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Nucleophilic Thioglycosylation of Pentafluorophenyl-Substituted Porphyrinoids: Synthesis of Glycosylated Calix[*n*]phyrin and [28]Hexaphyrin Systems

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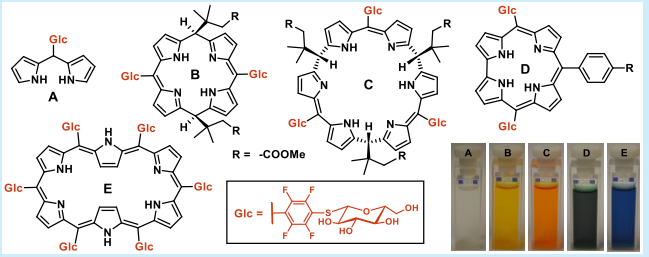
Supporting Information

ABSTRACT: The use of carbohydrate thiolates for facile, high-yielding, regio- and stereoselective nucleophilic substitution reactions of complex pentafluorophenyl-substituted porphyrinoids is reported. The title reaction has successfully been applied to calix[4]phyrin, calix[6]phyrin, and [28]-hexaphyrin substrates. The novel glycoporphyrinoid products with their extraordinary structures and unique photophysical properties are soluble in aqueous solutions and can serve as platforms for applications in biomedicine, catalysis, coordination, or redox chemistry.



In the field of tetrapyrrole chemistry, different methods for the preparation of carbohydrate-substituted derivatives have been studied and employed. The resulting glycoporphyrinoids have a broad potential for applications in biomedicine, biochemistry, or glycobiology.[1,2] The carbohydrate moieties of these glycoconjugates are often crucial to provide the highly lipophilic macrocyclic core with an improved solubility in polar solvents and support targeting in biological environments.[1,2]

Expanded porphyrins, including hexaphyrins, exhibit unique optical, electrochemical, and coordination properties.[3] Thus, they have potential in oxidation catalysis,[4b] as multimetal coordination ligands,[4a] as nonlinear optical (NLO) materials,[4c] or as NIR dyes.[4d] In addition, these unique compounds have great potential as deeper-penetrating PDT agents due to their large two-photon absorption (TPA) cross sections.[4e] Calix[*n*]phyrins, on the other hand, are macrocycles at the interface between porphyrins and calixpyrroles.[5] In contrast to the rooflike calix[4]phyrin systems which are studied in the field of coordination chemistry or catalysis or as ion sensors, calix[6]phyrins are relatively unexplored, in particular, when it comes to applications.[6] Unfortunately, such porphyrinoid systems are very unpolar and can hardly be used in biological or other aqueous media. One of the few published exceptions is a peptide-modified, water-soluble doubly *N*-confused hexaphyrin used as a Zn(II) ion sensor in water.[7]

With the aim of extending the scope of applications of some of the less-explored porphyrinoids to biological environments, we decided to search for a simple and general way to introduce glyco substituents. In order to avoid tedious protection/deprotection procedures of both the macrocyclic core heteroatoms as well as the sugar unit, a metal-free procedure using free sugars was preferred. Thus, a useful and elegant method seemed to be the direct introduction of an unprotected thiocarbohydrate into a pentafluorophenyl (PFP)-substituted porphyrinoid through a nucleophilic aromatic substitution. It has, however, to be noted that yields and selectivities of many published procedures would not be sufficient for substrates where two, three, or more sugars are to be introduced into a polyfunctional substrate.

The starting materials for this study, PFP-substituted corroles,[8] calix[4]phyrins, calix[6]phyrins,[9] [26]hexaphyrins,[10] and PFP-dipyrromethane[11] were prepared according to literature procedures. As known for other porphyrinoids with electron-withdrawing groups, the PFP substituents lead to quite stable corroles, dipyrromethanes, hexaphyrins, and calix[*n*]phyrins (with bridging *meso*-CH moieties). Our initial experiments on the glycosylation using a porphyrinoid precursor, dipyrromethane **1** (Table 1), were based on related literature procedures[12,2f] which used an excess of thiolate in DMF. Unfortunately, no clean products were isolable under these conditions. It turned out that despite the steric demand of the nucleophile, facile multiple substitutions occurred leading to an inseparable mixture of products. Careful optimization of stoichiometry and reaction conditions (see Table 1 and the Supporting Information for details) and conduction in a water-free medium under an inert atmosphere resulted in a precise tool for a controlled glycosylation.[13] Thus,

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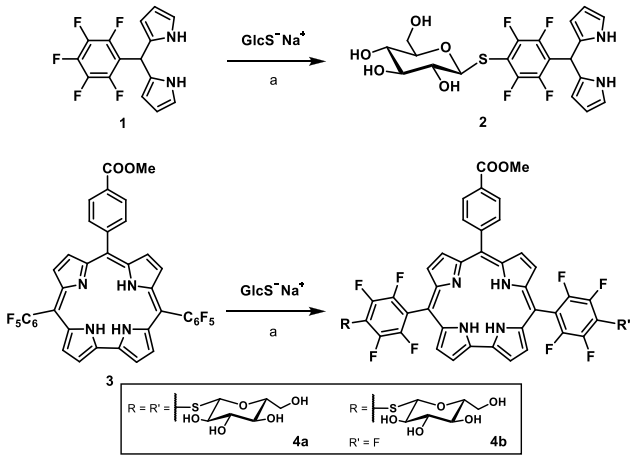
Table 1. Optimization of the Reaction Conditions for the Preparation of Thioglycosylated Dipyrromethane and Corrole[a]



entry	substrate	equiv[b]	T (°C)	time (h)	yield[c] (%)
1	DPM **1**	1.2	rt	0.5	72
2	DPM **1**	1.2	rt	1	68
3	DPM **1**	1.2	rt	6	34
4	DPM **1**	1.2	rt	12	19
5	Corr **3**	2.4	rt	1	37/44[d]
6	Corr **3**	2.4	rt	12	69/16[d]
7	Corr **3**	3.2	rt	12	73/14[d]
8	Corr **3**	4.2	rt	12	71/14[d]
9	Corr **3**	4.8	50	12–24	64/12[d]

[a]All reactions were carried out in dry DMF at rt or 50 °C under an argon atmosphere. [b]Equivalents refer to carbohydrate thiolate used per PFP unit. [c]Yield of isolated product(s) after purification. [d]Yields of bis- and monoglycosylated corroles **4a**/**4b**, respectively.

model substrate (**1**) was converted within 30 min to obtain the desired product **2** in 72% yield (Table 1, entry 1). At longer reaction times (>1 h), formation of side products was observed, leading to diminished yields (Table 1, entries 2–4).

As the first porphyrinoid, we tested the thioglycosylation of the A_2B-*trans*-substituted corrole **3** (Table 1).[2i,14] The starting corrole was prepared using the method described by Gryko and co-workers.[8] Longer reaction times as compared to the glycosylation of dipyrromethane **1** were necessary for the reaction to reach good conversions, but it proved not possible to fully glycosylate the corrole. Even with an excess of thiolate (thiolate/PFP unit = 4.8:1), heating at temperatures of up to 50 °C, and extended reaction times (24 h) incomplete conversion was observed. Under optimized conditions, the dithioglycosylated corrole **4a** was isolated in 73% yield together with the monothioglycosylated corrole **4b** obtained in 14% yield (Table 1, entry 7). Still, these yields are superior when compared to other thioglycosylation procedures.[15]

The next class of compounds investigated were the novel PFP-substituted calix[*n*]phyrins which were first described by Reissig, Wiehe, and co-workers in 2013.[9a] We tried to convert the roof-shaped calix[4]phyrin **5** and the mono-*meso*-spirolactone calix[4]phyrin **7** using a ratio of thiolate/PFP unit of 1.2:1. After 1 h reaction time, the respective thioglycosylated conjugates **6** and **8** were obtained in very good yields (85% and 83%, respectively) with no additional substitutions at the PFP unit being observed (Figure 1).

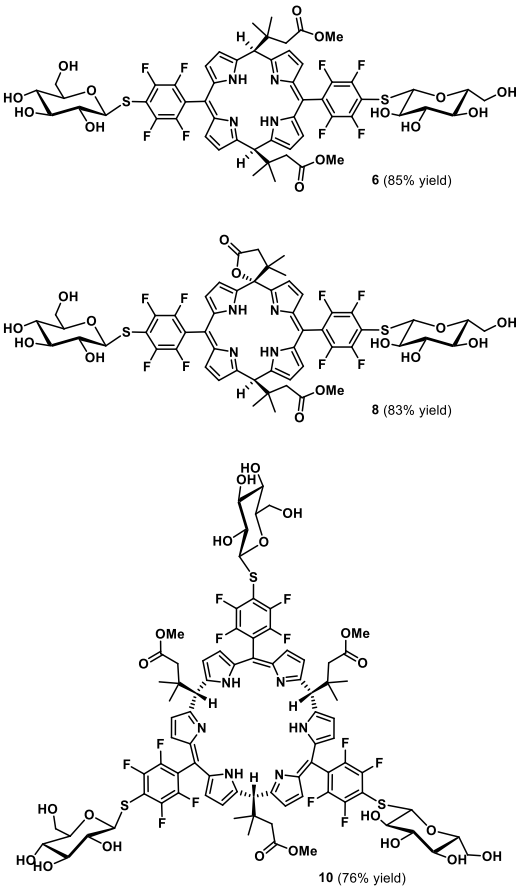


Figure 1. Preparation of calix[*n*]phyrins **6**, **8**, and **10**: GlcSNa (1.2 equiv/PFP unit), dry DMF, argon atmosphere, rt, 1 h.

We then set out to explore the thioglycosylation of the relatively unexplored calix[6]phyrin **9**. Pleasingly, using our standard substitution procedure, thioglycosylated calix[6]-phyrin **10** was obtained in 76% yield (Figure 1).

In effect, all three calix[*n*]phyrins were easily thioglycosylated using the same protocol. The success and regioselectivity of the substitution reaction can easily be followed through the disappearance of the signal of the *p*-fluorine substituent in the ^{19}F NMR spectrum as exemplified for the calix[6]phyrin system in Figure 2.

From the beginning of the project, a hexaphyrin substrate appeared to be the most interesting but also most challenging candidate for thioglycosylation. Motivated by a publication of Osuka and co-workers on regioselective nucleophilic substitution reactions of *meso*-hexakis(pentafluorophenyl)-substi-

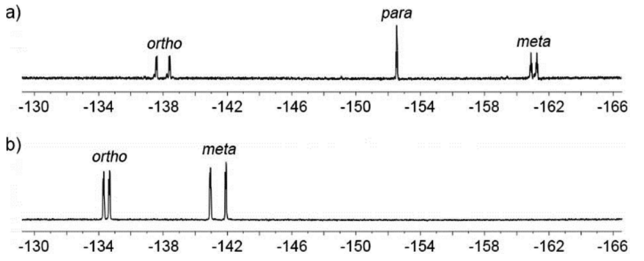


Figure 2. Comparison of ^{19}F NMR spectra: (a) **9** in $CDCl_3$ and (b) **10** in CD_3OD illustrating the disappearance of the *p*-fluorine signal as a result of the S_NAr reaction.

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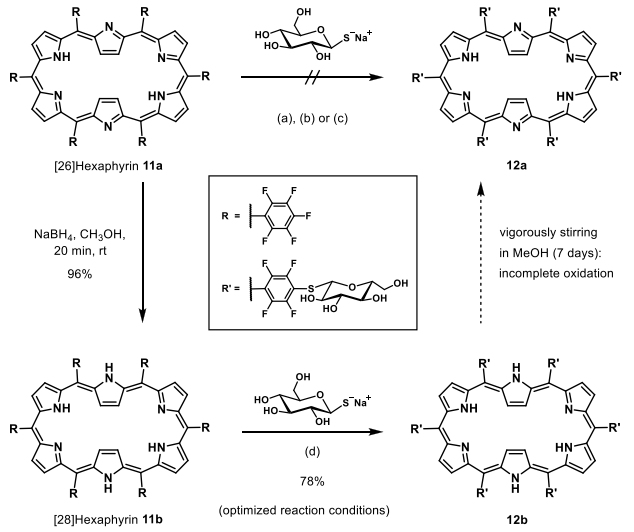
tuted [26]hexaphyrin with alcohol/base and an amine nucleophile containing unpolar aliphatic moieties,[16] we decided to apply our thioglycosylation procedure to this class of substrates. Thus, we investigated the glycosylation of the [26]hexaphyrin **11a** under various conditions (Scheme 1).

Scheme 1. Attempts To Create the First Glycosylated Hexaphyrin



However, any of these attempts proved unsatisfactory and delivered only traces of product **12a** together with various side products. TLC analysis indicated multiglycosylations at the [26]hexaphyrin and also partial conversion to the corresponding reduced form, the [28]hexaphyrin. In fact, this partial reduction was identified as the major obstacle even when an excess of thiolate was used in order to promote reduction of the substrate.[16] We therefore decided to fully reduce the [26]hexaphyrin using $NaBH_4$ prior to the glycosylation (Scheme 1). This strategy proved to be successful, and after optimization of the reaction conditions, the nucleophilic substitution of the *p*-fluorine substituent of all six PFP units led to the first glycosylated [28]hexaphyrin **12b** with 78% yield (Scheme 1). This excellent yield corresponds to 96% yield for each substitution event.

To our surprise, this porphyrinoid gave well-resolved ^{1}H, ^{13}C, and ^{19}F NMR spectra, clearly proving the identity of the target structure (Figure 3). Even the different carbohydrate positions (e.g., 4 × C-1, 2 × C-1′) could be differentiated, especially in the ^{13}C spectrum. The thioglycosylated [28]-hexaphyrin, dissolved in methanol, displayed its typical blue color slowly changing to purple after exposure to air for a longer period of time. This observation is indicative of a reoxidation to the [26]hexaphyrin. However, similar to other reports,[4b] this conversion remained incomplete (even after stirring for 1 week in an open vessel).

To the best of our knowledge, the glycosylated PFP-substituted dipyrromethane, *trans*-A_2B-corrole, calix[4]phyrin-(**1**.*1*.**1**.*1*), calix[6]phyrin(**1**.*1*.**1**.*1*.**1**.*1*), and [28]-hexaphyrin(1.1.1.1.1.1) systems have not been reported previously. It is important to note that all of these new glycoporphyrinoids are easily soluble in alcohol/water mixtures (see the SI), thus fulfilling the crucial requirement of better compatibility with aqueous biological environments.

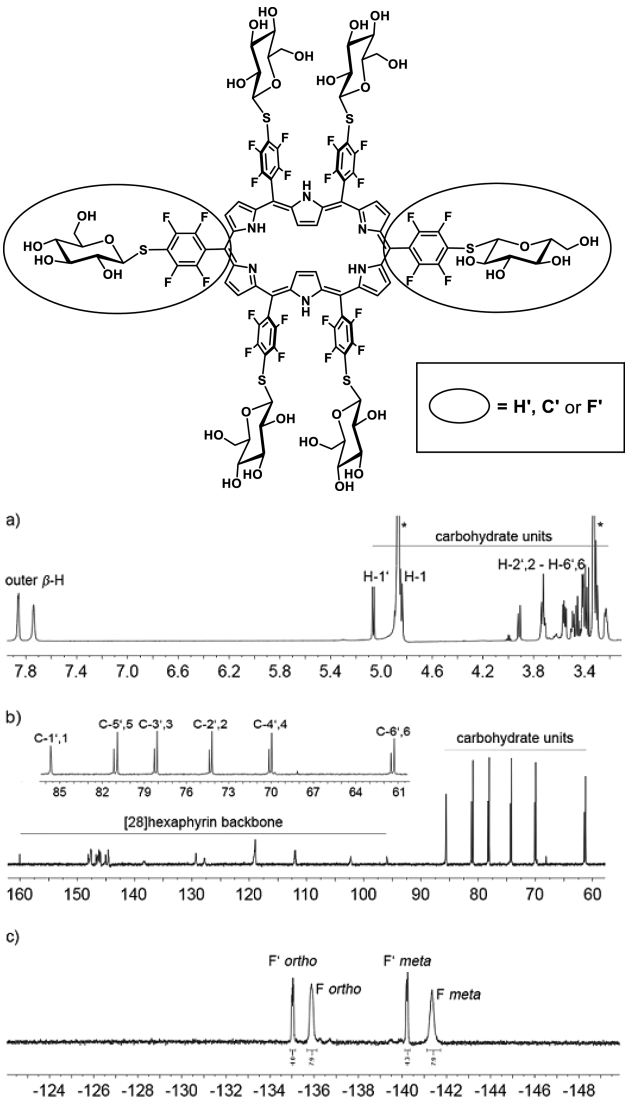


Figure 3. ^{1}H, ^{13}C, ^{19}F NMR spectra of **12b** in CD_3OD.

In summary, nucleophilic thioglycosylations have been used as a precise and powerful tool for a controlled regio- and stereoselective introduction of hydrophilic sugar units into various complex PFP-substituted porphyrinoids. The *para*-substituted products were obtained as the main regioisomer with the expected *β*-orientation of the glycosidic bond. There is no need to use an excess of the nucleophile (which was rather found to cause unwanted additional substitutions). The reactions proceed smoothly in the absence of any protecting groups and under essentially neutral conditions (no additional base required). Thus, even a 6-fold glycosylation proved possible in an excellent overall yield of 78%. The procedure described herein is believed to be useful to other applications using other base-labile and temperature-sensitive polar (bioactive) thiolates to prepare customized porphyrinoids.

■ ASSOCIATED CONTENT

Supporting Information

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Detailed experimental procedures, all NMR spectra (^{1}H, ^{13}C, ^{19}F), UV/vis spectra, and HRMS spectra (PDF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

Dedicated to Professor H.-U. Reissig on occasion of his 70th birthday.

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