porphyrins with very large amphiphilic substituents such as peptides, polymers, and dendrimeric structures are beyond the scope of the present review.

2. Uncharged amphiphilic porphyrins

2.1. Synthesis of porphyrins bearing hydroxyl groups

A broad variety of porphyrins bearing hydroxyl groups as either 4-hydroxyphenyl or hydroxyalkyl substituents at *meso*- or β-positions have been reported. These derivatives are usually used as precursors for further functionalization. Most amphiphilic porphyrins bearing hydroxyl groups are represented by sugar−porphyrin conjugates in which both components are vital for life. Linking these two compounds gives an important asset to biomedical applications,[8,9] but the delicate hydrophobicity/hydrophilicity balance must be maintained as it is an important factor influencing carbohydrate/porphyrin interactions with the cell surface membrane.[12] The nature and number of carbohydrate units rule the physicochemical properties of the porphyrins bearing such moieties.

2.1.1. Porphyrins with hydroxyphenyl substituents. Porphyrins bearing multiple hydroxyphenyl substituents are easily synthesized using the Bonar-Law method.[15] The desired hydrophobic/hydrophilic profile of such porphyrins can be changed via an alkylation reaction. Addition of alkyl chains is perfect for regulating the hydrophobicity of the porphyrins by varying not only the number of groups introduced but also the length of the carbon chain. Based on this methodology, a range of porphyrins were prepared—most often starting from 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrin (**1**, THPP), which is easily synthesized from 4-hydroxybenzaldehyde and pyrrole in anionic sodium