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Synthesis and Properties of Ionophore Conjugated Hypericin Derivatives

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Summary. Two types of derivatives substituted with ionophoric residues at the ω,ω'-methyl groups of hypericin were synthesized. On the one hand, an open chain triethylene glycol derivative did not form stable complexes with alkali metal ions. Embedded as its detergent salt in lipid bilayer membranes it did not provide specific proton, sodium, or potassium channels. On the other hand, crown-4 and crown-5 hypericin derivatives were able to complex sodium and potassium ions, with the crown-5 compound forming a stable potassium crown complex. In such systems, the hypericinate ion is intramolecularly compensated by the complexed cation, thereby forming an extremal structure within the series of hypericinates.

Key words. Crown ether; Hypericin; Absorption spectra; ^{1}H NMR.

Synthese und Eigenschaften von Ionophor-konjugierten Hypericinderivaten

Zusammenfassung. Zwei Typen von Derivaten mit ionophoren Resten an den ω,ω'-Methylgruppen des Hypericins wurden dargestellt. Einerseits bildete ein offenkettiges Triethylenglykolderivat keine stabilen Komplexe mit Alkalimetallionen. Eingebettet als sein Detergenssalz in eine Lipidmembran bildete es keinen spezifischen Kanal für Protonen, Natrium und Kalium. Andererseits waren Krone-4- und Krone-5-Hypericin imstande, mit Natrium- und Kaliumionen zu komplexieren, wobei die Krone-5-Verbindung einen stabilen Kaliumkronenkomplex bildete. In solchen Systemen wird das Hypericination intramolekular durch das komplexierte Kation kompensiert und bildet so eine Extremstruktur aus der Hypericinatreihe.

Introduction

Hypericin (**1**) is known for its notorious insolubility in a variety of solvents. This is mainly due to its tendency to dissociate at its highly acidic *bay* region hydroxylic group [1]. Therefore it seemed desirable to conjugate a moiety to the pigment which could be able to solvate the counter ion. In this context, one might think of appending ionophoric tentacles at its ω,ω'-methyl groups or of attaching crown ether units to these sites. These derivatives would also be of interest with respect to their photophysical and transport properties. The present report describes the synthesis and properties of such ionophore ω,ω'-conjugated hypericin derivatives.

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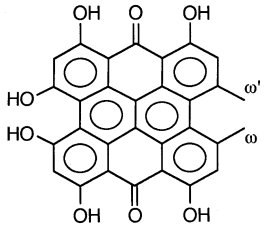
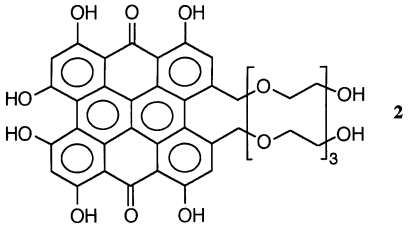


1

Results and Discussion

Linearly Appended Ionophoric Tentacles

As a derivative principally capable to complex cations or to transport cations within channels, the ω,ω'-appended triethyleneglycol derivative **2** was prepared. Its synthesis followed a previously established route [1, 2]. It started from ω-bromo-triacetoxy emodin, which underwent nucleophilic substitution upon treatment with triethylene glycol in presence of silver perchlorate. Reduction to the corresponding anthrone followed by conventional dimerization [3] then provided **2** in acceptable yield.

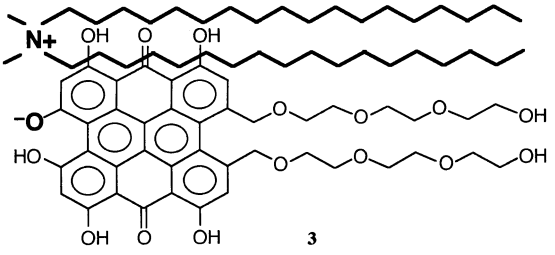


2

The *bay*-hypericinate ion of **2** did not show any significant tendencies to complex various counter ions in a specific way. Nevertheless, its alkali salts had a somewhat enhanced tendency to dissolve in non polar solvents than those of **1** itself.

A recent study of *Kobuke et al.* had demonstrated that oligoethylene glycol derivatives capped with an acid group and forming a salt with a long chain quaternary ammonium salt have been capable to provide a cation channel when incorporated into a bilayer membrane [4]. Since **1** has been shown to eject protons in its excited state [5], **2** in the form of its corresponding salt and incorporated into a vesicle could be thought of as a channel being able to transport cations and even yield vectorial light driven (500 through 600 nm) proton transport. Accordingly, the salt **3** formed from **2** and the dioctadecyldimethylammonium ion was incorporated into a planar and a vesicle lecithine bilayer membrane and probed for proton, sodium, potassium, and light driven proton transport. However, such membranes proved to be non-conducting up to pigment concentrations of 0.5% in the bilayer, whereas in control experiments small amounts ($\leq$0.004%) of channel forming compounds like valinomycin, gramicidin, and monensin provided ion selective conductivity. It should also be mentioned that a salt analogous to **3**, obtained from the recently described [1], ω,ω'-appended polyethyleneglycol-100 hypericin derivative, gave essentially the same results. Thus, **3** and its polyethyleneglycol analogon obviously do not form channels, and from these experiments doubts recently brought forward [6] about the interpretation of *Kobuke et al.* [4] were

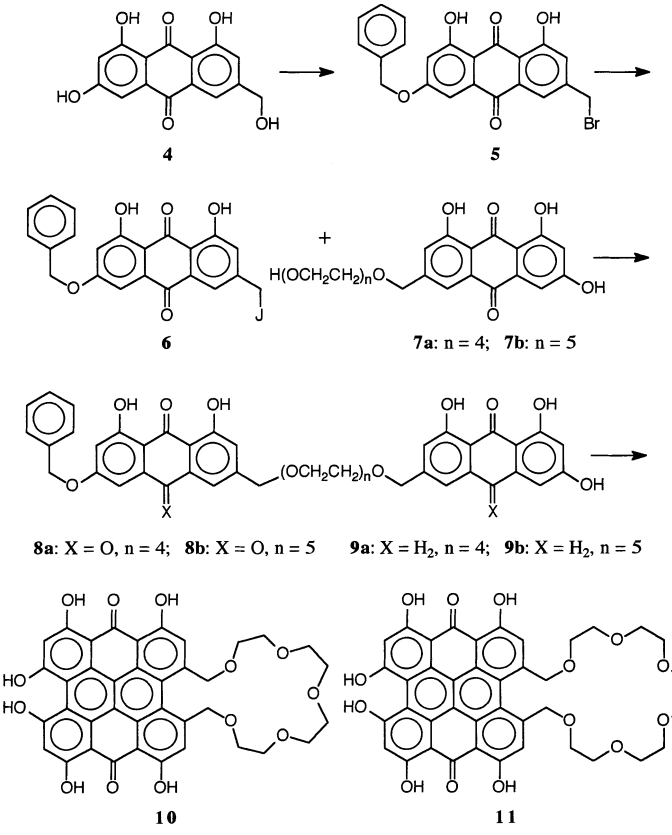
consolidated. In this system, the salt induces only unspecific bilayer membrane defects at best, which was also corroborated by its non-ion-selective behavior.



3

ω,ω′-Appended Hypericin Crown Ether Derivatives

The ω,ω′-crown-4 and -crown-5 derivatives of hypericin, **10** and **11**, were synthesized starting from triacetyl-ω-bromo-emodin. This was first converted nearly quantitatively into citreorosein (**4**) by means of a newly developed one pot procedure. Upon O-benzylation with benzyl bromide, synchronous bromine substitution at the ω-position took place to yield **5** (63%). Substitution of bromine for iodine with NaJ provided 95% **6** which then underwent nucleophilic substitution with the ω-tetraethylene glycol or ω-pentaethylene glycol emodin derivatives **7a** and **7b** (prepared in analogy to **2**) to yield the linear derivatives **8a** (75%) an **8b** (82%). After conventional reduction to the *bis*-anthrones **9a** (40%)



4 **5**

6 **7a**: n = 4; **7b**: n = 5

8a: X = O, n = 4; **8b**: X = O, n = 5 **9a**: X = H_2, n = 4; **9b**: X = H_2, n = 5

10 **11**

and **9b** (55%) they were cyclized by means of the anthrone – phenanthroperylene quinone dimerization procedure [3] of hypericin synthesis providing the crown ethers **10** and **11** in yields of about 10%.

Solutions of **10** and **11** in ethanol, ethanol-water mixtures, and acetone displayed the characteristic absorption and fluorescence spectroscopic features of the *bay*-hypericinate ion. Addition of NaCl, KCl, CsCl, $CaCl_2$, and $ZnCl_2$ to these solutions did not induce significant changes in their absorption and fluorescence spectra, but the fluorescence quantum yields became reduced by about 20%. However, this rather small change could not be attributed with certainty to a crown complex formation because such small changes in fluorescence quantum yields were also observed upon addition of these salts to solutions of **1**.

Addition of NaCl or KCl to an acetone-d_6 solution of **10** did not result in significant changes in its ^{1}H NMR spectrum. However, the FAB mass spectrum clearly indicated that **10** was able to form a sodium as well as a potassium crown complex. With **11**, formation of a stable potassium crown complex was indicated by its electrospray mass spectrum and significant ^{1}H NMR signal shifts of the crown moiety protons upon addition of KCl to its acetone-d_6 solution. It turned out that this complex was even stable enough to be isolated. Interestingly enough, **11** formed a stable hydrate with the water bonded within the crown cavity. This was indicated by signal shifts in the crown signal region of its ^{1}H NMR spectrum. The crown ethers **10** and **11** and their cation complexes are chiral with an intrinsically chiral crown ether moiety, and they represent interesting examples of a hypericinate ion stabilized by means of intramolecular charge compensation by the counter cation. Thus, it represents an extremal structural type within the series of hypericinate species which are presently under detailed investigation.

Conclusions

Two types of ionophoric groups were attached to the ω,ω' positions of hypericin (**1**). On the one hand, the open chain oligoethylene glycol derivative **2** did not form stable complexes with alkali metal ions, although the corresponding hypericinates seemed to be more soluble in apolar solvents. Embedded as its detergent salt **3** in membranes it did not result in specific proton, sodium, or potassium channels as was envisaged from earlier studies of such systems by *Kobuke et al.* [4]. On the other hand, the cyclo-oligoethylene glycol crown derivatives **10** and **11** were able to complex sodium and potassium, with **11** forming a stable potassium crown complex. Although their photophysical properties did not make them candidates for applications, they represent interesting examples of chiral crown ethers with inner charge compensation of the hypericinate type.

Experimental

Melting points were taken by means of a Kofler hot stage microscope (Reichert, Vienna). ^{1}H, ^{13}C, IR, UV/Vis, fluorescence, and mass spectra were recorded using Bruker DPX-200 and 500, Biorad-FT-IR-45, Perkin-Elmer IR-710B, Hitachi-U-3210 and F-4010, and API-5989 and HP 5989B plus HP 59987A electrospray instruments. For the determination of the fluorescence quantum yields, Rhodamine B fluorescence ($\Phi_f = 0.69$; ethanol) was used as the standard.

Vesicle and planar bilayer preparations

L-α-Phosphatidine choline vesicles were prepared from 20 mg egg lecithine (purified according to Ref. [7]) and salt **3** (0.1–0.5%) by dissolving them in 1 ml $CHCl_3$, evporating the solvent, and drying for 1 h in high vacuum. After addition of 1 ml of the inner buffer solution, the suspension was sonicated and freeze-thaw cycled for three times. Extrusion through a 0.2 nm nucleopore membrane filter [7] provided large multilamellar vesicles which were then gel filtered together with an external buffer solution over Sephadex G-25 M. Planar bilayers were produced and probed according to Ref. [8] in absence and presence of light (500 through 600 nm; 150 W tungsten lamp with cut-off filters).

Determination of vesicle proton permeation

An assay based on that of *Kamp et al.* [9] was used. The inner vesicle buffer consisted of 100 mmol NaH_2PO_4+20 mmol 2′,7′-*bis*-(2-carboxyethyl)-5,6-carboxyfluorescein brought to *pH* 5.8 by means of NaOH. As external buffer, 100 mmol Na_2HPO_4+5 mmol K_2SO_4 brought to *pH* 7.2 with NaOH was provided. Transport was monitored fluorimetrically ($\lambda_{exc} = 500$ nm, $\lambda_{em} = 535$ nm). The limiting permeability of the pigment-free vesicles was assessed with valinomycin (spontaneous unspecific proton transport).

Determinations of vesicle sodium and potassium permeability

An assay based on that of *Loew et al.* [10] was used. The internal buffer consisted of 100 mmol K_2SO_4+5 mmol *HEPES* brought to *pH* 7.0 by means of *TRIS*. As external buffer, 110 mmol Na_2SO_4+5 mmol *HEPES* brought to *pH* 7.0 by addition of NaOH together with 0.1 mmol 4-(2-(6-dibutylamino)-2-naphtalenyl)-ethenyl)-1-(3-sulfopropyl)-pyridinium hydroxide was used. Transport was monitored fluorometrically ($\lambda_{exc} = 475$ nm, $\lambda_{em} = 610$ nm). The limiting permeability was probed with valinomycin/monensin.

1,3,8-Trihydroxy-6-(2-(2-(2-hydroxyethoxy)-ethoxy)-ethoxymethyl)-10H-anthracene-9-one ($C_{21}H_{24}O_9$)

Since a previous preparation [2] had afforded the acetyl derivative due to the presence of acetic acid in the reduction medium, a new preparation method became necessary. 150 mg (0.42 mmol) 1,3,8-trihydroxy-6(2-(2-(2-hydroxyethoxy)-ethoxy)-ethoxymethyl)-anthracene-9,10-dione [2] were dissolved in 60 ml conc. HCl under heating, and 950 mg (4.2 mmol) $SnCl_2 \cdot 2H_2O$ dissolved in 5 ml conc. HCl were added. The solution was brought to 100 °C until the red color disappeared and was then immediately quenched by pouring it into 500 ml iced brine. It was filtered over paper after standing in the refrigerator for 1 h. Chromatography on silica ($CHCl_3$:CH_3OH = 18:1) afforded 116 mg (78%).

M.p.: 110°C; ^{1}H NMR (CD_3OD, δ, 200 MHz): 6.70, 6.65, 6.24, 6.13 (4s, 1H, H-ar), 4.44 (s, 2H, CH_2-O), 4.04 (s, 2H, ar-CH_2-ar), 3.5–3.7 (m, 12H, O(CH_2CH_2-O)$_3$) ppm; ^{13}C NMR (CD_3OD, δ, 50.3 MHz): 192.5 (C=O), 166.0, 165.9, 163.2, 147.8, 145.5, 142.7, 114.0, 109.9 (8 C-ar), 117.9, 115.34, 108.0, 102.0 (4 CH-ar), 73.4, 73.0, 71.4, 71.3, 71.1, 70.8, 62.0 (CH_2-(OCH_2CH_2)$_3$-OH), 33.4 (ar-CH_2-ar) ppm; UV/Vis (Ethanol): $\lambda_{max} = 358$ (16170), 270 (8700), 261 (8950), 221 (23970) nm (ε); IR (KBr): $\nu = 3225$, 2875, 1628, 1603 cm^{-1}.

1,3,4,6,8,13-Hexahydroxy-10,11-bis-(2-(2-(2-hydroxyethoxy)-ethoxy)-ethoxymethyl)-phenanthro[1,10,9,8-o,p,q,r,a]perylene-7,14-doine (**2**; $C_{42}H_{40}O_{18}$)

To 85 mg (0.1 mmol) of the derivative described above, 5 mg $FeSO_4 \cdot 7H_2O$ (5 mmol) and 57 mg pyridine-N-oxide (0.6 mmol) were added and stirred at 100°C under protection from light in an

argon atmosphere for 1 h in a mixture of 0.3 ml piperidine and 0.5 ml pyridine. The reaction mixture was cooled and acidified with 10% HCl. The precipitate was filtered, washed with water, dissolved in 200 ml acetone, filtered, and irradiated for 2 h by means of a 700 W tungsten bulb. The solution was filtered over silica, evaporated, and chromatographed on a silica preparative plate ($CHCl_3$:$CH_3OH = 5{:}1$). The main fraction was rechromatographed under the same conditions providing 15 mg (18%) of **2**.

M.p.: 290°C (dec.); ^{1}H NMR (acetone-d_6, δ, 200 MHz): 13.60, 13.11 (2s, 2H, OH-1, 6, 8, 13), 7.70 (s, 2H, H-9, 12), 6.59 (s, 2H, H-2, 5), 5.25, 477 (2d, 2H, $J = 12.1$ Hz, HCH-), 3.3–3.7 (m, 24H, -O($CH_2CH_2O)_3$-) ppm; ^{13}C NMR (*DMSO*, δ, 50.3 MHz); 183.4 (C=O), 174.9 (C-3, 4), 168.4 (C-1), 6), 161.8 (C-8, 13), 143.9 (C-10, 11), 127.0 (C-3a, 3b), 125.7 (C-6b, 14b), 121.4 (C-6c, 13c), 119.7 (C-10a, 10b), 119.1 (C-7b, 13b), 118.1 (C-9, 12), 109.7 (C-6a, 14a), 105.7 (C-2, 5), 102.2 (C-7a, 13a), 72.3, 69.6 (signal overlap), 69.1, 60.1 (CH_2-O($CH_2CH_2O)_3$-) ppm; UV/Vis (ethanol, $c = 1 \cdot 10^{-6}$ mol/l): $\lambda_{max} = 593$ (41700), 550 (19930), 512 (7000), 478 (10200), 384 (9100), 329 (23000), 287 (29600) nm (ε); IR (KBr) $\nu = 3422$, 2924, 2855, 1589, 1559, 1506 cm^{-1}; fluorescence (ethanol): $\lambda_{em} = 599$ (1), 647 (0.28) nm (rel. intensity), $\Phi_f = 0.17$.

N,N-Dimethyl-N,N-dioctadecyl-ammonium-1,3,4,6,8,13-hexahydroxy-10,11-bis-(2-(2-(2-hydroxyethoxy)-ethoxy)-ethoxymethyl)-phenanthro[1,10,9,8-o,p,q,r,a]perylene-7,14-dione-ate (**3**; $C_{80}H_{119}NO_{18}$)

Equimolar amounts of N,N-dimethyl-N,N-dioctadedecylammonium hydroxide and **2** were dissolved in methanol, stirred for 5 min, evaporated, and dried in high vacuum to provide the corresponding salt in quantitative yield. ^{1}H NMR (acetone-d_6, δ, 200 MHz): 18.75 (s, OH), 14.90 (s, 2OH), 14.40 (s, 2OH), 7.69 (s, 2H-ar), 6.62 (s, 2H-ar), 5.21 (A-part of AX-system, 2H, $J = 11.8$ Hz, *H*CH), 4.73 (X-part of AX-system, 2H, $J = 11.8$ Hz, HC*H*), 3.1–3.6 (m, 36H, -($OCH_2CH_2)_3OH$, ($CH_3)_2N^+(CH_2)_2$), 1.70 (m, 4H, N+CH_2CH_2-), 124 (m, 60H, -($(CH_2)_{15})_2$), 0.85 (t, 6H, $J = 6.7$ Hz, -($(CH_3)_2$) ppm; UV/Vis (ethanol): $\lambda_{max} = 593$ (1), 549 (0.61), 511 (0.32), 478 (0.42), 388 (0.41), 329 (0.88), 286) (1) nm (rel. intensity).

6-Hydroxymethyl-1,3,8-trihydroxy-anthracene-9,10-doine (Citreorosein) (**4**; $C_{15}H_{10}O_6$)

Citreorosein has been prepared by *Thiem et al.* [11] in a two step procedure starting from triacetyl-bromo-emodin. Here we present a single step procedure. 1245 mg (2.62 mmol) 6-bromomethyl-1,3,8-triacetoxy-anthraquinone [1] were dissolved in a mixture of 400 ml dioxane, 15 ml H_2O, and 10 ml conc. H_2SO_4 and refluxed for 1.5 h. The solution was concentrated to 50 ml, and 400 ml H_2O were added. The precipitate was filtered, washed with H_2O, dried, and washed with $CHCl_3$ to yield 735 mg (98%) of **4**.

M.p.: 280°C (Ref. [11]: m.p.: 280–281°C); ^{1}H NMR (acetone-d_6, δ, 200 MHz): 12.06, 12.05, 10.17 (3s, 1H, OH), 7.47, 7.35 (2s, 1H, H-ar), 7.20, 6.61 (2d, 1H, $J = 2.2$ Hz, H-ar), 4.70 (s, 2H, CH_2-O) ppm; ^{13}C NMR (*DMSO*, δ, 50.3 MHz): 189.3, 180.8 (2 C=O), 165.7, 164.5, 161.2, 146.88, 134.9, 133.4, 124.1, 119.9, 115.1, 108.9, 108.8, 107.9 (12 C-ar), 32.2 (CH_2OH) ppm; UV/Vis (ethanol): $\lambda = 439$ (7650), 290 (13030), 251 (13950), 226 (15260) nm (ε); IR (KBr): $\nu = 3394$, 3064, 1628 cm^{-1}.

3-Benzyloxy-6-bromomethyl-1,8-dihydroxy-anthracene-9,10-dione (**5**; $C_{22}H_{15}O_5Br$)

300 mg (1.05 mmol) **4** were suspended in 35 ml dry acetonitrile and dissolved by addition of 0.25 ml (1.4 mmol) N,N-diisopropyl-N-ethylamine. To this solution, 1.25 ml (10.5 mmol) benzylbromide were added. The resulting mixture was refluxed for 2 h. under argon and then concentrated to 3 ml. 100 ml 2 *N* HCl were added, and the solution was extracted four times with 50 ml $CHCl_3$, washed with H_2O, and dried over Na_2SO_4. Chromatography on silica ($CHCl_3$) yielded 290 mg (63%) of **5**.

M.p.: 172–174°C; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 12.23, 12.18 (2s, 1H, OH), 7.82, 7.30 (2d, 1H, $J = 1.8$ Hz, H-ar), 7.48, 6.68 (2d, $J = 2.6$ Hz, H-ar), 7.40 (m, 5H, benzyl-H), 5.21 (s, 2H, CH_2-phenyl), 4.46 (s, 2H, CH_2Br) ppm; ^{13}C NMR ($CDCl_3$, δ, 50.3 MHz): 190.5, 181.2 (2 C=O), 165.7, 165.4, 162.5, 148.5, 146.7, 135.0, 133.94, 128.8 (2C), 128.5, 127.6 (2C), 124.4, 120.4, 115.5, 110.3, 109.2, 107.7 (18 C-Ar), 70.8 (CH_2-phenyl), 31.1 (CH_2Br) ppm; UV/Vis (ethanol): $\lambda_{max} = 436$ (12140), 288 (16700), 266 (18800), 254 (18670), 225 (33370) nm (ε); IR (KBr): $\nu = 3031$, 1675, 1625 cm^{-1}.

*3-Benzyloxy-6-jodomethyl-1,8-dihydroxy-anthracene-9,10-dione (***6**; $C_{22}H_{15}O_5J$)

400 mg (0.91 mmol) **5** and 284 mg (1.89 mmol) NaJ sere refluxed in 200 ml dry acetone for 1.5 h. The solvent was evaporated, the residue dissolved in $CHCl_3$, the solution washed with 10% aqueous $Na_2S_2O_3$ and H_2O, and evaporated.

Yield: 420 mg (95%); m.p.: dec.; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 12.10, 11.99 (2s, 1H, OH), 7.71 (d, 1H, $J = 1.6$ Hz, H-ar), 7.4–7.6 (m, 6H, Phenyl-H, 1H-ar), 7.27, 6.96 (2d, 1H, $J = 2.5$ Hz, H-ar), 5.30 (s, 2H, CH_2-Phenyl), 4.69 (s, 2H, CH_2J) ppm; ^{13}C NMR (*DMSO*, δ, 50.3 MHz): 189.6, 180.8 (2 C=O), 165.2, 164.3, 161.28, 149.7, 135.8, 134.8, 133.5, 128.6 (2C), 128.2, 127.9 (2 C), 123.6, 120.1, 114.8, 110.1, 108.3, 107.5 (18 C-ar), 70.3 (CH_2-phenyl), 4.42 (CH_2J) ppm; UV/Vis (ethanol): $\lambda_{max} = 436$ (6930), 267 (11310), 225 (17690) nm (ε); IR (KBr): $\nu = 3030$, 1668, 1629 cm^{-1}.

1,3,8-Trihydroxy-6-(2-(2-(2-hydroxyethoxy)-ethoxy)-ethoxy)-ethoxymethyl)-anthracene-9,10-dione (**7a**; $C_{23}H_{26}O_{10}$)

7a was prepared in analogy to **2** from tetraethylene glycol.

Yield: 90%; m.p.: 101–104°C; ^{1}H NMR (CD_3OD, δ, 200 MHz): 7.52, 7.12 (2s, 1H, H-ar), 7.02, 6.45 (2d, 1H, $J = 2.4$ Hz, H-ar), 4.59 (s, 2H, CH_2-O), 3.6–3.8 (m, 14H, (O-CH_2CH_2)$_3$-O-CH_2-), 3.54 (t, 2H, $J = 4.5$ Hz, -CH_2-OH) ppm; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 11.84 (s, 2H, OH-1, 8), 9.10 (bs, 1H, OH-3), 7.24, 6.92 (2s, 1H, H-ar), 6.83, 6.35 (2d, 1H, $J = 2.1$ Hz, H-ar), 4.39 (s, 2H, CH_2-O-), 3.5–3.7 (m, 17H, -O-(CH_2CH_2-O)$_4$-OH) ppm; ^{13}C NMR ($CDCl_3$, δ, 50.3 MHz): 189.4, 180.9 (2 C=O), 164.9, 164.9, 162.1, 147.6, 134.5, 132.6, 121.7, 117.7, 114.1, 109.5, 109.0, 108.5 (12 C-ar), 72.2, 71.6, 70.8, 70.5, 70.4, 70.4, 70.3, 70.1, 70.0 (-CH_2-(OCH_2CH_2)$_4$-OH) ppm; UV/Vis (ethanol): $\lambda_{max} = 441$ (9220), 292 (14610), 254 (18060), 218 (27310) nm (ε); IR (KBr): $\nu = 3390$, 3064, 2870, 1677, 1629 cm^{-1}.

1,3,8-Trihydroxy-6-(2-(2-(2-(2-hydroxyethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxymethyl)-anthracene-9,10-dione (**7b**; $C_{25}H_{30}O_{11}$)

7b was prepared in analogy to **2** from pentaethylene glycol.

Yield: 90%; m.p.: 72–74°C; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 12.12, 12.10 (2s, 1H, OH-1, 8), 9.5 (bs, 1H, OH-3), 7.53, 7.07 (2 s, 1H, H-ar), 7.05 (d, 1H, $J = 2.4$ Hz, H-ar), 6.53 (d, 1H, $J = 2.5$ Hz, H-ar), 4.52 (s, 2H, CH_2O-), 3.60–3.80 (m, 21H, (O-CH_2-CH_2)$_5$-OH) ppm; ^{13}C NMR ($CDCl_3$, δ, 50.3 MHz); 189.7, 181.0 (2 C=O), 165.1, 165.0, 162.0, 147.7, 134.6, 132.7, 121.7 117.7, 114.1, 109.7, 109.0, 108.6 (12 C-ar), 72.2, 71.6, 70.4, 70.3, 70.2, 70.0, 70.0 (signal overlap), 61.4 (-CH_2-(OCH_2CH_2)$_5$-OH) ppm; UV/Vis (ethanol): $\lambda_{max} = 438$ (10600), 290 (17200), 266 (15800), 252 (16400) nm (ε); IR (KBr): $\nu = 3462$, 3051, 2875, 1675, 1627, 1612 cm^{-1}.

*3-Benzyl-1,8-dihydroxy-6-(1′,3′,8′-trihydroxy-6′-(2-(2-(2-methoxyethoxy)-ethoxy)-ethoxy)-ethoxymethyl-anthracene-9′,10′-doine-yl)-anthracene-9,10-dione (***8a**; $C_{45}H_{39}O_{14}$)

120 mg (0.25 mmol) **6**, 350 mg (0.76 mmol) **7a**, 130 mg (0.5 mmol) Ag*Tf*, and 35 mg K_2CO_3 were refluxed in 60 ml dry CH_2Cl_2 for 20 h. The reaction mixture was filtered, washed with 2 *N* HCl and

H_2O, dried over Na_2SO_4, evaporated, and chromatographed on silica ($CHCl_3$:CH_3OH = 20:1) to yield, besides 245 mg of the educt, 150 mg **8a** (75%).

M.p.: 65°C; ^{1}H NMR (CD_2Cl_2, δ, 200 MHz): 11.96, 11.83, 11.75, 11.74 (4s, 4H, OH-1, 1′, 8, 8′), 9.69 (bs, 1H, OH-3), 7.42 (m, 5H, phenyl-H), 7.33 (s, 1H, H-ar), 7.11 (d, 1H, $J = 2.5$ Hz, H-ar), 7.03 (s, 2H, H-ar), 6.78 (s, 1H, H-ar), 6.61 (d, 1H, $J = 2.3$ Hz, H-ar), 6.53 (d, 1H, $J = 2.5$ Hz, H-ar), 6.22 (d, 1H, $J = 2.4$ Hz, H-ar), 5.08 (s, 2H, CH_2-phenyl), 4.44, 4.28 (2s, 2H, CH_2-O), 3.73, 3.69, 3.67 (3s, 16H, $(OCH_2CH_2)_4$-) ppm; ^{13}C NMR ($CDCl_3$, δ, 50.3 MHz): 190.4, 189.6, 181.1, 180.5 (4 C=O), 165.5, 165.0, 164.9 (2 C), 162.4, 162.1, 148.5, 147.7, 135.3 (C-phenyl-1), 134.9, 134.4, 133.0, 132.5, 128.8 (2 phenyl-C-3), 128.5 (C-phenyl-4), 127.6 (2 phenyl-C), 121.8, 121.4, 118.0, 117.4, 114.4, 113.9, 110.2, 109.6, 109.0, 108.9, 108.6, 107.5 (30 C-ar), 71.7, 71.5, 70.8, 70.6, 70.5, 70.3 (11 C, signal overlap, -CH_2-$(OCH_2CH_2$-O$)_4$-CH_2-, phenyl-CH_2) ppm; UV/Vis (ethanol): $\lambda_{max} = 362$ (14800), 270 (10160), 260 (11070), 219 (25830) nm (ε); IR (KBr): $\nu = 3470$, 3078, 2867, 1630, 1613 cm^{-1}.

3-Benzyl-1,8-dihydroxy-6-(1′,3′,8′-trihydroxy-6′-(2-(2-(2-(2-methoxyethyl)-ethoxy)-ethoxy)-ethoxy)-ethoxymethyl-anthracene-9′,10′-dione-yl)-anthracene-9,10-dione (**8b**; $C_{47}H_{43}O_{15}$)

Prepared in analogy to **8a** to yield, besides educt **7b**, 82% of **8b**.

M.p.: 49–51°C; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 11.95, 11.83, 11.82, 11.78 (4s, 4H, OH-1, 1′, 8, 8′), 9.17 (s, 1H, OH-3), 7.40 (m, 6H, phenyl-H, 1H-ar), 7.18 (s, 1H, H-ar), 7.12, 6.50 (2d, 1H, J = 2.3 Hz, H-ar), 7.04 (s, 1H, H-ar), 6.83 (s, 2H, H-ar), 6.38 (d, 1H, $J = 2.1$ Hz, H-Ar), 5.03 (s, 2H, phenyl-CH_2), 4.45, 4.31 (2s, 2H, CH_2O-), 3.6–3.8 (m, 20H, O-$(CH_2$-CH_2-O$)_5$-) ppm; ^{13}C NMR ($CDCl_3$, δ, 50.3 MHz): 190.0, 189.4, 180.8, 180.5 (4 C=O), 165.3, 164.8 (2 C), 164.7, 162.2, 162.0, 148.3, 147.7, 135.2 (C-phenyl-1), 134.6, 134.3, 132.8, 132.4, 128.6 (2 phenyl-C), 128.3 (C-phenyl-4), 127.4 (2 phenyl-C), 121.8, 121.4, 117.9, 117.4, 114.2, 113.8, 109.9, 109.5, 108.8, 108.5, 108.4, 107.2 (30 C, C-ar), 71.6, 71.4, 70.5, 70.4, 70.3, 70.2, 70.1 (13 C, signal overlap, -CH_2-$(OCH_2CH_2$-O$)_5$-CH_2-, Phenyl-CH_2) ppm; UV/Vis (CH_3CN): $\lambda_{max} = 436$ (19950) nm (ε); IR (KBr): $\nu = 3470$, 3065, 2871, 1628 cm^{-1}.

Di-(1,3,8-trihydroxy-6-(2-ethoxy)-ethoxymethyl-10H-anthracene-9-one-yl)-ether (**9a**; $C_{38}H_{34}O_{15}$)

100 mg (0.12 mmol) **8a** were dissolved in 20 ml glacial acetic acid at 100°C and refluxed for 20 min after addition of 540 mg (2.4 mmol) $SnCl_2 \cdot 2H_2O$ in 2.5 ml conc. HCl · 200 ml ice water were added to the reaction mixture and the mixture was filtered. The residue was chromatographed on silica ($CHCl_3$:CH_3OH = 20:1) to yield 40 mg (40%) of **9a**.

M.p.: 62–64°C; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 12.31, 12.23, 10.85 (3s, 2H, OH), 6.64, 6.72, 6.38, 6.20 (4s, 2H, H-ar), 4.48 (s, 4H, CH_2-O), 4.28 (s, 4H, ar-CH_2-ar), 3.57 (m, 16H, $(OCH_2CH_2$-$)_4$O) ppm; UV/Vis (ethanol): $\lambda_{max} = 361$ (17930), 219 (37623) nm (ε); IR (KBr): $\nu = 3220$, 2873, 1626, 1603 cm^{-1}.

1,2-Bis-(1,3,8-trihydroxy-6-(2-oxyethoxy)-ethoxymethyl-10H-anthracene-9-one-yl)-ethane (**9b**; $C_{40}H_{38}O_{16}$)

Prepared in analogy to **9a** in a yield of 55%.

M.p.: 48–50°C; ^{1}H NMR ($CDCl_3$:CD_3OD = 1:2, δ, 200 MHz): 6.65, 6.62, 6.21 (3s, 2H, H-ar), 6.12 (d, 2H, $J = 2.3$ Hz, H-ar), 4.40 (s, 4H, CH_2-O), 4.00 (s, 4H, ar-CH_2-ar), 3.64 (m, 20H, (O-CH_2-CH_2-$)_5$O) ppm; ^{13}C NMR ($CDCl_3$:CD_3OD = 1:2, δ, 50.3 MHz): 192.3 (2 C=O), 165.9, 165.6, 163.0, 147.7, 145.2, 142.5, 113.8, 109.8 (8.2 C-Ar), 117.7, 115.2, 107.9, 101.9 (4.2 CH-ar), 72.9 (2 CH_2O-), 71.3 (-O$(CH_2CH_2O)_3$-), 70.75 (2 O-CH_2), 33.37 (2 ar-CH_2-ar) ppm; UV/Vis (ethanol): $\lambda_{max} = 361$ (18200), 219 (37800) nm (ε); IR (KBr): $\nu = 3220$, 2923, 2876, 1627, 1605 cm^{-1}.

10,11-(1,3,4,6,8,13-Hexahydroxy-phenanthro[1,10,9,8-o,p,q,r,a]perylene-7,14-dione)-19-crown-5 (**10**; $C_{38}H_{26}O_{15}$)

Prepared in analogy to **2** in a yield of 10%.

M.p.: not below 340°C; ^{1}H NMR (acetone-d_6, δ, 200 MHz): 18.8 (bs, 1H, OH-3), 14.89, 14.82 (2d, 1H, $J = 1.9$ Hz, OH), 14.40, 14.32 (2s, 1H, OH), 7.68 (s, 2H, H-9, 12), 6.57 (s, 2H, H-2, 5), 5.31, 4.89 (2d, 2H, $J = 12.3$ Hz, HCH), 3.5–3.8 (m, 16H, (O-CH_2CH_2)$_4$-O) ppm; UV/Vis (ethanol, $c = 1.10^{-6}$ mol/l): $\lambda_{max} = 593$ (30000), 550 (13800), 511 (4750), 477 (7650), 389 (8300), 326 (17500) nm (ε); IR (KBr): $\nu = 3455$, 2925, 2867, 1592, 1559, 1507 cm^{-1}; fluorescence (ethanol): $\lambda_{em} = 598$ (1), 646 (0.28) nm (rel. intensity), $\Phi_f = 0.14$. Upon recording the FAB mass spectrum, **10** formed-besides some protonated material ($m/z = 695.5$) – a stable quasi-molecule with Na^+ ($m/z = 717.7$) from the matrix, pointing to the formation of a crown complex. Upon addition of KCl, the potassium crown complex ($m/z = 733.9$) appeared in the MS which, judged by its relative intensity, was more stable than the sodium complex. Nevertheless, these complexes were too instable to be detected in solution.

10,11-(1,3,4,6,8,13-Hexahydroxy-phenanthro[1,10,9,8-o,p,q,r,a]perylene7,14-dione)-22-crown-6 (**11**; $C_{40}H_{34}O_{14}$)

Prepared in analogy to **2** in a yield of 10%.

M.p.: not below 340°C; ^{1}H NMR (acetone-d_6, δ, 200 MHz): 18.80 (bs, 1H, OH-3), 14.89, 14.81, 14.42, 14.34 (4s, 2H, OH-1, 6, 8, 13), 7.66 (s, 2H, H-9, 12), 6.63 (s, 2H, H-2, 5), 5.24, 4.89 (2d, 2H, $J = 12.5$ Hz, HCH), 3.4–3.8 (m, 20H, O-(CH_2-CH_2-O)$_5$) ppm; UV/Vis (ethanol, $c = 1 \cdot 10^{-6}$ mol/l): $\lambda_{max} = 593$ (29000), 550 (13900), 478 (8200), 388 (9400), 326 (21000), 286 (28000) nm (ε); IR (KBr): $\nu = 3455$, 2925, 2867, 1592, 1559, 1507 cm^{-1}; fluorescence (ethanol): $\lambda_{em} = 600$ (1), 647 (0.3) nm (rel. intensities), $\Phi_f = 0.19$; MS (electrospray, negative ion mode): $m/z = 737$ (M-2).

Potassium complex of **11** ($C_{40}H_{34}O_{14}K$)

11 was dissolved in dry acetone, a larger excess of powdered KCl was added, and the mixture was sonicated for 10 min. The resulting solution was filtered from KCl and evaporated.

Yield: quantitative; ^{1}H NMR (acetone-d_6, δ, 200 MHz): 18.80 (bs, 1H, OH-3), 14.89, 14.81, 14.42, 14.34 (4s, 2H, OH-1, 6, 8, 13), 7.59 (s, 2H, H-9, 12), 6.62 (s, 2H, H-2, 5), 5.18, 5.03 (AB-system, $J = 13.0$ Hz, 2HCH), 3.2–3.8 (m, 20H, O-(CH_2-CH_2-O)$_5$) ppm; MS (electrospray, positive ion mode): m/z (%) = 777 (100, M-1), 685 (70), 641 (80), 597 (70), 537 (70), 413 (12), 391 (75), 303 (75).

Hydrated potassium complex of **11**

The potassium complex of **11** described above was stirred in water for 20 min, filtered, and dried in vacuum.

^{1}H NMR (acetone-d_6, δ, 200 MHz): 18.80 (bs, 1H, OH-3), 14.89, 14.81, 14.42, 14.34 (4s, 2H, OH-1, 6, 8, 13), 7.53 (s, 2H, H-9, 12), 6.61 (s, 2H, H-2, 5), 5.13 (s, 2HCH), 3.2–3.8 (m, 20H, O-(CH_2-CH_2-O)$_5$) ppm; MS (electrospray, positive ion mode): m/z (%) = 777 (100, M-1), 685 (70), 641 (80), 597 (70), 537 (70), 413 (12), 391 (75), 303 (75).

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