1,4,8,11,15,18,22,25-Octafluorophthalocyaninato Zinc (F_8PcZn)

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Abstract: 1,4,8,11,15,18,22,25-Octafluorophthalocyanato zinc (F_8PcZn), which is not described in the literature up to date, was obtained from 3,6-difluorophthalonitrile in anhydrous DMF, DBU, and $Zn(OAc)_2$ at 145 °C. 3,6-Difluorophthalonitrile was synthesized by a multistep procedure.

Key words: 1,4,8,11,15,18,22,25-octafluorophthalocyanato zinc, glycosylated phthalocyanines, fluorinated phthalocyanines, 3,6-difluorophthalonitrile, phthalocyanato metals

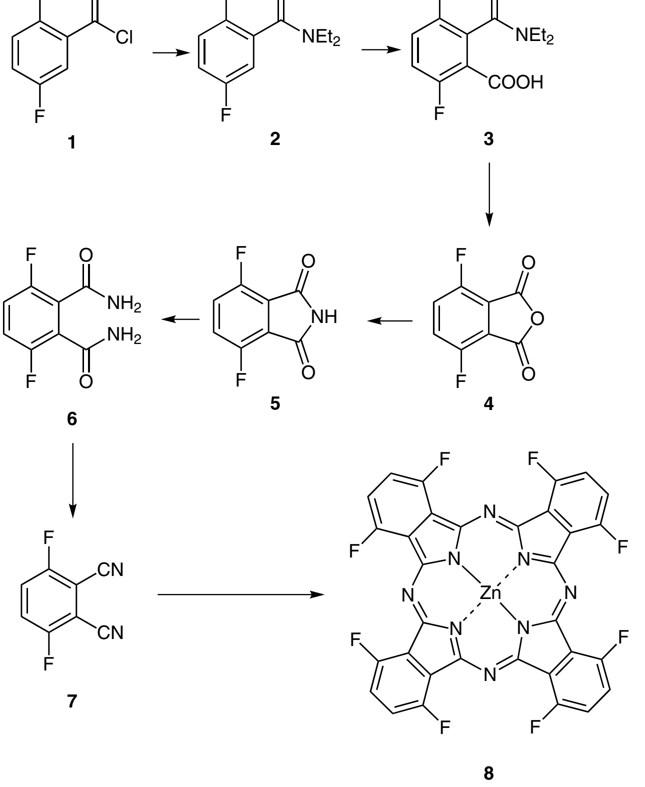
Phthalocyanines (Pc), especially phthalocyanato metals (PcM), received a lot of attention as dye pigments for various industrial applications.[1] In addition PcM are also used, for example, as optical limiters,[2] photocatalysts,[3] and semiconductors[4] in the field of material science and for medical applications like photodynamic therapy (PDT).[5] The chemical stability of the PcM and the opportunity to control their optical properties via the central metal atoms and the substitution pattern of the Pc macrocycle contributes to the importance and broad applications of PcM.

With regard to PDT, glycosylated phthalocyanines turned out to be attractive candidates for in vitro cell tests.[6] Previously, we could show that fluorinated phthalonitriles are suitable starting materials for the preparation of peripherally glycosylated phthalocyanines.[7] Perfluorophthalocyanines ($F_{16}PcM$) containing a variety of central metals, for example, Cu, Zn, and Fe are well known.[8] The synthesis of $F_{16}PcM$ follows the commonly applied route for the preparation of metal phthalocyanines, that is, reacting 4-fluorophthalonitrile with a metal salt, for example, $Zn(OAc)_2$ under basic reaction conditions. Perfluorometal phthalocyanines have also been studied in detail with regard to their physical properties[9] and application in PDT.[10] Polysubstituted phthalocyanines, some of which are inaccessible by other means, can be prepared by nucleophilic substitution reactions of $F_{16}PcZn$ with O-, N-, C-, and S-nucleophiles.[11]

So far, isomeric mixtures of tetrafluoro-[9a], 2,3,9,10,16,17,23,24-octafluoro-,[9a,12] and 1,3,8,10,15,17,22,24-octafluorophthalocyanies[13] containing Cu, Co, Ni, or Zn as central metal ions have been prepared starting from 4-fluorophthalonitrile and 4,5-difluorophthalonitrile, respectively, and a metal salt. For the syntheses of 1,3,8,10,15,17,22,24-octafluoro metal phthalocyanines (M = Cu, Co, Ni, Zn) a different multistep procedure was applied:[13] 3,5-Dinitrophthalic acid was reacted with urea and the corresponding metal salts in nitrobenzene. Reduction of the formed metal octanitrophthalocyanines gave the corresponding octaamino phthalocyanines. Diazotization and reaction with $NaBF_4$ yielded the metal octafluorophthalocyanines.

Quantum chemical calculations and UPS measurements on nonsubstituted and a variety of fluorinated metal phthalocyanines revealed the specific influence of fluorine substitution on the Pc macrocycle: HOMO and LUMO energy levels are shifted to lower energy, for example, in the series PcM > F_4PcM > F_8PcM > $F_{16}PcM$ (M = Cu, Zn).[13–15]

Here we report the synthesis and full characterization of 1,4,8,11,15,18,22,25-octafluorophthalocyanoto zinc (**8**), which has not been obtained in pure form yet. The synthesis of **8** was carried out as follows (Scheme 1).



Scheme 1 Synthesis of F_8PcZn

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Commercially available 2,5-difluorobenzoyl chloride (**1**) was converted with diethylamine into 2,5-difluoro-*N*,*N*-diethylbenzamide (**2**) which was subsequently reacted with *n*-butyllithium, CO_2, and water to afford 2-[diethylamino]carbonyl-3,6-benzoic acid (**3**).[16]

Next, 3,6-difluorophthalic anhydride (**4**) was obtained by heating **3** in a mixture of concentrated sulfuric acid and water under reflux. Anhydride **4** was purified by sublimation under reduced pressure.[16] Melting **4** with urea forms 3,6-difluorophthalimide (**5**), which was transformed into 3,6-difluorophthalic acid amide (**6**) by treatment with aqueous ammonia. Next, diamide **6** was reacted with thionyl chloride to give 3,6-difluorophthalonitrile (**7**). For the formation of 1,4,8,11,15,18,22,25-octafluorophthalocyanato zinc (**8**) a solution of phthalonitrile **7** in anhydrous DMF and $Zn(OAc)_2$ was heated with addition of DBU or hexamethyldisilazane, respectively.

Whereas the synthesis of compounds **1**–**4** was carried out under reaction conditions which are described,[16] formation of **5** was somewhat difficult. Reacting the acid anhydride **4** with urea under standard conditions at 200 °C for several hours resulted in a low yield (<20%). Lowering the temperature to 125–130 °C for four hours led to a yield of 83% for compound **5**. 3,6-Difluorophthalic acid amide (**6**) was obtained in 60% yield by treatment of **5** with aqueous ammonia at ambient temperature. Dehydration of **6** with thionyl chloride in anhydrous DMF at about 0 °C yielded 74% of phthalonitrile **7**. Title compound **8** has been received under reaction conditions mentioned before.

Purification of 1,4,8,11,15,18,22,25-octafluorophthalocyaninato zinc (**8**) was challenging due to the difficult removal of trace impurities. The best purification results were obtained by using chromatography on silica gel and aluminum oxide in addition with different solvent mixtures to obtain F_8PcZn (**8**) in 29% yield. An analytical sample was further purified by HPLC using a mixture of acetonitrile and water on a reverse-phase column. Purity of **8** was brought up to 96% as determined by LC–MS.

Compounds **5**–**8** were fully characterized using different spectroscopic techniques. ^1H NMR spectra of compounds **5**–**8** were in accordance with the expected results. The coupling constants were obtained by performing a full-lineshape iteration on the AA′ part of the AA′XX′ spin systems using gNMR 5.1.[17] The final values are given in Table 1.

Table 1 Calculated Coupling Constants for Compounds **5**, **6**, **7**, and **8**

Compound	$^3J_{H,H'}$ (Hz)	$^3J_{H,F}$ (Hz)	$^4J_{H,F}$ (Hz)	$^5J_{F,F}$ (Hz)
5	9.2	8.7	3.1	22.4
6	9.6	8.7	3.9	18.6
7	9.2	8.8	4.0	15.1
8	9.2	8.6	3.1	22.4

^{13}C NMR spectra of compounds **5**–**7** in DMSO confirmed the expected values. Due to the poor solubility of **8** in organic solvents no satisfying ^{13}C spectrum has been obtained. With a negative range starting from –109.3 ppm for compound **7** up to –120.6 for **5** ^{19}F NMR spectra of compounds **5**–**8** were recorded in DMSO.

The UV-vis spectrum of F_8PcZn (**8**) in chloroform with a sharp Q-band at λ = 690 nm and two small shoulders at λ = 660 nm and 622 nm is shown in Figure 1.

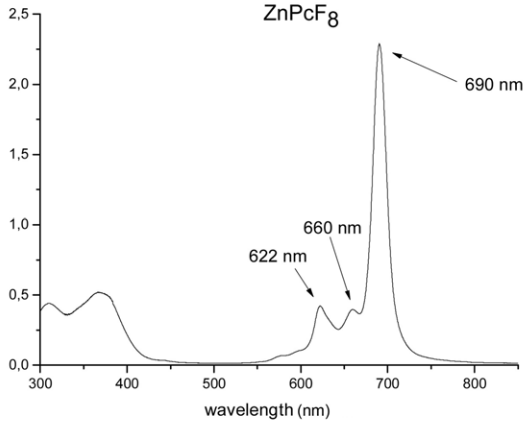

Figure 1 UV-vis spectrum of F_8ZnPc (**8**) in chloroform

F_8PcZn (**8**) was further characterized using MALDI-TOF and FT-ICR-MS.

In conclusion, we have prepared and fully characterized the last structural isomer **8** of octafluorophthalocyanines F_8PcZn. In addition one of the most promising precursors for glycosylated phthalocyanines, 3,6-difluorophthalonitrile (**7**), has been synthesized. Detailed experiments for glycosylated phthalocyanines starting from **7** are in progress.

Starting materials and reagents were purchased from ABCR GmbH (2,5-difluorobenzoyl chloride), Acros Organics (thionyl chloride), and Sigma-Aldrich (DBU) and were of the highest purity available. DMF was distilled from phosphorous pentoxide and was stored over MS 3 Å under an atmosphere of nitrogen until used. NMR spectra were recorded on a Bruker Avance 400 (^1H, ^{13}C) or a Bruker ARX 400 (^{19}F). Melting points are uncorrected and determined with a Büchi Melting Point M-560. Elemental analyses were performed on a HEKAtech Euro EA Analyzer. Coupling constants were calculated with gNMR (5.1). Maldi-TOF spectra were measured on a Bruker Daltonics. FT-ICR-MS were recorded on a Bruker Apex II FT-ICR-MS spectrometer.

3,6-Difluorophthalimide (5)

3,6-Difluorophthalic anhydride (**4**,[16] 10.9 g, 60.0 mmol) was intensely mixed with urea (7.6 g, 126.0 mmol) and subsequently fused at 125–130 °C for 4 h. The resulting hot slurry was poured into cold H_2O (150 mL) as fast as possible. The formed solid was collected by filtration, washed several times with H_2O, and dried in a vacuum oven (60 °C, $1\cdot10^{-2}$ mbar) over night. Recrystallization from toluene gave imide **5** (9.18 g, 83%) as a light-yellow solid; mp 185–186 °C. IR (KBr): 3253, 3090, 2696, 1783, 1738, 1258, 1063, 895 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.69 (t, 2 H, $^5J_{F,F}$ = 22.4 Hz, $^3J_{H-4,F-3}$ = $^3J_{H-5,F-6}$ = 8.7 Hz, $^4J_{H-4,F-6}$ = $^4J_{H-5,F-3}$ = 3.1 Hz, $^3J_{H-4,H-5}$ = 9.2 Hz, H-4, H-5), 11.58 (s, 1 H, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 119.6 (dd, $J_{C,F}$ = 9.9 Hz, $J_{C,F}$ = 6.0 Hz, 2 C), 125.1 (dd, $J_{C,F}$ = 18.3 Hz, $J_{C,F}$ = 13.4 Hz, 2 C), 152.8 (dd, $^1J_{C,F}$ = –259.8 Hz, $J_{C,F}$ = 3.8 Hz, 2 C), 165.1 (s, CO). ^{19}F NMR{^{1}H} (376.5 MHz, DMSO-d_6): δ = –120.46. MS–FAB: *m/z* (%) = 184 (20) [M + H]$^+$, 124 (18). Anal. Calcd for $C_8H_3F_2NO_2$: C, 52.47; H, 1.65; N, 7.65. Found: C, 52.13; H, 1.76; N, 7.40.

3,6-Difluorophthalamide (6)

3,6-Difluorophthalimide (**5**, 5,4 g, 29.4 mmol) and concd NH_3 solution (125 mL, 25% in H_2O) were stirred at r.t. for 48 h. The formed solid was collected by filtration, washed with H_2O until the filtrate was neutral and dried in vaccuo. Recrystallization from EtOH–H_2O (1:1) gave colorless crystals of **6** (3.53 g, 60%); mp 219–221 °C. IR (KBr): 3336, 3175, 2360, 1689, 1663, 1466, 1409, 915, 633 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.34 (t, 2 H, $^5J_{F,F}$ = 18.6 Hz, $^3J_{H\text{-}4,F\text{-}3}$ = $^3J_{H\text{-}5,F\text{-}6}$ = 8.7 Hz, $^4J_{H\text{-}4,F\text{-}6}$ = $^4J_{H\text{-}5,F\text{-}3}$ = 3.9 Hz, $^3J_{H\text{-}4,H\text{-}5}$ = 9.6 Hz, H-4, H-5), 7.70 (s, 2 H, NH_2), 7.84 (s, 2 H, NH_2). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 117.6 (dd, $J_{C,F}$ = 20.1 Hz, $J_{C,F}$ = 14.4 Hz, 2 C), 125.8 (dd, $J_{C,F}$ = 16.2 Hz, $J_{C,F}$ = 9.6 Hz, 2 C), 154.2 (dd, $^1J_{C,F}$ = –244.9 Hz, $J_{C,F}$ = 3.6 Hz, 2 C), 163.8 (s, 2 C, CO). ^{19}F NMR{^{1}H} (376.5 MHz, DMSO-d_6): δ = –120.63. MS–FAB: *m/z* (%) = 201 (20) [M + H]$^+$. Anal. Calcd for $C_8H_6F_2N_2O_2$: C, 48.01; H, 3.02; N, 14.00. Found: C, 47.98; H, 3.17; N, 14.06.

3,6-Difluorophthalonitrile (7)

Anhydrous DMF (70 mL) was cooled to 0 °C with an ice bath before $SOCl_2$ (3 mL, 41.0 mmol) was added dropwise. The solution was stirred at 0 °C for an additional hour. While maintaining the inner temperature below 5 °C 3,6-difluorophthalamide (**6**, 3.90 g, 19.5 mmol) was added in small portions. The reaction mixture was allowed to warm to r.t. and stirred over night. The reaction mixture was slowly poured onto crushed ice (200 mL), the formed precipitate was collected by filtration, washed several times with H_2O, and dried over P_4O_{10}. Colorless solid (2.37 g, 74%); mp 147–150 °C. IR (KBr): 3107, 3095, 3076, 2246, 1486, 1263, 927, 848, 735 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.05 (t, 2 H, $^5J_{F,F}$ = 15.1 Hz, $^3J_{H\text{-}4,F\text{-}3}$ = $^3J_{H\text{-}5,F\text{-}6}$ = 8.8 Hz, $^4J_{H\text{-}4,F\text{-}6}$ = $^4J_{H\text{-}5,F\text{-}3}$ = 4.0 Hz, $^3J_{H\text{-}4,H\text{-}5}$ = 9.2 Hz, H-4, H-5). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 104.2 (dd, $J_{C,F}$ = 15.4 Hz, $J_{C,F}$ = 8.3 Hz, 2 C), 110.9 (s, 2 C, CN), 124.5 (dd, $J_{C,F}$ = 18.8 Hz, $J_{C,F}$ = 13.3 Hz, 2 C), 159.1 (dd, $^1J_{C,F}$ = –257.2 Hz, $J_{C,F}$ = 3.4 Hz, 2 C). ^{19}F NMR{^{1}H} (376.5 MHz, DMSO-d_6): δ = –109.25. MS–FAB: *m/z* (%) = 164.1 (30) [M]$^+$. Anal. Calcd for $C_8H_2F_2N_2$: C, 58.55; H, 1.23; N, 17.07. Found: C, 58.94; H, 1.29; N, 16.84.

1,4,8,11,15,18,22,25-Octafluorophthalocyanato Zinc (8)

A mixture of 3,6-difluorophthalodinitrile (**7**, 820 mg, 5.0 mmol), $Zn(OAc)_2$ (710 mg, 3.86 mmol), and DBU (250 μL) in anhydrous DMF (5 mL) was stirred and heated at 145 °C overnight under a nitrogen atmosphere. The cooled solution was poured into MeOH (20 mL) and the greenish blue precipitate was collected by filtration. The obtained solid was dried and purified on a short pad of silica gel. The crude product was further purified by column chromatography using basic Al_2O_3 first with CH_2Cl_2 and EtOAc containing 0–20% MeOH. The obtained product was absorbed on silica gel and eluted with PE–EtOAc (2:1), followed by EtOAc containing 0–20% MeOH to yield a deep-green solid (262 mg, 29%). An analytical sample was further purified on a reversed-phase HPLC C-18 column using MeCN and H_2O to yield **8** as a green solid; mp >400 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.71 (t, 8 H, $^5J_{F,F}$ = 22.4 Hz, $^3J_{H\text{-}2,F\text{-}1}$ = $^3J_{H\text{-}3,F\text{-}4}$ = 8.6 Hz, $^4J_{H\text{-}2,F\text{-}4}$ = $^4J_{H\text{-}3,F\text{-}1}$ = 3.1 Hz, $^3J_{H\text{-}2,H\text{-}3}$ = 9.2 Hz, H_β-Pc). ^{19}F NMR{^{1}H} (376.5 MHz, DMSO-d_6): δ = –120.03. UV-vis ($CHCl_3$): λ_{max} (log ε) = 690 (7.22), 660 (6.46), 622 (6.48), 368 (6.57). FT-ICR-MS (ESI): *m/z* [M + H]$^+$ calcd for $C_{32}H_9F_8N_8Zn$: 721.010841; found: 721.010744; Δ = 0.14 ppm. MS-Maldi-TOF: *m/z* [M]$^+$ calcd for $C_{32}H_8F_8N_8Zn$: 720.004; found: 719.995.

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