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Synthesis and photosensitizing properties of fluoroalkoxyl phthalocyanine metal complexes

Lindong Gao[a], Xuhong Qian[b,*]

[a]Institute of Pharmaceuticals & Pesticides, East China University of Science & Technology, Shanghai 200237, China
[b]State Key Laboratory of Fine Chemicals, Dalian University of Technology, P.O. Box 40, 158 Zhongshan Rd., Dalian 116012, China

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Abstract

Nine fluoroalkoxyl phthalocyanine metal complexes (Zn, AlCl, Mg, Co, Cu, FeCl) were synthesized from 4-(polyfluoroalkoxyl) phthalic anhydride. The fat-soluble phthalocyanines were characterized by elemental analysis, IR, ^{1}H NMR and fast-atom-bombardment mass spectroscopy. Zinc and aluminum chloride complexes show higher photooxidation ability in solution containing 20% perfluorocarbons than in hydrocarbon solvents. © 2002 Published by Elsevier Science B.V.

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1. Introduction

For many years, phthalocyanines have attracted great interest in research fields such as chemical sensors, electrochromism, batteries, semiconductors, molecular metals, catalysts, liquid crystals and nonlinear optics [1]. As the second generation photosensitizers for photodynamic therapy (PDT) in the treatment of cancer, phthalocyanines, particularly the aluminum and zinc derivatives, are the most recently studied [2]. Although some of these materials show excellent PDT behavior and low general toxicity in animal models, they still have yet to find widespread clinical acceptance. There is still a clear need to explore in greater depth relationships between the structure of phthalocyanine sensitizers and their PDT behavior.

Zinc and aluminum phthalocyanines because of their poor water and fat solubility are utilized in liposomal form and have shown sufficient PDT activity to justify their commercialization [3,4]. Some polar derivatives that have received attention include sulfonated derivatives, amino substituted derivatives and octahydroxy derivatives [5,6]. Non-polar derivatives of PDT interest have included octa-*n*-butoxyl and tetra(dibenzobarrelene)-octabutoxyl derivatives [7–9], etc. Owning to the effects of fluorine-containing anti-tumor drugs such as 5-fluorouracil, we have now designed and synthesized some new fluorine-containing phthalocyanines in order to find better photosensitizers which will be expected to be used in PDT. Compared to typical phthalocyanines, these tetra(fluoroalkoxyl) phthalocyanine metal complexes show good fat solubility. Synthetic routes to phthalocyanine metal complexes may involve either the initial synthesis of the metal free phthalocyanine derivatives, followed by metalization with metal salts or may incorporate the metal ion concurrently with the synthesis of the phthalocyanine ring system from a simple benzenoid precursor. The precursor may be a phthalic anhydride or a phthalonitrile derivative.

PDT dyes are recognized as efficient sensitizers of singlet oxygen and the involvement of singlet oxygen in the PDT process is now widely accepted, thus, the relative photooxidation rate by singlet oxygen catalyzed by these dyes have been examined. The Diels–Alder reaction and the ene reaction are two widely used application of singlet oxygen with olefins [10,11]. Here we have examined the structural effects of the synthesized dyes as sensitizers by using the Diels–Alder reaction with furan-2-carboxylic acid (**10**) as a model reaction (Scheme 1). Perfluorocarbons have shown that they can dissolve substantial amounts of oxygen and other gases (CO_2, F_2), and have also been reported to enhance the photosensitized oxidation of histidine [12,13], so we also examined the photooxidation ability of these compounds in solvent containing perfluorocarbons.

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* Corresponding author. Tel.: +86-411-3673466/3631333x3244/21-64253589/2945; fax: +86-411-3673466/21-64251386.
E-mail addresses: xhqian@dlut.edu.cn, xhqian@ecust.edu.cn (X. Qian).

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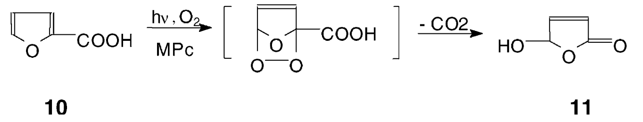


Scheme 1.

2. Results and discussion

The desired compounds were prepared according to the route shown in Scheme 2. The nucleophilic substitution of the dimethyl-4-nitrophthalate with 2,2,2-trifluoro-ethanol or 2,2,3,3,4,4,4-heptafluorobutanol in *N*,*N*-dimethylformamide using sodium hydride as base at room temperature for 24 h gave compounds **2a** or **b** in about 80% yield. **2a** and **b** were base hydrolyzed and neutralized to give 4-fluoroalkoxy phthalic acid, which was heated to melting to give **3a** or **b** as a solid in more than 90% yield. The condensation reaction of **3a** and **b** with urea and a metal salt may be carried out in a high boiling point solvent (nitrobenzene, trichlorobenzene, etc.) or in the melt. In our experiments, the latter is better. The condensation products were purified by different methods according to their physical properties. For instance, zinc 4,8,12,16-tetra(trifluroethoxyl) phthalocyaninate (**4a**) can be dissolved in most organic solvents such as ethyl acetate, acetone, chloroform, methanol etc., it could be purified by column chromatography followed by re-crystallization from ethyl acetate/petroleum ether. Cobalt and copper complexes are less soluble in organic solvents and can be purified by re-crystallization from concentrated sulfuric acid and water. The structure of these compounds were identified by elemental analysis, IR, ^{1}H NMR, FAB-MS, etc.

Table 1
Photooxidation of furan-2-carboxylic acid

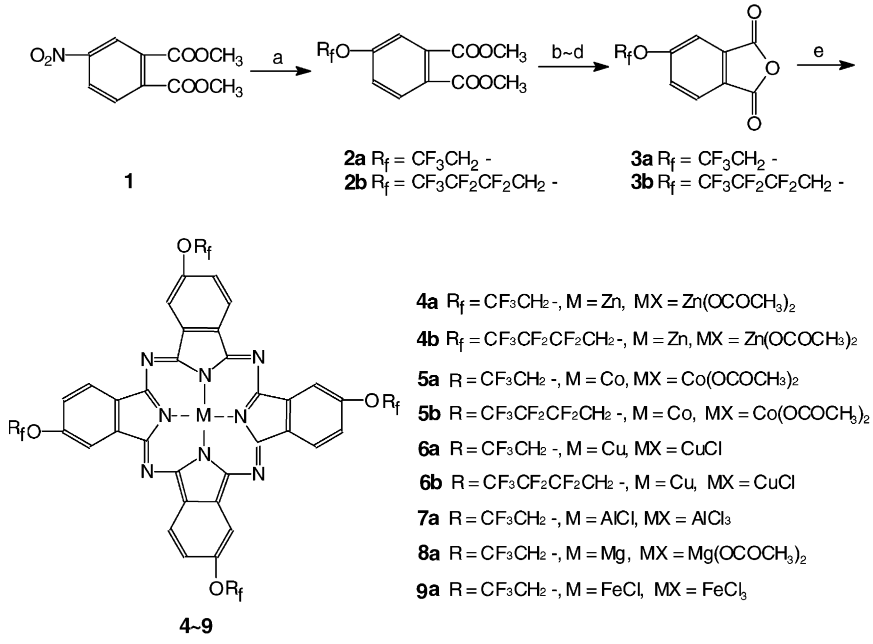
Compound	Solvent	Time (h)	Yield[a]	
			11	**10**
4a	CH_3OH	5	4.2	95.8
		12	13.4	86.6
4a[b]	CH_3OH/C_6F_{14}	5	4.9	95.1
		12	29.4	70.6
7a	CH_3OH	5	12.3	87.7
7a[b]	CH_3OH/C_6F_{14}	5	15.5	85.5
5a[c]	CH_3OH	12	0	100

[a] Dye:furan-2-carboxylic acid = 1:200 (molecular ratio), yield based on gas chromatography.

[b] Perfluorohexane:methanol = 4:1 (volume ratio).

[c] Compounds **5b**, **6a**, **6b**, **8a**, **8b** included show the same result, i.e. **11**:**10** = 0:100.

Photolysis of the acid (**10**) in methanol in the presence of 0.5 mol% of compounds **4a** and **b** or **7a** (zinc and aluminum centered phthalocyanines), with a 300 W tungsten lamp, gave the lactone (**11**) in >10% yield. The other dyes (cobalt, magnesium, iron and copper centered phthalocyanines) do not show such activity. The photooxidation yield catalyzed by **4a** was increased from 13.4% (in methanol) to 26.4% (with 20% perfluorohexanes in methanol) for 12 h (Table 1), the results may be explained that perfluorocarbons could dissolve more oxygen which is favorable to the production of singlet oxygen.



Scheme 2. (a) CF_3CH_2OH or $CF_3CF_2CF_2CH_2OH$/NaH, DMF, room temperature; (b) NaOH/H_2O; (c) HCl; (d) heat and (e) H_2NCONH_2, MX, NH_4Cl, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$.

3. Experimental

Infrared spectra were recorded on a Nicolet Magna-IR550 infrared spectrophotometer, using potassium bromide pellets of solids. ^{1}H NMR spectra with TMS as the internal standard were recorded on a Brucker AM-500 nuclear magnetic resonance spectrometer. Electron ionization mass spectra were recorded on a Hitachi M-80 mass spectrometer. Fast-atom-bombardment mass spectra with *m*-nitrobenzyl alcohol as a matrix were recorded on a Jeol JMS-HX 110 mass spectrometer. Combustion analysis for elemental composition was carried out on an Italian MOD-1106 analyzer run by the analysis center of the East China University of Science & Technology. Gas chromatography was carried out on a 1102G gas chromatograph. Methyl-4-nitrophthalate was prepared by the reference method [14].

*3.1. Synthesis of dimethyl-4-trifluoroethoxyphthalate (**2a**)*

2,2,2-Trifluoroethanol (1 ml, 1.37 g, 13.7 mmol) was added dropwise to a mixture of sodium hydride (60%, 0.6 g, 15 mmol) and *N,N*-dimethylformamide (18 ml) (over 4□ molecule sieve) over 20 min at room temperature, hydrogen was evolved. The mixture was stirred for another 20 min, and then dimethyl-4-nitrophthalate (2 g, 8.37 mmol) was added and the reaction mixture was stirred for 24 h at room temperature.

After addition of hydrochloric acid (5%, 36 ml), the mixture was extracted with ethyl ether (3 ml × 30 ml), washed with water (3 ml × 30 ml), dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, the residue crude oil product was purified by column chromatography on silica gel with petroleum ether:-ethyl acetate (8:1–4:1, v/v) as eluant to give a light yellow solid (1.9 g, 79%), mp 48–50 °C. IR (KBr): ν_{max} 2952, 1725, 1613, 1582, 1448, 1381, 1285, 1230, 1159, 1083, 978 cm^{-1}. ^{1}H NMR (CDCl$_3$): $\delta = 3.88$ (s, 3H, CH$_3$), 3.92 (s, 3H, CH$_3$), 4.41 (q, 2H, CH$_2$), 7.06 (q, 1H, Ar–H$_5$), 7.16 (d, 1H, Ar–H$_6$), 7.81 (d, 1H, Ar–H$_3$). EI-MS (*m/z*, %): 292 (*M* +, 52), 262 ($M - 2 \times \mathrm{CH_3}$, 27), 261 ($M - 1 - 2 \times \mathrm{CH_3}$, 100).

*3.2. Synthesis of dimethyl-4-heptafluorobutoxyphthalate (**2b**)*

The procedure is similar to that of **2a** using a 10 mmol scale. **2b** was produced as a light yellow thick liquid in 87% yield. IR (KBr): ν_{max} 2952, 1725,1613, 1582, 1448, 1381, 1285, 1230, 1159, 1083, 978 cm^{-1}. ^{1}H NMR (CDCl$_3$): $\delta = 3.87$ (t, 3H, CH$_3$), 3.90 (t, 3H, CH$_3$), 4.52 (t, 2H, CH$_2$), 7.05 (m, 1H, Ar–H$_5$), 7.14 (t, 1H, Ar–H$_6$), 7.80 (q, 1H, Ar–H$_3$). EI-MS (*m/z*, %): 392 (*M* +, 25), 362 ($M - 2 \times \mathrm{CH_3}$, 20), 361 ($M - 1 - 2 \times \mathrm{CH_3}$, 100).

*3.3. Synthesis of 4-trifluoroethoxyphthalic anhydride (**3a**)*

A mixture of dimethyl-4-trifluoroethoxyphthalate (1.9 g, 6.51 mmol), methanol (5 ml), and aqueous sodium hydroxide (10%, 5 ml) was heated under reflux for 30 min. The mixture was then cooled to room temperature, hydrochloric acid was added to pH = 1–2, extracted with ethyl ether (3 ml × 20 ml), dried over anhydrous sodium sulfate. Ethyl ether was evaporated and the resulting solid was heated to melting for 20 min, cooled and solidified to give a light yellow solid (1.5 g, 94%), mp 78–80 °C. IR (KBr): ν_{max} 1855, 1782, 1623, 1601, 1498, 1458, 1309, 1280, 1185, 900 cm^{-1}.

*3.4. Synthesis of 4-heptafluorobutoxyphthalic anhydride (**3b**)*

The procedure is similar to that of **3a** on a 10 mmol scale, **3b** was formed as a light yellow solid in 97% yield, mp 62–64 °C. IR (KBr): ν_{max} 1855, 1782, 1623, 1601, 1498, 1458, 1309, 1280, 1185, 900 cm^{-1}.

*3.5. Synthesis of zinc 4,8,12,16-tetra(trifluoroethoxy) phthalocyaninate (**4a**)*

A mixture of trifluoroethoxyphthalic anhydride (1.5 g, 6.10 mmol), urea (2.9 g, 48.33 mmol), zinc acetate (0.55 g, 2.51 mmol), ammonium chloride (0.24 g, 4.49 mmol), ammonium molybdate (0.034 g, 0.03 mmol) was ground, heated with stirring at 135 °C for 40 min, then heated to 180 °C for 1 h, and then heated to 200–210 °C for 4 h. The reaction mixture was cooled to room temperature, hydrochloric acid (1N, 100 ml) was added and the mixture was heated with reflux for 1 h. The resulting black-green precipitate was filtered while hot, the filtered residue was washed with hot water, and the solid was again treated with 10% sodium hydroxide solution once by the same procedure.

The crude product was dried, dissolved in acetone, and the solution was filtered to remove the insoluble precipitate, which was washed with acetone, the filtrate was condensed under reduced pressure. The residue was purified twice by column chromatography on silica gel using chloroform:-methanol (15:1–10:1, v/v) as eluant. The product was further purified by re-crystallization from a mixed solvent of ethyl acetate:petroleum ether (50:1, v/v) to give a blue-green solid, 160 mg (11%). $\mathrm{C_{40}H_{20}F_{12}N_8O_4Zn}$ requires: C, 49.52; H, 2.08; N, 11.55. Found: C, 49.78; H, 2.35; N, 11.49%. IR (KBr): ν_{max} 3030 (=C–H), 2905 (CH$_2$), 1605, 1490 (C=C), 1405 (CH$_2$), 1340, 1280 (C–O), 1175 (C–F), 1125 (ring), 1090 (C–O), 975, 820, 750 cm^{-1}. ^{1}H NMR (CD$_3$COCD$_3$): $\delta = 4.93$ (s, br, 8H, $4 \times \mathrm{OCH_2CF_3}$), 7.46 (s, br, 4H, Ar–H), 8.08 (s, br, 4H, Ar–H), 8.54 (s, br, 4H, Ar–H). FAB-MS (*m/z*, %): 971 ($M + 1$, 100), 970 (M +, 50), 888 ($M + 1 -$ CH$_2$CF$_3$, 55), 872 ($M + 1 -$ OCH$_2$CF$_3$, 38).

*3.6. Zinc 4,8,12,16-tetra(heptafluorobutoxy) phthalocyaninate (**4b**)*

The synthesis procedure is similar to that for **4a**, 4 mmol **3b** was used to give **4b** as a dark blue solid in 8% yield.

$C_{48}H_{20}F_{28}N_8O_4Zn$ requires: C, 42.07; H, 1.47; N, 8.18. Found: C, 42.44; H, 1.56; N, 8.78%. IR (KBr): ν_{max} 3015 (=C–H), 2905 (CH_2), 1610, 1495 (C=C), 1395 (CH_2), 1340, 1230 (C–O), 1180 (C–F), 1125 (ring), 1015 (C–O), 950, 820, 750 cm^{-1}.

*3.7. Synthesis of cobalt 4,8,12,16-tetra(trifluoroethoxy) phthalocyaninate (**5a**)*

A mixture of trifluoroethoxyphthalic anhydride (2.0 g, 8.13 mmol), urea (3.9 g, 65 mmol), cobaltous acetate (1.05 g, 4.22 mmol), ammonium chloride (0.32 g, 5.98 mmol), ammonium molybdate (0.04 g, 0.03 mmol) was ground and treated as above to give a dark blue solid. The crude product was dried and dissolved in concentrated sulfuric acid at room temperature. The resulting solution was slowly poured into water while stirring, the precipitate was collected by suction. The product was re-crystallized twice from concentrated sulfuric acid and water as above to give a dark blue solid with purple reflection, 500 mg (26%). $C_{40}H_{20}$-$F_{12}N_8O_4Co$ requires: C, 49.85; H, 2.10; N, 11.63. Found: C, 49.90; H, 2.18; N, 12.10%. IR (KBr): ν_{max} 3030 (=C–H), 2900 (CH_2), 1610, 1490 (C=C), 1395 (CH_2), 1230 (C–O), 1180 (C–F), 1125 (ring), 1100 (C–O), 970, 820, 750 cm^{-1}.

*3.8. Cobalt 4,8,12,16-tetra(heptafluorobutoxy) phthalocyaninate (**5b**)*

The synthesis procedure is similar to that for **5a** on a 5 mmol scale. **5b** is a dark blue solid with purple reflection, yield 23%. $C_{48}H_{20}F_{28}N_8O_4Co$ requires: C, 42.27; H, 1.48; N, 8.22. Found: C, 41.47; H, 1.52; N, 8.59%. IR (KBr): ν_{max} 3015 (=C–H), 2905 (CH_2), 1610, 1495 (C=C), 1390 (CH_2), 1350, 1230 (C–O), 1180 (C–F), 1125 (ring), 1020 (C–O), 950, 820, 750 cm^{-1}.

*3.9. Copper 4,8,12,16-tetra(trifluoroethoxy) phthalocyaninate (**6a**)*

Prepared on a 5 mmol scale as cited for **5a** to give a dark blue solid with purple reflection, yield 24%. $C_{40}H_{20}F_{12}N_8O_4Cu$ requires: C, 49.62; H, 2.09; N, 11.58. Found: C, 49.87; H, 2.30; N, 12.00%. IR (KBr): ν_{max} 3045 (=C–H), 2895 (CH_2), 1605, 1490 (C=C), 1402 (CH_2), 1340, 1230 (C–O), 1160 (C–F), 1125 (ring), 1095 (C–O), 980, 820, 750 cm^{-1}.

*3.10. Copper 4,8,12,16-tetra(heptafluorobutoxy) phthalocyaninate (**6b**)*

Prepared on a 5 mmol scale as cited for **5a** to give a dark blue solid, yield 21%. $C_{48}H_{20}F_{28}N_8O_4Cu$ requires: C, 42.13; H, 1.48; N, 8.19. Found: C, 42.06; H, 1.47; N, 8.44%. IR (KBr): ν_{max} 3015 (=C–H), 2905 (CH_2), 1610, 1490 (C=C), 1410 (CH_2), 1350, 1230 (C–O), 1180 (C–F), 1125 (ring), 1020 (C–O), 970, 820, 760 cm^{-1}.

*3.11. Aluminum chloride 4,8,12,16-tetra(trifluoroethoxy) phthalocyaninate (**7a**)*

The synthesis procedure was similar to that for **4a** on a 5 mmol scale, but the reaction mixture was not treated with hot dilute acidic or alkali solution, to give a dark blue microcrystalline solid, yield 8%. $C_{40}H_{20}F_{12}N_8O_4AlCl$ requires: C, 49.67; H, 2.09; N, 11.59. Found: C, 49.13; H, 2.34; N, 11.93%. IR (KBr): ν_{max} 3035 (=C–H), 2905 (CH_2), 1610, 1490 (C=C), 11402 (CH_2), 1340, 1230 (C–O), 1170 (C–F), 1125 (ring), 1085 (C–O), 950, 820, 750 cm^{-1}.

*3.12. Magnesium 4,8,12,16-tetra(trifluoroethoxy) phthalocyaninate (**8a**)*

Prepared on a 5 mmol scale as cited for **4a** to give a dark blue solid, yield 7%. $C_{40}H_{20}F_{12}N_8O_4Mg$ requires: C, 51.71; H, 2.17; N, 12.06. Found: C, 51.76; H, 2.29; N, 11.94%. IR (KBr): ν_{max} 3085 (=C–H), 2900 (CH_2), 1610, 1490 (C=C), 1390 (CH_2), 1285, 1230 (C–O), 1170 (C–F), 1125 (ring), 1010 (C–O), 980, 820, 750 cm^{-1}.

*3.13. Iron chloride 4,8,12,16-tetra(trifluoroethoxy) phthalocyaninate (**9a**)*

Prepared on a 5 mmol scale as cited for **7a** to give a dark blue solid, yield 4%. $C_{40}H_{20}F_{12}N_8O_4FeCl$ requires: C, 48.25; H, 2.03; N, 11.26. Found: C, 48.45; H, 2.23; N, 11.72%. IR (KBr): ν_{max} 3035 (=C–H), 2900 (CH_2), 1605, 1490 (C=C), 1402 (CH_2), 1340, 1235 (C–O), 1180 (C–F), 1125 (ring), 1080 (C–O), 980, 820, 750 cm^{-1}.

3.14. General procedure for photooxidation of furan-2-carboxylic acid with metal phthalocyanates

The experiments in Table 1 were carried out as described below. A mixture of furan-2-carboxylic acid (224 mg, 2.00 mmol) and zinc phthalocyanine (9.7 mg, 0.01 mmol) in methanol (20 ml) was irradiated with a water-cooled 300 W halogen tungsten lamp from a distance of 5 cm, while oxygen was passed through the reaction mixture for 5–12 h. The internal temperature was 15–20 °C. A simple was analyzed by gas chromatography to determine the conversion yield. The reaction mixture was concentrated under reduced pressure below 50 °C and purified by flash column chromatography (petroleum ether:ethyl acetate 10:1–4:1, v/v) to verify the structure of the photooxidation product [15].

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