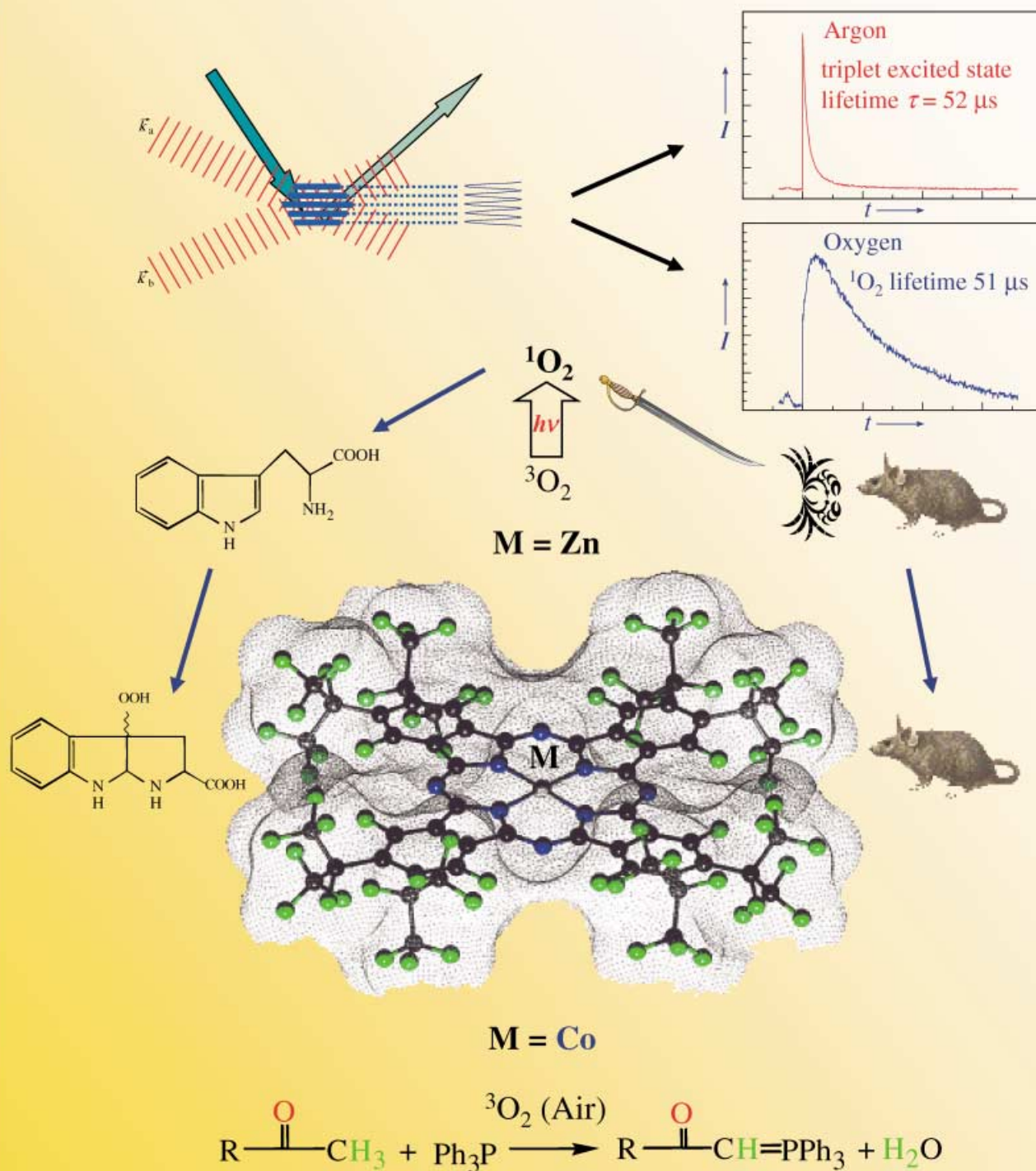


Perfluoroalkyl Phthalocyanines



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Introduction of Bulky Perfluoroalkyl Groups at the Periphery of Zinc Perfluorophthalocyanine: Chemical, Structural, Electronic, and Preliminary Photophysical and Biological Effects**

Barbara A. Bench, Andrew Beveridge,
Wesley M. Sharman, Gerald J. Diebold,*
Johan E. van Lier,* and Sergiu M. Gorun*

Phthalocyanines (Pcs) are a class of molecules that continue to elicit interest as pigments and dyes, nonlinear optical media, chemical sensors, catalysts, optical storage media, and phototherapeutic drugs.^[1] Peripheral substituents have been used to tune the steric and electronic features of phthalocyanines, to yield both electron-rich and electron-poor species, the latter including the important class of halogenated phthalocyanines. The peripheral substituents for the electron-poor compounds, however, are restricted almost exclusively to the halogens themselves, which translates into both poor solubility in organic solvents, paucity of substituent types, and a restriction of the molecular geometry to planar architectures. Consequently, the structural diversity of such electron-poor phthalocyanines is extremely limited and their solid-state structural characterization at atomic level is apparently unknown.^[2] Furthermore, planar phthalocyanines tend to aggregate by π - π stacking interactions or single-atom bridges, a disadvantage if high solubility or single-site isolation is desired, for example, for homogeneous catalysis. The introduction of bulky, peripheral substituents encourages the formation of isolated, monomeric species. If such substituents are perhalogenated, preferably perfluorinated, materials that are both soluble and resistant to self-oxidation might result. Such materials may be suitable for homogeneous catalysis under harsh conditions, which include the presence of reactive species such as singlet oxygen and free radicals.

We report here the facile synthesis and single-crystal X-ray structural characterization of $F_{64}PcZn$, the first nonplanar, biconcave, halogenated metallophthalocyanine. We also report the chemical, electronic, and preliminary photophysical and biological effects of the introduction of bulky, perfluorinated substituents (R^F groups). The above effects are likely to be found in related molecules belonging to the same class but yet to be prepared.

Perfluoro-(4,5-di-isopropyl)phthalonitrile,^[3] **1**, was melted with zinc acetate at 180 °C to yield a blue-green solid. Chromatographic purification yields a blue material, the intensely colored solutions of which in organic solvents exhibit UV/Vis spectra characteristic of phthalocyanines. The ¹³C and ¹⁹F NMR spectra of this material have the same number of peaks as **1**, but are shifted by up to $\delta = 42.1$ for the nitrile C and $\delta = -7.7$ for the aromatic F atoms, respectively. These changes indicate the formation of $[F_{64}PcZn(\text{acetone})_2]$ (**2**; Scheme 1).



Scheme 1. Synthesis of $[F_{64}PcZn(\text{acetone})_2]$ (**2**) (acetone molecules omitted); $R^1 = CF(CF_3)_2$, $R^2 = F$.

Complex **2** readily forms large single crystals, a likely consequence of the peripheral bulky R^F (iC_3F_7) groups that both decrease π - π stacking interactions and increase solubility. The X-ray structure (Figure 1),^[4] reveals a zinc-centered Pc ring, the orientation of the CF_3 groups of the iC_3F_7 substituents above and below the phthalocyanine plane, and the axial coordination of two acetone molecules. The presence of ligands above and below the phthalocyanine plane imparts an overall bulky or biconcave character to the complex. Crystallographically authenticated acetone solvates are not known for any other Pc compounds, while sterically

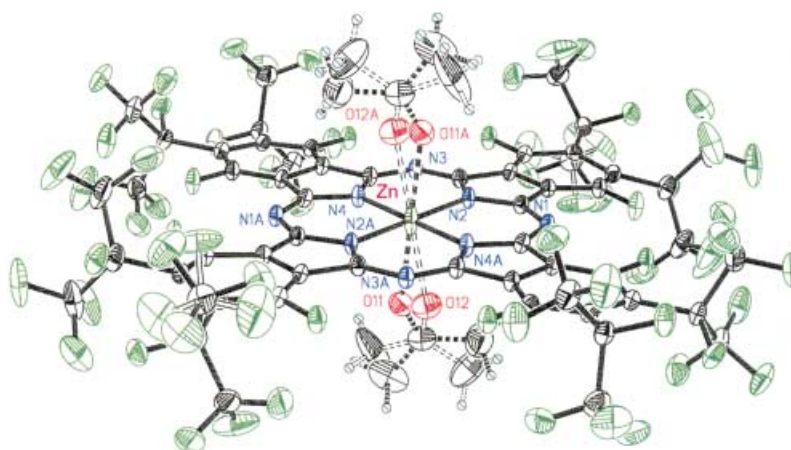


Figure 1. Molecular structure of **2** with thermal ellipsoids set at 30 % probability level. Two symmetry equivalent axial acetone molecules are disordered over two positions. Selected bond lengths [Å] and angles [°]: Zn-N2 2.008(2), Zn-N4 2.004(2), Zn-O11 2.446(10), Zn-O12 2.376(10); N2-Zn-O12 83.3(2), N4-Zn-O12 94.3(2); F green, N blue, O red, C gray.

[*] Prof. Dr. G. J. Diebold, Prof. Dr. S. M. Gorun,
B. A. Bench, A. Beveridge
Department of Chemistry
Brown University
Providence, RI 02912 (USA)
Fax: (+1) 401-863-2594
E-mail: Gerald_Diebold@Brown.edu
Sergiu_Gorun@Brown.edu

Prof. Dr. J. E. van Lier, W. M. Sharman
Department of Nuclear Medicine and Radiobiology
University of Sherbrooke
Sherbrooke, QC J1H 5N4 (Canada)
Fax: (+1) 819-564-5442
E-mail: Jvanlier@courrier.usherb.ca

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unencumbered, strictly planar PcZn complexes are tetra- and penta-, but not hexacoordinated.^[2] Despite longer Zn–N bonds ($2.006 \pm 0.002(3)$ Å) in **2** compared with planar, tetracoordinated PcZn^[5a] and Zn naphthalocyanine ($1.980 \pm 0.002(2)$ Å),^[5b] the Pc ring is perfectly planar. No π – π stacking is observed in solid state. Complex **2** is surprisingly stable as a solvated solid. A crystal of **2** gave the same X-ray structure (including the axial acetone molecules) after storage in air for one year. We ascribe the stability of the metal–acetone bonds to the bulky R^F groups, which lower the metal charge density (favoring donation from the axial ligands) and provide some steric hindrance. A favorable packing may be more important in the solid-state. The same electronic and steric factors stabilize acetone in the analogous paramagnetic cobalt complex^[6] and make acetone competitive with O₂ for the copper site in fluorinated tris(pyrazolyl)borate complexes.^[7] Unlike **2**, the strictly planar zinc perfluorophthalocyanines [F₁₆PcZn] (**3**; of similar electronic structure, R¹ = R² = F in Scheme 1)^[8] and protio PcZn^[9] do not retain solvent when precipitated from acetone. Thus, the coordination differences can be ascribed at least in part to the decrease in steric dimensionality (that is from nonplanar, biconcave to planar).

The Q band of **2** (686 nm in acetone), is 23 nm bathochromically shifted from the Q band of **3** (665 nm). A similar bathochromic trend for the Q band is observed in pyridine, a solvent that favors deaggregation: **2** and **3** absorb at 698 and 679 nm, respectively.

The molar extinction coefficient of **2** is significantly larger than that of **3**, 1.73×10^5 versus 2.9×10^4 M^{−1} cm^{−1}. The first reduction potential of **2** shifts to -0.25 V, from -0.84 V in **3**.^[10] Collectively, the UV/Vis and electrochemical results suggest a narrowing of the HOMO–LUMO gap and an increase in electronegativity of the substituents upon perfluoroalkylation.

These changes could be rationalized by considering primarily the electronic effects of the peripheral substituents, since in both **2** and, presumably **3**, the aromatic macrocycle retains its planarity in solution. Hammett constants for *i*C₃F₇ are not reported, but values for CF₃ (from benzene derivatives) could be used as an approximation for Pc.^[11a] For F and CF₃, the inductive effect values are 0.74 and 0.64, while the resonance values are -0.60 and 0.76 , respectively.^[11b] Both CF₃ and F have σ withdrawing effects, but the resonance effects have the opposite sign, being larger by 0.16 for F in absolute terms. The increase in electron density in **2** relative to **3** because of the $+0.1$ decrease in inductive effect in changing from F (0.74) to CF₃ (0.64) is more than compensated by the resonance contributions with the exchange of the -0.60 contribution of F for the $+0.76$ of CF₃. In the framework of Gouterman's four orbitals model,^[12] the LUMO (e_g) is stabilized more than the HOMO (a_{1u}) by the loss of aromatic fluorine conjugation. The large extinction coefficient of the Q band in **2** establishes that R^F derivatization maintains the nondegeneracy of the a_{1u} and a_{2u} orbitals, and hence the applicability of Gouterman's model.

Generally, ring distortions notwithstanding, the higher degree of fluorination achieved by increasing the ratio of ring-attached R^F to aromatic F groups in this Pc unit is likely

to result in red-shifted Q bands and increase molecular electron deficiency. An alternative method for fluorine enrichment of Pcs, namely elongation of the R^F groups, will have a significantly smaller effect upon the above parameters, which will include smaller shifts in the λ_{\max} and first reduction potentials. This latter notion is in line with the classical view of the inductive effect, whereby electronic influences progressively decrease as the chain is elongated. Considering the potential versatility of Scheme 1 and demonstrated ring planarity of **2** and its cobalt analogue,^[6] this generalization may be valuable as a synthetic strategy.

The peripheral bulkiness is expected to prevent π – π stacking not only in solid-state but also in solution, thus favoring single-site isolation. Correy–Pauling–Koltun (CPK) models suggest that the lower limit of cofacial approach of two molecules of **2**, rotated by 45° to minimize steric repulsions, is about 3.9 Å. Tilting and/or shifting may slightly reduce this limit, but both distortions place R^F groups above the aromatic ring and block metal coordination. Consistent with this model, the ¹⁹F NMR spectra of **2** is concentration independent; the Lambert–Beer law of the Q band, a sensitive probe of aggregation, is also obeyed up to 10 μM, unlike the electronically similar, but planar **3**. No significant NMR signal or UV/Vis absorption band broadening is observed either.

The effect of R^F substitution upon the activation of O₂ by **2**, and its oxidation resistance was probed by testing **2** as a sensitizer for the photochemical production of ¹Δ_g O₂ from O₂. If **2** were to function as photosensitizer, a preliminary requirement is that the lifetime, τ , of its triplet excited state T₁, is sufficiently long for the productive T₁–³O₂ interactions to occur. We have measured τ for **2** and **3** by a transient grating method that relies upon the photoacoustic effect produced by the nonradiative deactivation of excited molecular states and a refractive index change resulting from the transfer of population from the ground state to T₁. The decay of the thermal mode of the grating, measured with a probe laser, yields τ .^[13] Our method gives for the lifetime of singlet oxygen in acetone 51 ± 3 μs, consistent with the literature values (50.5 , 51 , and 51 μs).^[14] In acetone, in the absence of oxygen, τ is 52 ± 3 μs for **2** (at 10 μM) and < 1 μs for **3**.^[15] The observed difference in τ , which is known to decrease with increased aggregation, further confirms that R^F substitution results in less aggregation. The photochemical production of ¹Δ_g O₂ was independently corroborated using a standard L-tryptophan photooxidation test, which can distinguish between free radicals and singlet-oxygen products.^[16] Both **2** and **3** produce peroxides, thus proving that **2** is a photosensitizer. Significantly, bleaching was not observed during our chemical or photochemical experiments with **2**, thus confirming its robustness.

These data suggests that **2** might be useful for applications that use ¹Δ_g O₂. Considering also the favorable bathochromic shift, solubility, excited-state lifetime and lack of aggregation of **2** in the context of the known photodynamic activity of phthalocyanines,^[17] the biological consequences of the non-planar, biconcave geometry were preliminarily evaluated in vivo. Using EMT-6 mammary tumors in mice, **2** produced 100 % tumor regression at a dose of 2.5 μmol kg^{−1}. In the case

of **3**, a dose of 5 $\mu\text{mol kg}^{-1}$ induced 60 % regression.^[18] These results suggest that the introduction of bulky perfluoroalkyl groups results in higher tumor regression at lower photosensitizer doses; the molecular and pharmacological reasons for the differences between **2** and **3** in vivo remain to be elucidated.

In summary, our results provide a simple (classical) yet efficient approach to nonplanar perhalogenated phthalocyanines, of which $[\text{F}_{64}\text{PcZn}]$ is only the first representative. Other metals and R^{F} groups will yield compounds with a diversity of size, shape, and depth of fluorinated cavities around a reactive metal center. Their thermal, photochemical, and chemical stability, coupled with their potential synthetic versatility and favorable solubility, suggest that this class of molecules might be effective for photophysical, chemical, and perhaps, medical uses. Applications requiring stability under harsh conditions and/or aggressive reagents, or solubility in nonconventional solvents might be considered.

Experimental Section

2: A mixture of zinc acetate (0.123 g, 0.668 mmol) and **1**, (1.337 g, 2.67 mmol) was heated under Ar at 180 °C for 60 min. Chromatography on silica gel using 20–30 % acetone/hexanes, followed by diffusion of hexanes into an acetone solution gave crystalline **2** in 21 % yield; m.p. > 300 °C; FAB MS $[m/z]$ 2064.84 $[M^+]$. Elemental analysis: calcd (%) for $\text{ZnC}_{63.5}\text{H}_{15}\text{N}_8\text{O}_{2.5}\text{F}_{64}$: (Zn $\text{C}_{56}\text{N}_8\text{F}_{64} \cdot 2.5$ acetone), C 34.49, H 0.68, N 5.07; found: C 34.38, H 0.73, N 5.09. The extra half acetone molecule was not detected crystallographically. ^{19}F NMR (376.497 MHz, $[\text{D}_6]$ acetone, CFCl_3): $\delta = -71.3$ (6F), -103.9 (1F), -164.6 (1F); ^{13}C NMR (100.613 MHz, $[\text{D}_6]$ acetone): $\delta = 154.6$, 152.0, 130.9, 121.5, 117.5, 95.2. UV/Vis [nm] (log ϵ), acetone, 322 (4.38), 396 (4.56), 620 (4.42), 686 (5.24).

Biological tests: Suspensions of **2** or **3** in 10 % CRM (CRM = cremofor) were administered intravenously. The tumors were illuminated with 650–700 nm light (1 kW Xenon lamp, LL650 and LS700 filters) at fluence rates of 200 mW cm^{-2} , 400 J cm^{-2} per tumor. Absence of a palpable tumor three weeks post irradiation was considered regression.

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Synthesis and Structure of a Biconcave Cobalt Perfluorophthalocyanine and Its Catalysis of Novel Oxidative Carbon–Phosphorus Bonds Formation by Using Air**

Barbara A. Bench, William W. Brennessel, Hyun-Jin Lee, and Sergiu M. Gorun*

One of the major challenges of modern chemistry, homogeneous aerobic oxidations, poses the additional challenge of designing suitable catalysts that are not only active, but resist self-oxidation as well. For transition metal complexes, this

[*] Prof. Dr. S. M. Gorun, B. A. Bench, H.-J. Lee
Department of Chemistry
Brown University
Providence, RI, 02912 (USA)
Fax: (+1) 401-863-2594
E-mail: Sergiu_Gorun@Brown.Edu
W. W. Brennessel
Department of Chemistry
University of Minnesota
Minneapolis, MN, 55455 (USA)
Fax: (+1) 612-626-7541

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