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103. β-Cyclodextrin-Mediated Regioselective Hydrolysis of 5,10,15,20-Tetrakis[2,4-bis(pivaloyloxy)phenyl]-21*H*,23*H*-porphine

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(25.II.94)

The four *peripheral* ester moieties of the title compound **5** are regioselectively hydrolyzed under mild conditions in the presence of β-cyclodextrin (**10**), providing a new entry to tetraphenylporphyrin derivatives with differently substituted Ph groups in the *meso*-positions. UV, ^{1}H-NMR and mass spectroscopy of the inclusion complex **9** of 2,6-*O*-dimethyl-β-cyclodextrin (**12**) and **5** indicate a stoichiometry of 2:1 for **10**/**5**. Moreover, calculations confirm NOE experiments consistent with the fact that the cyclodextrins **10** and **12** approach the Ph groups of the porphyrin with the small opening of the cavity (primary face).

Introduction. – In recent years, several *face-protected* metal tetraphenylporphyrin (TPP) derivatives have been prepared in order to study the oxygen binding [1], to investigate the redoxchemistry related to additional axial ligands coordinating to the metal [2], and to mimic the spectroscopy [3] and chemical reactivity of enzymes employing these complexes in their active site [4].

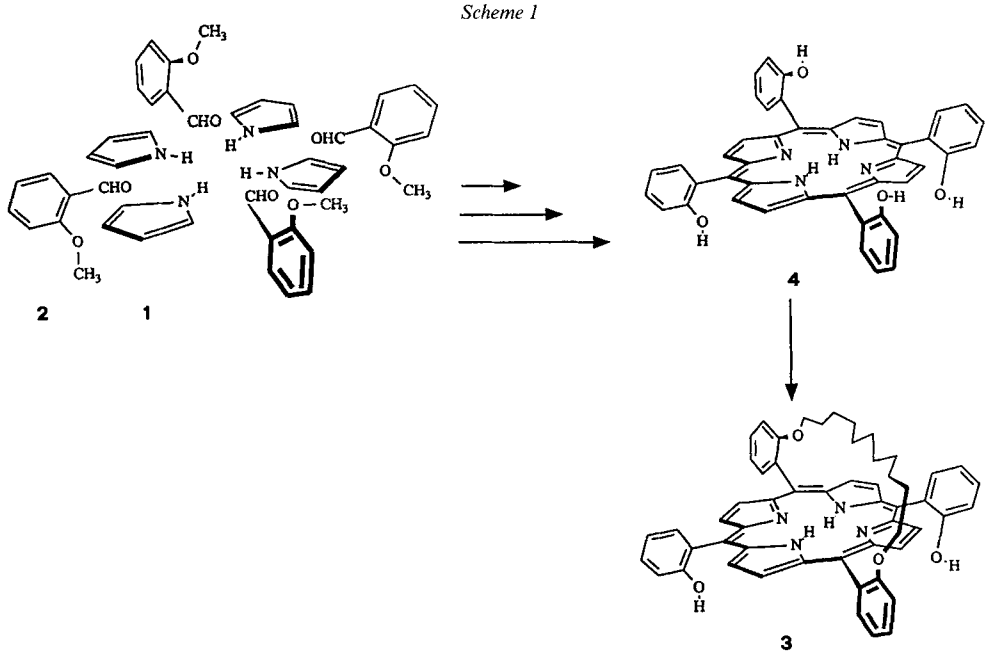
In this context, the preparation of active-site analogues of cytochrome P-450 has been a particular target mainly due to its significance in the oxidative metabolism of endogenous compounds and xenobiotics [5]. From all the synthetic concepts, aiming at P-450 models, the *picket-fence* and the *doubly-bridged* porphyrins became the most popular and useful for avoiding μ-oxo-dimer formation in the presence of O_2. Accordingly, the latter approach was rather successful, since advanced P-450 enzyme model systems could be prepared, and even O_2 cleavage and subsequent O-insertion into non-activated C–H bonds was demonstrated which is characteristic of native P-450 enzymes [4].

The synthesis of *doubly-bridged* porphyrins, named by *Momenteau* as *basket-handle* porphyrins [6], is rather simple using pyrrol **1** and suitably substituted aldehydes **2** which are condensed in the presence of $Zn(OAc)_2$ in boiling propionic acid. The only synthetic challenge is encountered when different bridges are required, and pure mono-bridged porphyrins **3** must be prepared. Generally, metal-free porphyrins such as **4** are obtained in *ca.* 10% yield, which is acceptable if the components **1** and **2** are easily available [3] (*Scheme 1*).

However, for the synthesis of porphyrins with substrate recognition sites [7], or water-soluble [8], polymer-linked porphyrins [9], and *doubly-bridged* porphyrins suitable for the production of chemically modified catalytic antibodies [10], one faces the problem of a lengthy aldehyde synthesis and, thus, a non-economic access to the desired porphyrins. Therefore, we decided to develop an alternative route employing β-cyclodextrin for the modification of easily available porphyrins.

Formation of cyclodextrin complexes of aromatic compounds has been known for nearly 40 years [11], and the first remarkable result for a regiospecific reaction at an

Scheme 1



aromatic compound in the hydrophobic cavity of β-cyclodextrin was reported by *Breslow* and *Campell* [12]. Since then, the cyclodextrins and their derivatives have attracted increasing interest in analytical chemistry [13]. They have been used as templates in order to mimic enzymatic reactions [14] and also simply to render lipophilic compounds water-soluble [13] [15].

Surprisingly, however, except for one example, concerning the regioselective cleavage of adenosine 2′,3′-cyclic phosphate [16], the regioselective hydrolysis of esters has not been reported. The cleavage of *m*- and *p*-nitrophenyl-alkanoates has been studied extensively in the presence of cyclodextrins, and, in general, rate acceleration has been observed ($k_m \geqslant k_p$) which was attributed to the mode of substitution at the aromatic ring, distinctly stabilizing the transition state of hydrolysis [17]. Recently, more systematic investigations revealed that the hydrolysis of certain phenyl esters also depend on the length of the aliphatic chain, if this part of the ester is introduced into the cavity of a second cyclodextrin. Accordingly, the reaction is either retarded or accelerated in the presence of α- and β-cyclodextrin derivatives mainly due to the formation of 1:1 and 2:1 inclusion complexes [18].

Results and Discussion. – In view of the remarkable properties of cyclodextrins to encapsule benzene derivatives [19], we anticipated that β-cyclodextrin would sheathe the Ph groups in the *meso*-positions of tetraphenylporphyrin derivatives [20]. Thus, (alkylcarbonyl)oxy substituents in *ortho*-position of these Ph groups should be more resistant to hydrolysis than those in *para*-position. These *peripheral* ester moieties were considered to be more exposed to nucleophilic attack by HO^- in solution, or, in case of a suitable orientation of the cyclodextrin cavity, they would be prone to 'intramolecular' attack by one of the OH groups at C(2) and C(3) at the rim of the cyclodextrin [17], *vide infra*.

To verify this hypothesis the tetrakis[2,4-bis(pivaloyloxy)phenyl]porphine **5** was prepared from pyrrol **1** and the aldehyde **8** *via* 5,10,15,20-tetrakis(2,4-dimethoxyphenyl)- (**6**) and 5,10,15,20-tetrakis(2,4-dihydroxyphenyl)porphine (**7**). Formation of the inclusion complex **9** was achieved by treating **5** with a 20-fold excess of β-cyclodextrin (**10**; 9.4 mM in EtOH/H_2O 2:1). With $NaHCO_3/Na_2CO_3$, hydrolysis took place at 25° during 20 h, and the pure tetrakis[4-hydroxy-2-(pivaloyloxy)phenyl]porphine **11** was isolated in 87.3% yield based on 64% consumption of the starting material; unchanged **5** was recovered in 36% (*Scheme 2*). Accordingly, the regioselectivity of hydrolysis can be quantified as *para/ortho* $\geqslant$ 7. When the same experiment was carried out in the absence of β-cyclodextrin (βCD, **10**), the selectivity of hydrolysis was found to be *para/ortho ca.* 1.2. From both reactions, the catalytic factor was calculated k_{cat}/k_{uncat} = 1.45, well in agreement with data reported for other reactions catalyzed by cyclodextrins [19].

To obtain information on the structure of the '*productive*' complex **9**, UV, MS, and ^{1}H-NMR studies were performed using 2,6-*O*-dimethyl-β-cyclodextrin (**12**; MeβCD) as a host. Compound **12** was choosen, because its inclusion complexes are significantly more soluble in EtOH/H_2O, whereas the cavities of **10** and **12** are of similar size and hydrophobicity [21]. The UV titration revealed that λ_{max} value of 412 nm for **5** remained constant, but the absorbance (*A*) changed on addition of MeβCD (**12**; see *Fig. 1*). Note that in two different experiments ΔA was found to be independent of the porphyrin concentration.

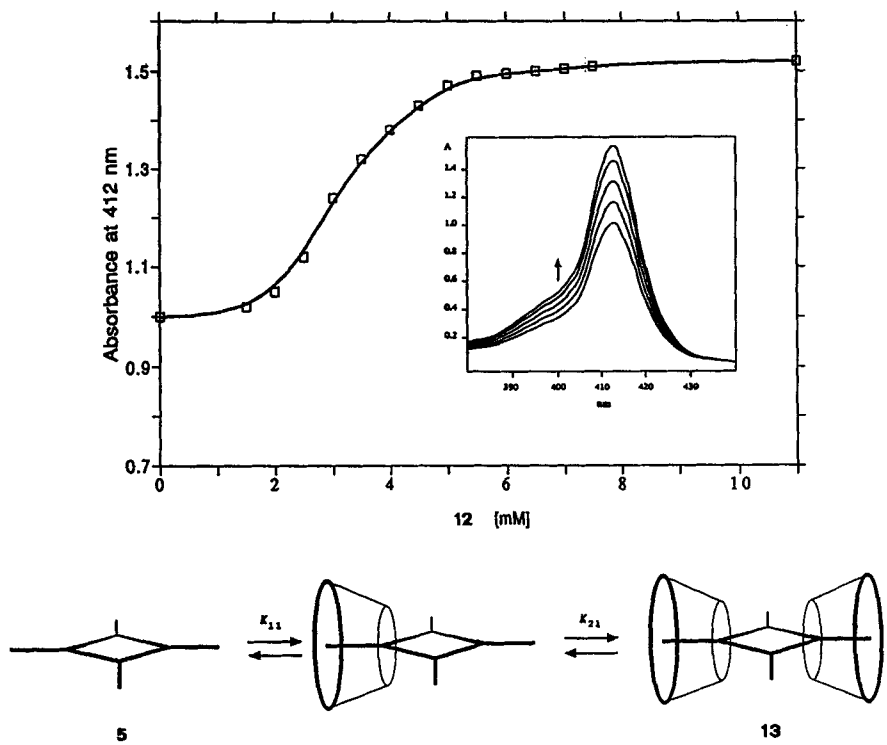
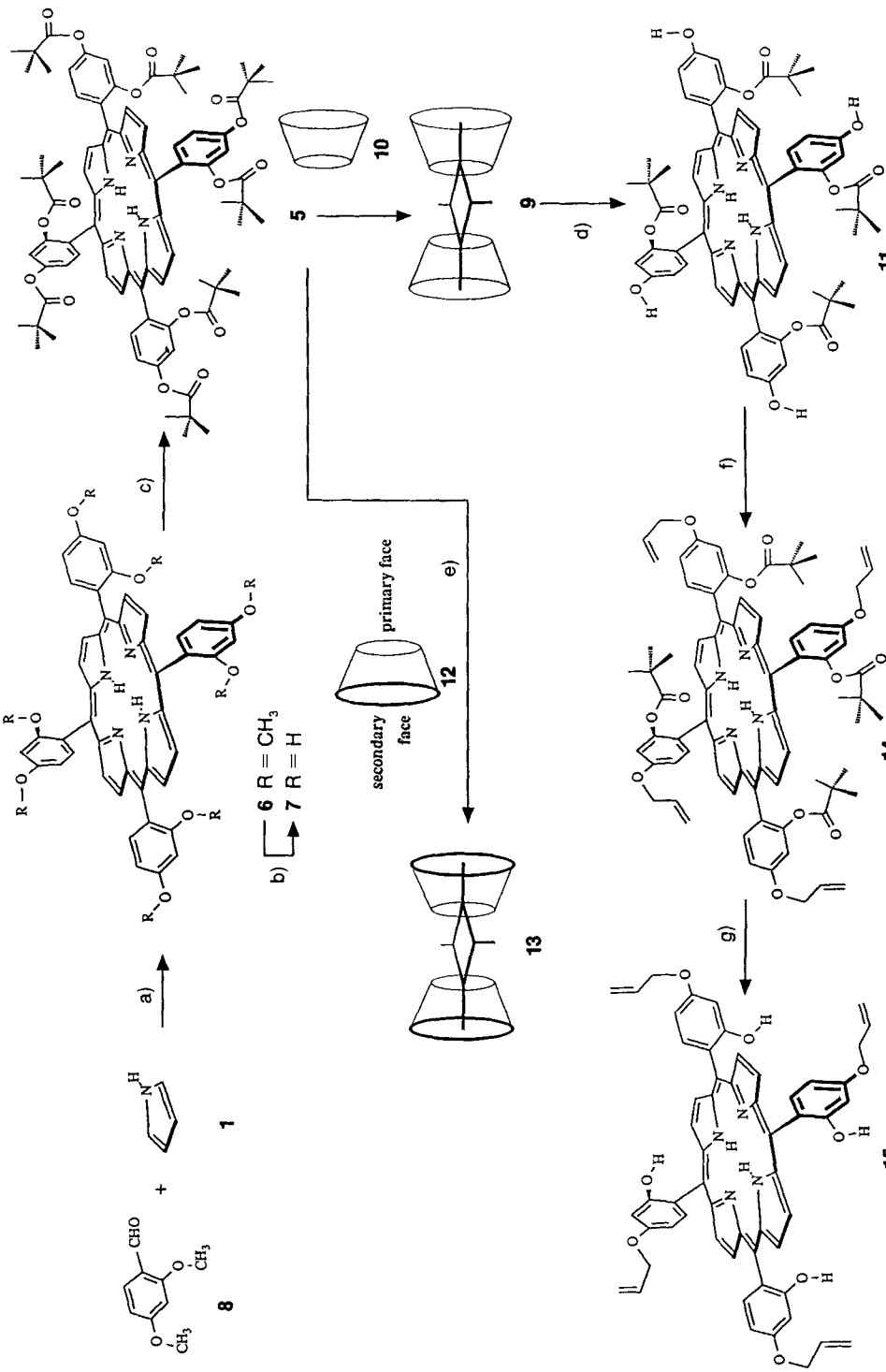


Fig. 1. *Change of absorbance (A) with increasing concentration of* **12** *at constant concentration of* **5** (4.24 μM)

Scheme 2



a) $Zn(OAc)_2$, propionic acid, reflux, 4 h; DDQ, CH_2Cl_2, reflux 1 h; 18% HCl, r.t., 10 min, 6.6% overall yield. b) BBr_3, CH_2Cl_2, −50° ⇒ r.t., 12 h, 77%. c) $((t\text{-}Bu)CO)_2O$, Cs_2CO_3, Et_2O, reflux, 16 h, 96%. d) $NaHCO_3/Na_2CO_3$, EtOH/H_2O 2:1, r.t., 20 h, 87.3%. e) EtOH/H_2O 2:1. f) Allyl bromide, Na_2CO_3, DMF, 100°, 2 h, 85%. g) EtOH/1N NaOH 3:1, r.t., 12 h, 91%. **10**: *β*-cyclodextrin; **12**: 2,6-di-*O*-methyl-*β*-cyclodextrin.

Mathematical treatment of the function $A = f(\mathbf{12})$ according to *Connors* [22] was consistent with the formation of **13**, a 2:1 complex of **12** and **5**, yielding two association constants $K_{11} = 5.4 \cdot 10^3$ M^{-1} and $K_{21} = 1.8 \cdot 10^4$ M^{-1}. K Values for the corresponding βCD complex **9** could be larger, *e.g.*, the association constants for several aromatic compounds in H_2O were measured and found to be significantly larger with βCD than with MeβCD [23].

The 2:1 stoichiometry was also supported by ESI-MS, indicating that the inclusion complex **13** carries 3+ charge (M^{3+} 1358) which corresponds to M^+ 4074. When the ESI experiment was performed in CD_3CD_2OD/D_2O, M^+ 4090 was calculated from the observed M^{3+} 1363, consistent with complete deuteration of the exchangeable H-atoms of guest and host.

Precipitation of **13** from CD_3CD_2OD/D_2O 3:1 yielded a pink powder, which, after removal of excess **12** with D_2O and solvation in CD_3CD_2OD, led to a ^{1}H-NMR spectrum displaying separate signals for **12** and **5** in the ratio 2:1. The ^{1}H-NMR spectrum of the supernatant, however, provided interesting clues for the mode of complexation of **5** with **12**. Significant shift changes were only observed for the guest molecule **5**. In particular, the six resonances (atropisomers) for the Me groups of the pivaloyloxy groups in *ortho*-positions were shifted upfield by 0.2–0.5 ppm relative to their position in EtOH (*Fig. 2*).

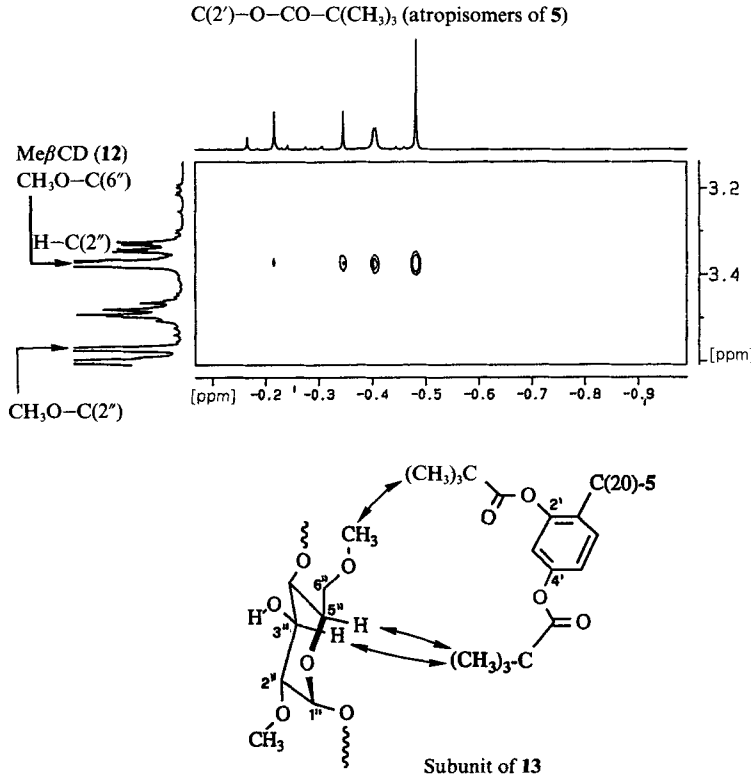


Fig. 2. *Part of the 2D ROESY NMR spectrum of* **13**, *and significant NOEs between host and guest in a substructure of* **13**

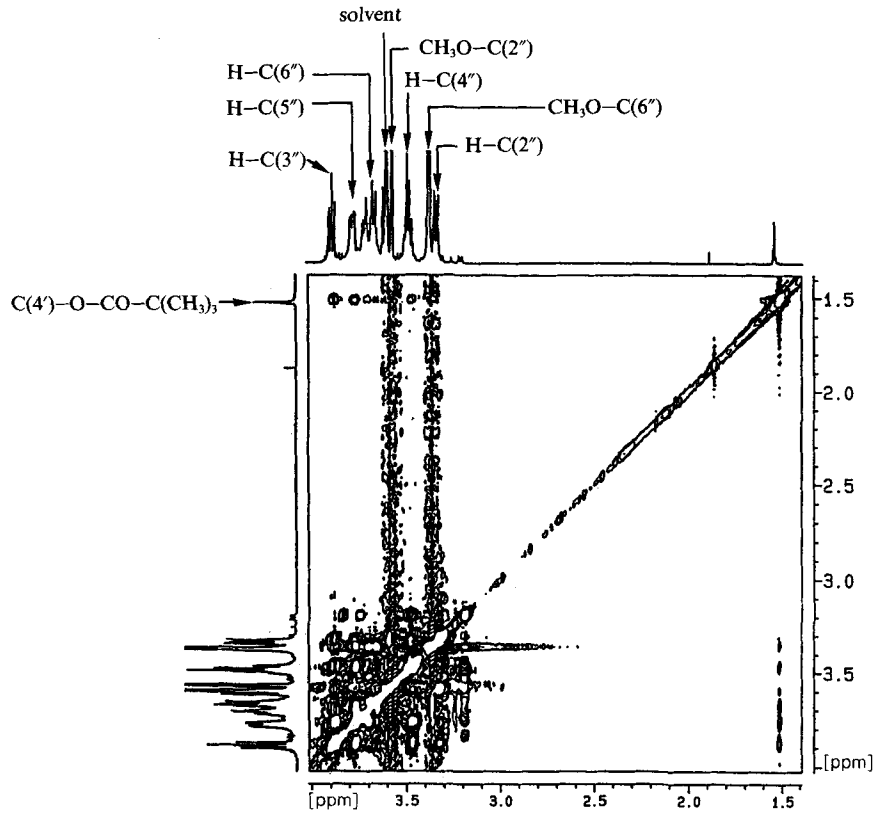


Fig. 3. *Essential part of the 2D ROESY NMR spectrum of* **13** *showing the relation between the pivaloyloxy group in* para-*position in* **5** *and Meβ CD* (**12**), *including the assignments of the resonances of* **12**

In contrast, the *singlet* for the *peripheral* pivaloyloxy groups (in *para*-position) remained at 1.5 ppm (*Fig. 3*). This result was also obtained with the corresponding complex between **5** and *β* CD (**10**), accounting for the similarity of both inclusion complexes **9** and **13**, and indicating that, due to steric hindrance with both Me*β* CD (**12**) and *β* CD (**10**), the pivaloyloxy groups in *ortho*-positions in **5** are bent towards the core of the porphyrin and thus more exposed to the ring current. The 2D-ROESY spectrum of the same solution of **13** revealed a strong NOE between the Me groups of the pivaloyloxy substituents in *para*-position and both *H*–C(3″) and *H*–C(5″) of Me*β* CD (**12**), which are located inside the cavity of the cyclodextrin, indicating encapsulation of the Ph groups (*Fig. 3*). In contrast, NOEs between the Me groups of the pivaloyloxy substituents in *para*-positions and the protons of the exterior surface of the cyclodextrin are considerably weaker. Thus, a random attachment of the cyclodextrin to the porphyrin chromophore can be excluded. A significant NOE was also observed between the Me groups of the pivaloyloxy substituent in *ortho*-position of **5** and *Me*O–C(6″) of **12** (*Fig. 2*). Since this MeO group is attached to the rim of the small opening of the cyclodextrin, it follows that **12** is approaching the Ph groups of the porphyrin with the primary face first. This argument is

also supported by the fact that NOEs are not observed between the Me groups of the pivaloyloxy substituent in *ortho*-position, and H–C(2″) and *Me*O–C(2″) of **13** (*Fig. 2*), which would be detectable in case of an approach towards the secondary face of the cyclodextrin. Since this result is quite surprising and contrasts with a recent report [20], which suggests a reverse encapsulation *via* the large opening, we decided to investigate this orientation problem with the aid of computer-generated host-guest complexes.

Using conformations known from the X-ray structures of α,α,α,α-**5**, one atropisomer of **5** with all four pivaloyloxy groups on one side of the porphyrin plane [24], and of β CD (**10**) [25], the α,α,α,α-tetrakis[2,4-bis(pivaloyloxy)phenyl]porphine was docked into the cavity of **12** by both secondary- and primary-face entry. After minimizing both 1:1 complexes using force-field calculations ('Discover'), the second host molecule **12** was approached also in two orientations to generate symmetrical 2:1 host-guest complexes having either the primary or the secondary face directed to the porphyrin. To obtain minimum-energy structures, the docking procedure for each class of complexes was repeated ⩾ 8 times starting from different spatial arrangement. Finally, the two sets of inclusion compounds were optimized free of restriction with respect to all geometrical parameters.

From the calculations of these relative minimum-energy assemblies, it became clear that only two cyclodextrins can sheathe the two 'diagonal' Ph groups in *meso*-positions (*e.g.*, at C(5) and C(15)) simultaneously (*Fig. 4*). 'Vicinal' encapsulation of the Ph groups in *meso*-position (*e.g.*, at C(5) and C(10)) is impossible due to severe steric congestions. Furthermore, the NOE's observed between **12** and **5** are only compatible with the small opening of **12** pointing towards the porphyrin center (*Fig. 4*) and exclude the reverse mode of binding. In the latter case, all distances measured between protons for which NOE's were observed are significantly larger than for the primary-face approach, *e.g.*, the minimal distance between the Me groups of the pivaloyl substituents in *ortho*-position of **5** and *Me*O–C(6″) of **12** is 2.4 Å for the complex shown in *Figs. 4* and *5*, and 7.8 Å for the unfavored orientation.

The mechanism of cyclodextrin-catalyzed ester hydrolysis has been shown to involve both the OH groups ar C(2) and C(3) at the secondary face of the cyclodextrins. Most likely due to its lower pK_a, the *HO*–C(2) is deprotonated under basic conditions and stabilized by *HO*–C(3). Subsequent attack on the ester C=O group yields an acylated cyclodextrin which can be isolated [19]. The position of acylation, and hence identification of HO–C(2) as the first nucleophile, is uncertain, because the product esters tend to equilibrate between C(2) and C(3). Furthermore, the position of acylation may be substrate-dependent due to different steric constraints between host and guest in the course of the nucleophilic displacement [26]. In view of these results, and considering the dependence of k_{cat}/k_{uncat} of the distance between *HO*–C(2) and the C=O of different substrates, calculated from ^{1}H-NMR experiments [27], it is important to note that, in our docking experiment (see *Figs. 4* and *5*), the minimal distances between O–C(3″) and O–C(2″) and the C=O groups of the pivaloyloxy groups are 4.2 Å and 4.5 Å, respectively, in agreement with a low magnitude of rate acceleration.

In conclusion, we have shown that the β-cyclodextrin-mediated hydrolysis of **5** involves the formation of a 2:1 complex of **10** and **5** in which the cyclodextrin envelops two 'diagonal' Ph groups at the porphyrin in a slightly tilted orientation with its primary face pointing to the center of the chromophore (*Fig. 4*).

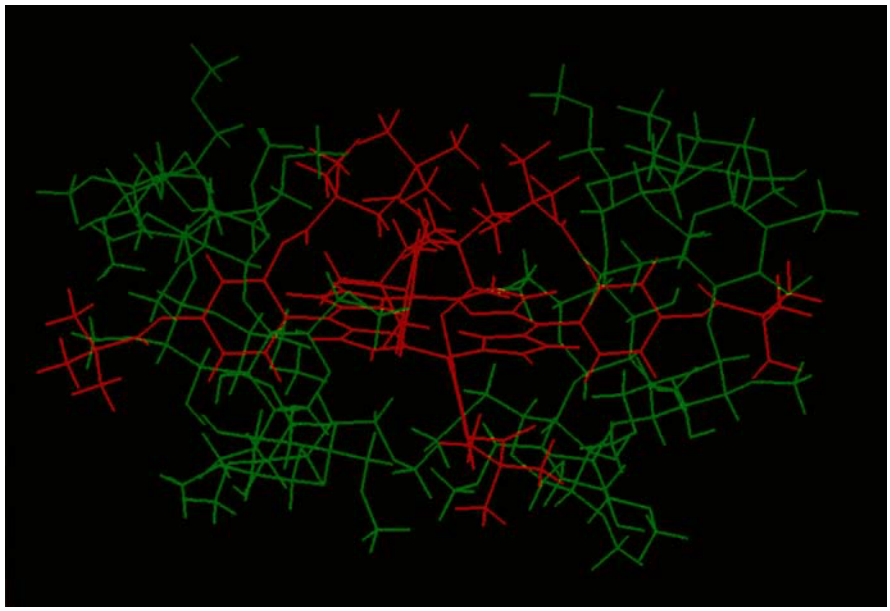


Fig. 4. *Optimized structure of* **13**: *view slightly from above the porphyrin plane showing the encapsulation of* diagonal *Ph groups in* meso-*positions of* **5** *by two Meβ CD* (**12**). Porphyrin: red, cyclodextrin: green.

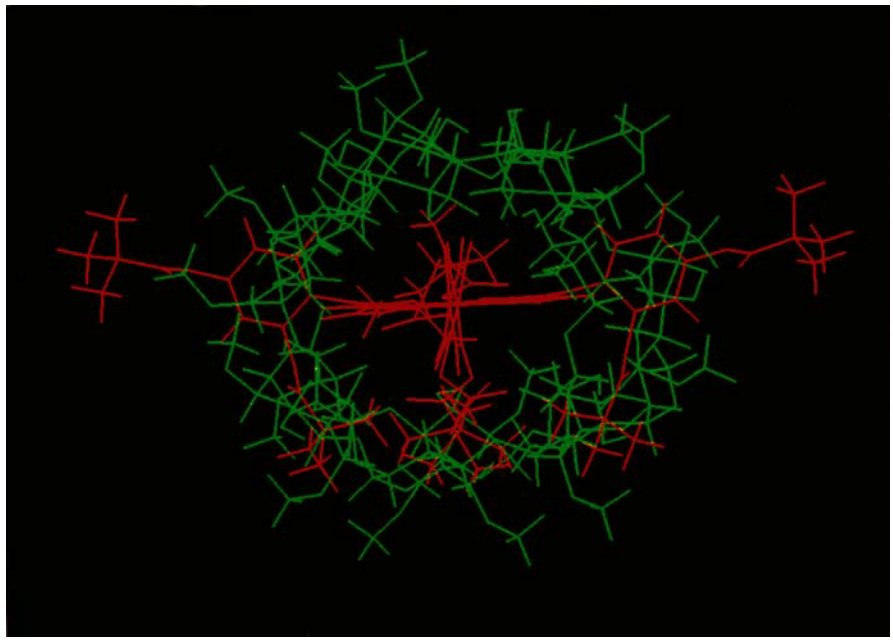


Fig. 5. *Optimized structure of* **13**: *view into the cavity (secondary face) of* **12** *sheathing two* diagonal *Ph groups in* meso-*positions of αααα*-**5**. Porphyrin: red, cyclodextrin: green.

Moreover, from the preparative point of view, this method is quite valuable, since allylation of the peripheral OH groups of **11** gave **14** which was hydrolyzed to yield the tetrakis[4-(allyloxy)-2-hydroxyphenyl]porphine **15** (*Scheme 2*). Thus, overall this procedure allows a convenient preparation of tetraphenylporphyrin derivatives with a free OH group in *ortho*-position and a protected OH group in *para*-position, suitable, *e.g.*, for the synthesis of *doubly-bridged* porphyrins [3].

Financial support by the *Swiss National Science Foundation* and *F. Hoffmann-La Roche AG*, Basel, is gratefully acknowledged. We are also indebted to Prof. *R. Neier* (Université de Neuchâtel) for valuable comments, and we thank *M. Salzmann* for assistance in calculating association constants.

Experimental Part

General. See [3]. Flash column chromatography (FC): $p(N_2) = 0.4$ bar; SiO_2 (0.040–0.063 mm, 230–400 mesh ASTM; *Merck*). ^{1}H-NMR: *Bruker AM-300* (300 MHz) and *Bruker AM-600* (600 MHz). ESI-MS: *Finnigan-TSQ-700* spectrometer.

Complexation Studies. Titrations of **5** with **12** were performed at 20° using a thermostable cell equipped with a cell-stirring module (*Hewlett-Packard 89054A*). Changes in absorbance were recorded at 412 nm and plotted against the host concentration using the *KaleidaGraph V 2.1.3* (*Abelbeck Software*) program. Calculation of the association constants was performed with the MATLAB 4.0 program (*The MathWorks, Inc.*) using the equations for multiple equilibria described by *Connors* [22]. Force-field calculations of the cyclodextrin complex structure were performed on a *SiliconGraphics IRIS*, using the program *Discover V 2.2.0* as a part of the *Insight II* package (*BIOSYM Technologies*).

*5,10,15,20-Tetrakis(2′,4′-dimethoxyphenyl)-21*H*,23*H*-porphine* (**6**). Compound **6** was prepared according to [3] by heating **8** (83.1 g, 0.50 mol), **1** (33.6 g, 0.50 mol), and $Zn(OAc)_2$ (27.4 g, 125 mol) in propionic acid (2.5 l) under reflux. Subsequent oxidation with an excess of DDQ in CH_2Cl_2 (250 ml) and removal of Zn^{2+} with 18% aq. HCl (300 ml) yielded the crude product, which was purified by FC (360 g of SiO_2, CH_2Cl_2) and crystallized from CH_2Cl_2/MeOH to give anal. pure **6** (7.05 g, 6.6%) as deep purple crystals. TLC (CH_2Cl_2): R_f 0.08 (αααα-**6**), 0.16 (ααα*β*-**6**), 0.24 (αα*ββ*-**6** and α*β*α*β*-**6**). VIS ($CHCl_3$): 654 (2.2), 592 (5.4), 550 (5.8), 516 (16.1), 419 (426.1). IR ($CHCl_3$): 3000*m*, 2940*m*, 2840*m*, 1820*w*, 1700*w*, 1620*s*, 1580*s*, 1505*s*, 1465*s*, 1440*m*, 1415*m*, 1350*w*, 1300*s*, 1280*s*, 1185*w*, 1160*s*, 1130*m*, 1040*m*, 995*w*, 980*w*, 965*m*, 840*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.75, 8.74 (2*s*, 8 H, pyrrole); 7.84, 7.78, 7.75 (3*d*, $^3J(5',6') = 7.0$, rel. int. 1:2:1, 4 H–C(6′)); 6.86–6.84 (*m*, 4 H–C(3′)); 6.70–6.67 (*m*, 4 H–C(5′)); 4.02 (*s*, 4 MeO–C(4′)); 3.61, 3.58, 3.55 (3*s*, rel. int. 1:2:1, 4 MeO–C(2′)); –2.23 (*s*, 2 NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 161.12 (C(4′)); 160.20 (C(2′)); 135.95, 135.87 (C(6′)); 130.46, 130.41, 130.30 (br., C, pyrrole); 124.02 (C(1′)); 115.21, 115.17 (C(*meso*)); 103.38 (C(5′)); 98.49 (C(3′)); 55.83 (*Me*O–C(4′)); 55.73, 55.62, 55.40, 55.36 (*Me*O–(C(2′)). EI-MS: 857 (8), 856 (25), 855 (55), 854 (100, $M^{+\cdot}$), 427 (16, $M^{2+\cdot}$). $C_{52}H_{46}N_4O_8$ (854.93).

*5,10,15,20-Tetrakis(2′,4′-dihydroxyphenyl)-21*H*,23*H*-porphine* (**7**). To a soln. of **6** (6.40 g, 7.49 mmol) in CH_2Cl_2 (250 ml) Br_3B (20.68 g, 82.39 mmol) was slowly added at –78° under Ar. After stirring for further 1.5 h at –50°, the soln. was allowed to reach 25° overnight. Then the soln. was cooled to 0°, sat. aq. $NaHCO_3$ soln. was added dropwise until the color of the soln. turned violet. AcOEt (500 ml) was added, the org. layer washed with brine (3 × 500 ml), dried (Na_2SO_4), and evaporated (15 Torr) to give 5.33 g (7.19 mmol) crude product. Purification (CC; SiO_2 (300 g), AcOEt/MeOH 25:3) yielded anal. pure **7** (4.27 g, 77%) as deep purple crystals. TLC (AcOEt): R_f 0.25 (αααα-**7**), 0.32 (ααα*β*-**7**), 0.48 (αα*ββ*-**7**, α*β*α*β*-**7**). VIS ($CHCl_3$): 654 (2.2), 592 (5.4), 550 (5.9), 516 (16.3), 419 (428.2). IR (KBr): 3600–3000*s* (br.), 2960*m*, 2920*m*, 2850*m*, 1820*w*, 1730*m*, 1620*s*, 1580*s*, 1500*w*, 1455*s*, 1350*w*, 1305*w*, 1250*w*, 1220*w*, 1165*w*, 1105*w*, 975*m*, 840*w*, 805*m*, 730*w*. ^{1}H-NMR (300 MHz, CD_3SOCD_3): 9.72 (*s*, 4 HO–C(4′), exchange with D_2O); 9.47, 9.45, 9.42, 9.39 (4*s*, 4 HO–C(2′), rel. int. 1:2:2:1, exchange with D_2O); 8.87 (*s*, 8 H, pyrrole); 7.84, 7.78, 7.75 (3*d*, $^3J(5',6') = 7.0$, rel. int. 1:2:1, 4 H–C(6′)); 6.86–6.84 (*m*, H–C(3′)); 6.69–6.67 (*m*, 4 H–C(5′)); 4.02 (*s*, 4 MeO–C(4′)); 3.61, 3.58, 3.55 (3*s*, rel. int. 1:2:1, 4 MeO–C(2′)); –2.23 (*s*, 2 NH, exchange with D_2O). ^{13}C-NMR (50 MHz, $CDCl_3/CD_3OD$ 9:1): 158.60 (C(4′)); 157.90 (C(2′)); 135.95, 135.87 (C(6′)); 128.78–128.33 (br., C, pyrrole); 121.11 (C(1′)); 115.21, 115.17 (C(*meso*)); 102.37 (C(5′)); 101.89 (C(3′)). EI-MS: No signals until 400°. $C_{52}H_{46}N_4O_8$ (854.93).

*5,10,15,20-Tetrakis[2′,4′-bis(2,2-dimethylpropanoyloxy)phenyl]-21*H*,23*H*-porphine* (**5**). To a soln. of **7** (4.80 g, 5.61 mmol) in dry Et_2O (450 ml), pivalic anhydride (9.39 g, 50.5 mmol) and Cs_2CO_3 (16.44 g, 50.5 mmol) were added. The mixture was refluxed overnight (16 h). After cooling, sat. aq. NH_4Cl soln. (500 ml) and Et_2O (50 ml)

were added to the mixture. The org. layer was extracted with sat. aq. NH_4Cl soln. (3 × 500 ml), washed with brine (1 × 500 ml), dried (Na_2SO_4), and evaporated (15 Torr and 0.01 Torr) to afford 8.18 g (5.78 mmol) crude product. Purification (FC; SiO_2 (360 g), CH_2Cl_2) yielded 100% HPLC-pure **5** (7.62 g, 96%) as deep purple crystals. Separation of the four atropisomers was achieved on prep. TLC (CH_2Cl_2): R_f 0.09 (αααα-**5**), 0.13 (αααβ-**5**, ααββ-**5**, αβαβ-**5**); when the run was repeated three times: R_f 0.25 (αααα-**5**), 0.38 (αααβ-**5**), 0.41, 0.43 (ααββ-**5**, αβαβ-**5**). The pure αααα-**5** was isomerized at 110° in toluene (1 h) to a mixture of the four isomers in a statistical ratio of 1:2:4:1 (αβαβ/ααββ/αααβ/αααα), established by HPLC analysis. TLC (CH_2Cl_2): R_f 0.09 (αααα-**5**), 0.13 (αααβ-**5**, ααββ-**5**, and αβαβ-**5**). VIS ($CHCl_3$): 654 (2.2), 592 (5.4), 550 (5.8), 516 (16.1), 419 (425.8). IR ($CHCl_3$): 3020*s*, 2980*m*, 2400*w*, 1820*m*, 1755*s*, 1620*w*, 1520*w*, 1480*m*, 1420*w*, 1400*w*, 1220*s*, 1210*s*, 1145*m*, 1115*s*, 1050*m*, 1040*w*, 1010*w*, 930*w*, 840*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.87 (*s*, 8 H, pyrrole); 8.09, 8.07, 8.05, 8.02, 7.98, 7.94 (6*d*, $^3J(5',6')$ = 8.1, rel. int. 1:2:2:1:1:1, 4 H–C(6′)); 7.41–7.32 (*m*, 4 H–C(3′), 4 H–C(5′)); 1.49 (*s*, 4 C(4′)–OCO(*t*-Bu)); –0.15, –0.17, –0.18, –0.19, –0.26, –0.30 (6*s*, rel. int. 1:2:1:1:2:1, 4 C(2′)–OCO(*t*-Bu)); –2.23 (*s*, 2 NH). ^{1}H-NMR (300 MHz, $CDCl_3$, αααα-**5**): 8.87 (*s*, 8 H, pyrrole); 7.96 (*d*, $^3J(5',6')$ = 8.1, 4 H–C(6′)); 7.38 (*d*, $^3J(5',6')$ = 2.0, 4 H–C(3′)); 7.35 (*dd*, $^3J(5',6')$ = 8.1, $^3J(5',3')$ = 2.0, 4 H–C(5′)); 1.49 (*s*, 4 C(4′)–OCO(*t*-Bu)); –0.17 (*s*, 4 C(2′)–OCO(*t*-Bu)); –2.23 (*s*, 2 NH). ^{13}C-NMR (50 MHz, $CDCl_3$): 176.67, 175.70, 175.59, 175.51, 173.80 (OCO(*t*-Bu)); 151.70 (C(4′)); 151.09, 150.99, 150.89, 150.85 (C(2′)); 135.55, 135.43, 135.37, 135.26 (C(6′)); 131.86 (C(1′)); 131.81–130.76 (br., C, pyrrole); 117.64 (C(5′)); 116.08 (C(3′)); 113.80, 113.71, 113.60 (C(*meso*)); 40.06, 39.25, 38.02, 37.95 (OCO*C*(CH_3)$_3$); 27.15, 26.40, 25.61 (OCOC(CH_3)$_3$). EI-MS: 1418 (7), 1417 (21), 1416 (53), 1415 (94), 1414 (100, M^+), 1333 (7), 1332 (18), 1331 (33), 1330 (46, $[M - COC(CH_3)_3]^+$), 1329 (25), 1247 (10), 1246 (15, $[M - 2\ COC(CH_3)_3]^+$), 1245 (11). Anal. calc. for $C_{84}H_{94}N_4O_{16}$ (1415.70): C 71.29, H 6.65, N 3.96; found: C 71.03, H 6.88, N 3.66.

*Complex of 5,10,15,20-Tetrakis[2′,4′-bis(2″,2″-dimethylpropanoyloxy)phenyl]-21*H*,23*H*-porphine* (**5**) *with 2″,6″-Di-*O*-methyl-β-cyclodextrin* (**12**). VIS: A mixture of ααββ-**5**, αβαβ-**5**, αααβ-**5**, and αααα-**5** (6 mg, 4.24 μmol) was dissolved in 666 ml of EtOH and 333 ml of H_2O. Aliquots (15 × 15 ml) were taken from this stock soln., and **12** was added (0 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 320 mg). After 1 h in the ultrasonic bath, these ten samples were stored overnight at 4°. VIS (EtOH/H_2O 2:1, *c*(**5**) = 4.24 μM, *T* = 20°, *c*(**12**) = 0 mM): 652 (3.4), 584 (5.1), 540 (4.4), 508 (14.4), 412 (236.0). VIS (*c*(**12**) = 1.5 mM): 652 (3.5), 584 (5.25), 540 (4.5), 508 (14.8), 412 (243.1). VIS (*c*(**12**) = 2.0 mM): 652 (3.6), 584 (5.4), 540 (4.6), 508 (15.1), 412 (247.8). VIS (*c*(**12**) = 2.5 mM): 652 (3.8), 584 (5.7), 540 (4.9), 508 (16.1), 412 (264.3). VIS (*c*(**12**) = 3.0 mM): 652 (4.2), 584 (6.3), 540 (5.5), 508 (17.9), 412 (292.6). VIS (*c*(**12**) = 3.5 mM): 652 (4.5), 584 (6.7), 540 (5.8), 508 (19.0), 412 (311.5). VIS (*c*(**12**) = 4.0 mM): 652 (4.7), 584 (7.0), 540 (6.1), 508 (19.9), 412 (325.7). VIS (*c*(**12**) = 4.5 mM): 652 (4.9), 584 (7.3), 540 (6.3), 508 (20.6), 412 (337.5). VIS (*c*(**12**) = 5.0 mM): 652 (5.0), 584 (7.5), 540 (6.5), 508 (21.2), 412 (346.9). VIS (*c*(**12**) = 5.5 mM): 652 (5.1), 584 (7.6), 540 (6.6), 508 (21.5), 412 (351.6). VIS (*c*(**12**) = 6.0 mM): 652 (5.1), 584 (7.7), 540 (6.6), 508 (21.6), 412 (354.0). VIS (*c*(**12**) = 6.5 mM): 652 (5.1), 584 (7.7), 540 (6.6), 508 (21.6), 412 (354.0). VIS (*c*(**12**) = 7.0 mM): 652 (5.1), 584 (7.7), 540 (6.6), 508 (21.7), 412 (356.3). VIS (*c*(**12**) = 7.5 mM): 652 (5.1), 584 (7.7), 540 (6.6), 508 (21.7), 412 (356.3). VIS (*c*(**12**) = 11.0 mM): 652 (5.2), 584 (7.8), 540 (6.7), 508 (22.0), 412 (361.1). The same procedure was applied adding **12** (0, 40 mg, 60 mg) to aliquots (3 × 15 ml) taken from a soln. of **5** (3.89 μm). VIS (EtOH/H_2O 2:1, *c*(**12**) = 0, *c*(**5**) = 3.89 μm, *T* = 20°): 652 (3.8), 584 (5.6), 540 (4.8), 508 (15.8), 412 (236.0). VIS (*c*(**12**) = 2.5 mM): 652 (3.8), 584 (5.6), 540 (4.8), 508 (15.8), 412 (263.7). VIS (*c*(**12**) = 3.5 mM): 652 (4.5), 584 (6.7), 540 (5.8), 508 (18.9), 412 (310.8). ^{1}H-NMR: A mixture of ααββ-**5**, αβαβ-**5**, αααβ-**5**, and αααα-**5** (3 mg, 2.12 μmol) was dissolved in 0.6 ml CD_3CD_2OD and the reference ^{1}H-NMR-spectra (*a*) was measured. Then, **12** (56.4 mg, 42.4 μmol) in 0.2 ml of D_2O was added, and the NMR tube was exposed 1 h to ultrasound and stored overnight at 4°. The pale red solid was removed by filtration, and the supernatant taken for the ^{1}H-NMR spectra (*b*) and ROESY experiments. The red solid was carefully washed with D_2O, dissolved in CD_3CD_2OD, and the ^{1}H-NMR spectrum (*c*) was measured. The same procedure was applied to measure the ^{1}H-NMR spectra of the inclusion complex of β CD (**10**) with **5** and those of both inclusion complexes and a solvent composition of CD_3CD_2OD/D_2O 2:1. *a*) ^{1}H-NMR (300 MHz, CD_3CD_2OD): 9.00–8.60 (br. *s*, 8 H, pyrrole); 8.25–8.05 (*m*, 4 H–C(6′)); 7.50–7.25 (*m*, 4 H–C(3′), 4 H–C(5′)); 1.51 (*s*, 4 C(4′)–OCO(*t*-Bu)); –0.18, –0.26, –0.29, –0.34 (4*s*, rel. int. 1:1:2:2, 4 C(2′)–OCO(*t*-Bu)). *b*) ^{1}H-NMR (600 MHz, CD_3CD_2OD/D_2O 3:1): 9.0–8.6 (br. *s*, 8 H, pyrrole); 8.3–8.0 (*m*, 4 H–C(6′)); 7.6–7.2 (*m*, 4 H–C(3′), 4 H–C(5′)); 5.06 (*d*, $^3J(1'',2'')$ = 3.58, 155 H–C(1″)); 3.88 (*dd*, $^3J(3'',2'')$ = 9.13, $^3J(3'',4'')$ = 9.13, 155 H[1]), H–C(3″)); 3.78–3.76 (*m*, 155 H, H–C(5″)); 3.72–3.66 (*m*, 310 H, H–C(6″)); 3.57 (*s*, 155 H, MeO–C(2″)); 3.50–3.47 (*m*, 155 H, H–C(4″)); 3.37 (*s*, 155 H,

[1]) The number of the protons of cyclodextrin **12** is calculated from the integral with the number of pyrrol protons of the porphyrin **5** as internal standard.

MeO–C(6″)); 3.33 (*dd*, $^3J(2'',1'') = 3.58$, $^3J(2'',3'') = 9.13$, 155 H, H–C(2″)); 1.52 (*s*, 4 C(4′)–OCO(*t*-Bu)); – 0.23, – 0.36, – 0.42, – 0.50 (4*s*, rel. int. 1:1:2:2, 4 C(2′)–OCO(*t*-Bu)). *c*) ^{1}H-NMR (300 MHz, CD_3CD_2OD): 9.0–8.6 (br. *s*, 8 H, pyrrole); 8.3–8.0 (*m*, 4 H–C(6′)); 7.6–7.2 (*m*, 4 H–C(3′), 4 H–C(5′)); 5.06 (*d*, $^3J(1'',2'') = 3.58$, 14 H–C(1″)); 3.88 (*dd*, $^3J(3'',2'') = 9.13$, $^3J(3'',4'') = 9.13$, 14 H–C(3′)); 3.78–3.76 (*m*, 14 H–C(5″)); 3.72–3.66 (*m*, 28 H–C(6″)); 3.57 (*s*, 14 MeO–C(2″)); 3.50–3.47 (*m*, 14 H–C(4″)); 3.37 (*s*, 14 MeO–C(6″)); 3.33 (*dd*, $^3J(2'',1'') = 3.58$, $^3J(2'',3'') = 9.13$, 14 H–C(2″)); 1.51 (*s*, 4 C(4′)–OCO(*t*-Bu)); – 0.18, – 0.26, – 0.29, – 0.34 (4*s*, rel. int. 1:1:2:2, 4 C(2′)–OCO(*t*-Bu)). ESI-MS: The sample used for the ^{1}H-NMR spectrum *b* was taken for ESI-MS investigations. To assure the results, an emulsion of **5** (3.5 mM) and **12** (70 mM) in EtOH/H_2O 3:1 was prepared, and filtered off as described above. It was checked that in the solvent mixture EtOH/H_2O 3:1 neither **5** nor **12** are enough soluble to enable a good ESI spectrum. ESI-MS (EtOH/H_2O 3:1, range from 1900 to 1100): 1815–1803 (15, $[M(\mathbf{5}) + 3\ M(\mathbf{12}) + H_2O + Na^+ + 2\ H^+]^{3+}$, $[M(\mathbf{5}) + 3\ M(\mathbf{12}) + H_2O + 3\ H^+]^{3+}$, $[M(\mathbf{5}) + 3\ M(\mathbf{12}) + 3\ H^+]^{3+}$), 1385–1380 (44, $[M(\mathbf{5}) + 2\ M(\mathbf{12}) + 3\ Na^+]^{3+}$), 1371–1366 (100 $[M(\mathbf{5}) + 2\ M(\mathbf{12}) + Na^+ + 2\ H^+]^{3+}$), 1364–1361 (35, $[M(\mathbf{5}) + 3\ M(\mathbf{12}) + H_2O + 4\ H^+]^{4+}$), 1356–1352 (70, $[M(\mathbf{5}) + 3\ M(\mathbf{12}) + H_2O + 4\ H^+]^{4+}$). ESI-MS ($CD_3CD_2OD/D_2O$ 3:1): 1818–1805 (40, $[M(\mathbf{5}) + 3\ M(\mathbf{12}) + D_2O + Na^+ + 2\ D^+]^{3+}$, $[M(\mathbf{5}) + 3\ M(\mathbf{12}) + 3\ D^+]^{3+}$), 1387–1382 (35, $[M(\mathbf{5}) + 2\ M(\mathbf{12}) + 3\ Na^+]^{3+}$), 1373–1368 (90, $[M(\mathbf{5}) + 2\ M(\mathbf{12}) + Na^+ + 2\ D^+]^{3+}$), 1366–1363 (80, $[M(\mathbf{5}) + 3\ M(\mathbf{12}) + D_2O + 4\ D^+]^{4+}$), 1358–1354 (100, $[(M(\mathbf{5}) + 3\ M(\mathbf{12}) + 4\ D^+]^{4+}$).

*5,10,15,20-Tetrakis[2′-(2″,2″-dimethylpropanoyloxy)-4′-hydroxyphenyl]-21*H*,23*H*-porphine* (**11**). In a 10-l *Erlenmeyer*-flask, **5** (3.00 g, 2.12 mmol) was suspended in EtOH (3 l) and H_2O (1.5 l); under these conditions, the porphyrin is insoluble, and the solvent remains colorless. After the addition of **10** (48.12 g, 42.4 mmol) and 1 h at r.t. in the ultrasonic bath, the color of the emulsion became purple, and the dark solid disappeared. $NaHCO_3$ (48.12 g) was added, and the mixture was exposed to ultrasound for another h. Then EtOH (3 l) and 10% aq. Na_2CO_3 soln. (1.5 l) were added, and the mixture was stirred at r.t. for 20 h. To the mixture, 1N HCl was slowly added, until its color turned green, and the white precipitate disappeared. The hydrophobic compounds were extracted with CH_2Cl_2/toluene 10:1 (2 × 300 ml), neutralized with sat. aq. $NaHCO_3$ soln. (3 × 300 ml, color change to purple), dried (Na_2SO_4), and evaporated (15 Torr and 0.01 Torr) to give 2.67 g (117%) of the crude product. Purification by FC (360 g of SiO_2, CH_2Cl_2/MeOH 10:1) yielded **5** (1.08 g, 36%, 64% conversion) and **11** (1.28 g, 56%, 87.7% for 64% conversion) as deep purple crystals. A reaction time of 7 d converted **5** completely to the mono-, di-, tri-, and tetraesters, but the yield of **11** decreased to 30–40%. Compound **5** (93 mg, 0.066 mmol) was converted by exactly the same procedure without β-CD (**10**) to 96 mg of crude product. Purification by FC (90 g of SiO_2, CH_2Cl_2/MeOH 10:1) yielded **5** (52.2 mg, 56%, 44% conversion) and **11** (17.4 mg, 24.5%, 56% for 44% conversion) as a deep purple solid. **11**: TLC (CH_2Cl_2/MeOH 10:1): R_f 0.10 ($\alpha\alpha\alpha\alpha$-**11**, $\alpha\alpha\alpha\beta$-**11**, $\alpha\alpha\beta\beta$-**11**, and $\alpha\beta\alpha\beta$-**11**). VIS ($CHCl_3$): 654 (2.2), 592 (5.4), 550 (5.8), 516 (16.2), 419 (426.7). IR (CHCl): 3450–3200*m*, 3020*s*, 2980*m*, 1820*m*, 1755*s*, 1620*w*, 1520*w*, 1480*m*, 1420*w*, 1400*w*, 1220*s*, 1210*s*, 1145*m*, 1115*s*, 1050*m*, 1040*w*, 1010*w*, 930*w*, 840*w*. ^{1}H-NMR (300 MHz, CD_3SOCD_3): 9.72 (*s*, 4 HO–C(4′), exchange with D_2O); 8.78 (*s*, 8 H, pyrrole); 7.98–7.84 (*m*, 4 H–C(6′)); 7.19–7.12 (*m*, 4 H–C(3′)); 7.09–7.06 (*m*, 4 H–C(5′)); – 0.14 – 0.30 (6*s*, 4 C(2′)–OCO(*t*-Bu)); – 2.23 (*s*, 2 NH, exchange with D_2O). ^{13}C-NMR (100 MHz, CD_3OD): 177.91, 177.85, 177.74 (OCO(*t*-Bu)); 160.37, 160.21 (C(4′)); 153.36, 153.29, 153.12, 153.00, 152.92 (C(2′)); 137.30, 137.27, 137.18, 137.05, 136.99, 136.94 (C(6′)); 136.80–134.56, 129.47–128.94 (br., C, pyrrole); 127.25, 127.07 (C(1′)); 115.96, 115.90, 115.83 (C(*meso*)); 113.29, 113.24, 113.00, 112.90, 112.81 (C(5′)); 110.98, 110.76, 110.73, 110.66, 110.62 (C(3′)); 39.43, 39.37, 39.33, 39.25 (OCO*C*$(CH_3)_3$); 26.79, 26.38, 26.24 (OCOC(*C*$H_3)_3$). ESI-MS ($CHCl_3$/MeOH 1:2): 1079 (100, $[M + H^+]^+$). $C_{64}H_{62}N_4O_{12}$ (1079.21).

*5,10,15,20-Tetrakis[2′-(2″,2″-dimethylpropanoyloxy)-4′-(prop-2‴-enyloxy)phenyl]-21*H*,23*H*-porphine* (**14**). To a soln. of **11** (1.20 g, 1.13 mmol) and Na_2CO_3 (500 mg) in DMF (50 ml) under Ar, freshly dist. allylbromide (547 mg, 4.52 mmol) in DMF (3 ml) was injected, and the mixture was stirred at 100° for further 2 h. After cooling to r.t., the solvent was removed (0.01 Torr), the remaining dark solid was dissolved in Et_2O (200 ml), extracted with sat. aq. $NaHCO_3$ soln. (3 × 200 ml), washed with brine (1 × 200 ml), dried (Na_2SO_4), and evaporated (15 Torr and 0.01 Torr) to give 1.33 g (95%) of the crude product. Purification by FC (360 g of SiO_2, CH_2Cl_2/hexane 3:2) afforded anal. pure **14** (1.19 g, 85%) as a purple solid. TLC (CH_2Cl_2/hexane 2:1): R_f 0.34 ($\alpha\alpha\alpha\alpha$-**14**, $\alpha\alpha\alpha\beta$-**14**, $\alpha\alpha\beta\beta$-**14**, and $\alpha\beta\alpha\beta$-**14**). VIS ($CHCl_3$): 654 (2.2), 592 (5.4), 550 (5.9), 516 (16.4), 419 (429.7). IR ($CHCl_3$): 2920*m*, 2860*m*, 1755*s*, 1620*m*, 1505*w*, 1475*m*, 1460*w*, 1420*w*, 1350*w*, 1280*s*, 1240*w*, 1160*m*, 1125*s*, 995*w*, 970*w*, 935*w*, 895*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.81 (br. *s*, 8 H, pyrrole); 8.12, 8.00, 7.96, 7.93, 7.88, 7.82 (6*d*, $^3J(5',6') = 8.4$, 4 H–C(6′)); 7.23–7.17 (*m*, 4 H–C(3′)); 7.17–7.09 (*m*, 4 H–C(5′)); 6.27 (*ddt*, $^3J(2'',3''a) = 17.2$, $^3J(2'',3''b) = 10.5$, $^3J(1'',2'') = 5.2$, 4 H–C(2″)); 5.63 (*ddt*, $^3J(2'',3''a) = 17.2$, $^2J(3''a,3''b) = {}^4J(1'',3''a) = 1.6$, 4 H_a–C(3″)); 5.46 (*ddt*, $^3J(2'',3''b) = 10.5$, $^2J(3''a,3''b) = {}^4J(1'',3''b) = 1.6$, 4 H_b–C(3″)); 4.84 (*ddd*, $^3J(1'',2'') = 5.2$, $^4J(1'',3''a) = {}^4J(1'',3''b) = 1.6$, 8 H–C(1″)); – 0.14 – 0.30 (6*s*, 4 (C(2′)–OCO(*t*-Bu)); – 2.23 (*s*, 2 NH). ^{13}C-NMR (50 MHz, $CDCl_3$): 177.85, 177.63 (OCO(*t*-Bu)); 161.24 (C(4′)); 151.61, 151.21, (C(2′)); 138.00 (C(1′)); 134.76 (C(2″)); 132.89–130.96 (br., C, pyrrole); 128.87 (C(6′)); 117.66 (C(3″)); 114.32 (C(*meso*)); 110.83 (C(3′)); 109.32 (C(5′)); 69.55 (C(1″)); 39.33 (OCO*C*$(CH_3)_3$); 26.28

(OCOC(CH_3)$_3$). EI-MS: 1241 (13), 1240 (40), 1239 (87), 1238 (100, $M^{+\cdot}$), 1198 (8), 1155 (9), 1154 (18), 1153 (19, [M – COC(CH_3)$_3$]$^+$). ESI-MS ($CHCl_3$/MeOH 1:2): 1239 (100, [M + H^+]$^+$). $C_{76}H_{78}N_4O_{12}$ (1239.47).

*5,10,15,20-Tetrakis[2′-hydroxy-4′-(prop-2″-enyloxy)phenyl]-21*H*,23*H*-porphine* (**15**). A fine dispersion of **14** (1.00 g, 0.81 mmol) in EtOH/1N NaOH 3:1 (4 l) was generated under ultrasonic conditions. After stirring overnight, the mixture was carefully neutralized with 6N HCl (*ca.* 170 ml), until the color changed from purple to green. The porphyrin **15** was extracted with AcOEt (2 × 300 ml), neutralized with sat. aq. $NaHCO_3$ soln. (3 × 300 ml), dried (Na_2SO_4), and evaporated (15 Torr and 0.01 Torr) to give 730 mg (100%) of the crude product. CC → FC (300 g of SiO_2, CH_2Cl_2/MeOH 20:1) and crystallization (EtOH) yielded anal. pure **15** (663 mg, 91%) as deep purple crystals. TLC (CH_2Cl_2/MeOH 20:1): R_f 0.13 (αααα-**15**), 0.21 (αααβ-**15**), 0.45 (ααββ-**15**), and 0.57 (αβαβ-**15**); rel. int. 1:4:2:1. M.p. > 300°. VIS ($CHCl_3$): 654 (2.2), 592 (5.4), 550 (5.8), 516 (16.1), 419 (426.0). IR ($CHCl_3$): 3540*s*, 3500–3100*m*, 2920*m*, 2860*m*, 1730*w*, 1640*s*, 1580*m*, 1505*s*, 1460*w*, 1420*w*, 1350*w*, 1320*m*, 1280*m*, 1245*s*, 1170*m*, 1150*s*, 1120*w*, 1105*w*, 1025*m*, 995*w*, 970*w*, 935*w*, 835*w*. ^{1}H-NMR (300 MHz, $CDCl_3$/CD_3OD 10:1): 8.93 (br. *s*, 8 H, pyrrole); 7.85–7.80 (*m*, 4 H–C(6′)); 6.95–6.85 (*m*, 8 H–C(3′), –C(5′)); 6.26 (*ddt*, ^3J(2″,3″a) = 17.2, ^3J(2″,3″b) = 10.5, ^3J(1″,2″) = 5.2, 4 H–C(2″)); 5.62 (*ddt*, ^3J(2″,3″a) = 17.2, ^2J(3″a,3″b) = ^4J(1″,3″a) = 1.6, 4 H_a–C(3″)); 5.45 (*ddt*, ^3J(2″,3″b) = 10.5, ^2J(3″a,3″b) = ^4J(1″,3″b) = 1.6, 4 H_b–C(3″)); 4.80 (*ddd*, ^3J(1″,2″) = 5.2, ^4J(1″,3″a) = ^4J(1″,3″b) = 1.6, 8 H–C(1″)). ^{13}C-NMR (50 MHz, $CDCl_3$): 161.26, (C(4′)); 158.72 (C(2′)); 136.55 (C(1′)); 134.75 (C(2″)); 132.10–130.10 (br., C, pyrrole); 122.29 (C(6′)); 117.60 (C(3″)); 117.55 (C(*meso*)); 105.69 (C(3′)); 102.71 (C(5′)); 69.55 (C(1″)). ESI-MS: 903 (100, [M + H^+]$^+$). $C_{76}H_{78}N_4O_{12}$ (903.22).

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