

Photochemical & Photobiological Sciences

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Synthesis, Properties and Drug Potential of the Photosensitive Alkyl- and Alkylsiloxy-Ligated Silicon Phthalocyanine Pc 227

Jun Li, Yang Yang, Ping Zhang, James R. Sounik and Malcolm E. Kenney*

Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106, USA

*Email: mek9@case.edu.

Abstract

The photosensitive, alkyl- and alkylsiloxy-ligated silicon phthalocyanine, $\text{SiPc}[(\text{CH}_2)_3\text{SH}][\text{OSi}(\text{CH}_3)_2(\text{CH}_2)_3\text{N}(\text{CH}_3)_2]$, **Pc 227**, has been prepared and characterized. This phthalocyanine yields the experimental photodynamic therapy (PDT) drug **Pc 4**, $\text{SiPc}[\text{OH}][\text{OSi}(\text{CH}_3)_2(\text{CH}_2)_3\text{N}(\text{CH}_3)_2]$, when irradiated with red light. To provide an understanding of the process by which **Pc 227** and other alkyl-alkylsiloxy-silicon phthalocyanines such as **Pc 227** are photolyzed, bond dissociation energy, natural bond orbital (NBO) charge distribution, spin density distribution, nucleus-independent chemical shift (NICS), and electron localization function (ELF) calculations have been carried out on two models related to it. These show that the lowest energy pathway for the photolysis of **Pc 227** is a homolysis involving a phthalocyanine π radical having a low $\text{Si}_{\text{pc}}\text{-C}$ bond dissociation energy. The promise of the results of this study for synthetic chemistry and drug development is discussed.

Introduction

The widespread use of alkylsiloxanes in research and industry is due in large part to the resistance of normal Si-C bonds to thermal, chemical and photolytic attack. However, early in the development of the chemistry of alkyl-alkylsiloxysilicon phthalocyanines it was found that the Si_{Pc}-C bond in such phthalocyanines is not stable to white light. After further investigation, it was found that this bond is photolyzed by light in the 410 - 480 and 620 - 670 nm ranges (ranges which overlap partly and completely the Soret and Q-bands of silicon phthalocyanines), but that it resists photolysis in the 470 - 530 nm range. It was further found that it resists attack by concentrated sulfuric acid and methanolic NaOH, and pyrolysis by temperatures up to about 350°. ¹ These findings opened a path to the synthesis of a variety of silicon phthalocyanines including the extensively-studied experimental photodynamic therapy (PDT) drug SiPc[OH][OSi(CH₃)₂(CH₂)₃N(CH₃)₂], **Pc 4**, Figure 1a. ²⁻¹⁴ The photochemical properties of phthalocyanines have made them promising PDT drugs and prodrugs. ¹⁵⁻¹⁸

We now have made the new alkyl-alkylsiloxysilicon phthalocyanine SiPc[(CH₂)₃SH][OSi(CH₃)₂(CH₂)₃N(CH₃)₂], **Pc 227**, Figure 1b. This compound has significant structural similarities to **Pc 4** and forms a conjugate with gold nanoparticles which gives **Pc 4** when irradiated with red light in a nonpolar medium. ¹⁹ It has the potential to be dispersible in biological systems, transportable in them to malignant tissues, and then photolyzable with red light to **Pc 4**. ¹⁹⁻²⁰ In short, **Pc 227** provides a key building block for a conjugate that has the potential to be an intravenous prodrug able to deliver **Pc 4** to malignant tissues. Further, it has the potential to be a topical prodrug which can deliver **Pc 4** to such tissues. ²⁰

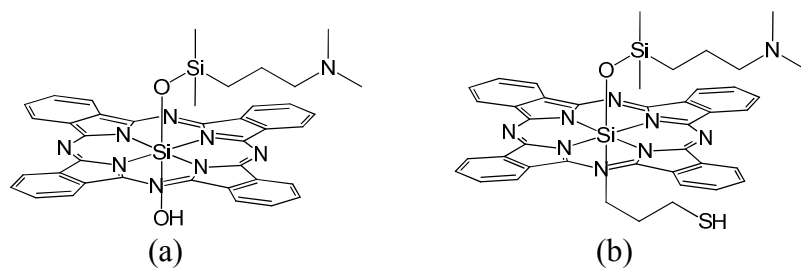


Figure 1. The structures of (a) SiPc[OH][OSi(CH₃)₂(CH₂)₃N(CH₃)₂], **Pc 4**, and (b) SiPc[(CH₂)₃SH][OSi(CH₃)₂(CH₂)₃N(CH₃)₂], **Pc 227**.

Because the photolysis of the Si_{Pc}-C bond in alkyl-alkylsiloxysilicon phthalocyanines has both synthetic and potential practical uses, the mechanism of its photolysis is of interest. In order to gain

more understanding of this, we have carried out bond dissociation energy, natural bond orbital (NBO) charge distribution, spin density distribution, nucleus-independent chemical shift (NICS), and electron localization function (ELF) calculations on two model species. These calculations indicate that the photolysis of the Si_{Pc}-C bond in alkyl-alkylsiloxysilicon phthalocyanines proceeds by a homolytic pathway, and that a transient phthalocyanine π radical in this pathway is stabilized by delocalization. They also indicate that this stabilization makes a major contribution to a reduction in the bond dissociation energy of the Si_{Pc}-C bond, and that it is this reduction that allows the photolysis to proceed with low-energy, red light.

Experimental Details

Instrumentation. A Perkin-Elmer IR 598 spectrometer (Perkin Elmer, Shelton, CT) was used to collect the infrared spectra, a Perkin-Elmer Lambda 25 Spectrometer and fused silica cells (1.00 cm Fisher Scientific, Pittsburgh, PA) were used to collect the UV-vis spectra, and a Varian INOVA 400 MHz spectrometer (Varian, Palo Alto, CA) was used to collect the NMR spectra. A KRATOS MS-50 Mass Spectrometer (Ion Tech, Manchester, UK) was used by the Washington University Center for Biomedical and Bioorganic Mass Spectrometry Center (St Louis, MO) to obtain the mass spectra.

Synthesis. SiPc[Cl][(CH₂)₃Cl], **Pc 309**. A mixture of 1,3-diiminoisindoline (1.0 g), Cl(CH₂)₃SiCl₃ (0.92 mL), and 2,6-lutidine (7 mL) was refluxed for 6 h, concentrated to a slurry by rotary evaporation (40°C), diluted with H₂O (~50 mL) and filtered. The solid was washed (H₂O) and vacuum dried (80°C).

SiPc[(CH₂)₃Cl][OSi(CH₃)₂(CH₂)₃N(CH₃)], **Pc 220**. A mixture of the crude **Pc 309** made in the previous step, CH₃OSi(CH₃)₂(CH₂)₃N(CH₃)₂ (0.16 g) and chlorobenzene (30 mL) was refluxed for 3 h, and evaporated to dryness by rotary evaporation (40°C). The solid was chromatographed (basic Al₂O₃ III, CH₂Cl₂-N(CH₂CH₃)₃ solution, 150:1), vacuum dried (room temperature), and weighed (65 mg, 5% based on 1,3-diiminoisindoline). UV-vis (toluene) λ_{\max} , nm (log ϵ): 678 (5.3). NMR (CDCl₃): δ 9.63 (m, 8H, 1,4-Pc H), 8.35 (m, 8H, 2,3-Pc H), 1.56 (s, 6H, NCH₃), 0.85 (t, 2H, Si(CH₂)₂CH₂), 0.78 (t, 2H, Si(CH₃)₂(CH₂)₂CH₂), -1.22 (m, 2H, Si(CH₃)₂CH₂CH₂), -2.37 (t, 2H, Si(CH₃)₂CH₂), -2.99 (s, 6H, SiCH₃), -3.51 (m, 2H, SiCH₂CH₂), -6.16 (t, 2H, SiCH₂). LRMS-ESI (m/z): [M]⁺ calcd for C₄₂H₄₀ClN₉OSi₂, 777.26; found, 777.73. **Pc 220** is a green solid. It is soluble in CH₂Cl₂, dimethylformamide, and toluene, and insoluble in hexanes.

SiPc[(CH₂)₃S(O)(CH₃)][OSi(CH₃)₂(CH₂)₃N(CH₃)₂], **Pc 226**. A mixture of **Pc 220** (100 mg), potassium thioacetate (324 mg), and dimethylformamide (16 mL) was warmed (50 °C) for 6 h and evaporated to dryness by rotary evaporation (40°C). The solid was treated with H₂O (~50 mL) and

extracted with CH_2Cl_2 (3 times, ~ 30 mL each time). The extract was evaporated to dryness by rotary evaporation (40°C) and the solid was chromatographed (basic Al_2O_3 III, CH_2Cl_2 -ethyl acetate solution, 5:1), vacuum dried (room temperature), and weighed (49 mg, 46%). UV-vis (toluene) λ_{max} , nm (log ϵ): 678 (5.4). NMR (CDCl_3): δ 9.64 (m, 8H, 1,4-Pc H), 8.31 (m, 8H, 2,3-Pc H), 1.55 (s, 6H, NCH_3), 1.52 (s, 3H, $\text{CH}_2\text{SC}(\text{O})\text{CH}_3$), 0.79 (t, 2H, $\text{Si}(\text{CH}_3)_2(\text{CH}_2)_2\text{CH}_2$), 0.29 (t, 2H, $\text{Si}(\text{CH}_2)_2\text{CH}_2$), -1.23 (m, 2H, $\text{Si}(\text{CH}_3)_2\text{CH}_2\text{CH}_2$), -2.38 (t, 2H, $\text{Si}(\text{CH}_3)_2\text{CH}_2$), -2.99 (s, 6H, SiCH_3), -3.72 (m, 2H, SiCH_2CH_2), -6.13 (t, 2H, SiCH_2). LRMS-ESI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{44}\text{H}_{43}\text{N}_9\text{O}_2\text{SSi}_2$, 817.28; found, 817.60. **Pc 226** is a green solid. It is soluble in CH_2Cl_2 , dimethylformamide, and toluene, and insoluble in hexanes.

$[\text{S}(\text{CH}_2)_3\text{SiPcOSi}(\text{CH}_3)_2(\text{CH}_2)_3\text{N}(\text{CH}_3)_2]_2$, **Pc 228**. A solution of **Pc 226** (15 mg) in ethanol (3 mL) was treated with an aqueous solution of NaOH (2.0 N, 20 μL), stirred for 1 h and evaporated to dryness by rotary evaporation (room temperature). The solid was chromatographed (basic Al_2O_3 III, CH_2Cl_2 -triethylamine solution, 70:1), air-dried and weighed (5 mg, 18%). UV-vis (toluene) λ_{max} , nm (log ϵ): 675 (5.3). NMR (CDCl_3): δ 9.46 (m, 16H, 1, 4-Pc H), 8.23 (m, 16H, 2, 3-Pc H), 1.53 (s, 12H, NCH_3), 0.76 (t, 4H, $\text{Si}(\text{CH}_3)_2(\text{CH}_2)_2\text{CH}_2$), -0.98 (t, 4H, $\text{Si}(\text{CH}_2)_2\text{CH}_2$), -1.31 (m, 4H, $\text{Si}(\text{CH}_3)_2\text{CH}_2\text{CH}_2$), -2.42 (t, 4H, $\text{Si}(\text{CH}_3)_2\text{CH}_2$), -3.06 (s, 12H, SiCH_3), -4.38 (m, 4H, SiCH_2CH_2), -6.52 (t, 4H, SiCH_2). HRMS-ESI (m/z): $1/2[\text{M}+2\text{H}]^{2+}$ calcd for M as $\text{C}_{84}\text{H}_{80}\text{N}_{18}\text{O}_2\text{S}_2\text{Si}_4$, 775.2688; found, 775.2696. **Pc 228** is a green solid. It is soluble in CH_2Cl_2 , $\text{C}_2\text{H}_5\text{OH}$, dimethylformamide and toluene, and insoluble in hexanes. Solutions of **Pc 228** in CH_2Cl_2 and toluene are photosensitive, and solutions of it in 1,2,3,4-tetrahydronaphthalene are thermally unstable above $\sim 170^\circ\text{C}$.

$\text{SiPc}[(\text{CH}_2)_3\text{SH}][\text{OSi}(\text{CH}_3)_2(\text{CH}_2)_3\text{N}(\text{CH}_3)_2]$, **Pc 227**. Under Ar, a cooled (0°C) Ar-purged solution of **Pc 226** (80 mg) and ethanol (50 mL) was treated with a cooled ($\sim 0^\circ\text{C}$) aqueous NaOH solution (1.6 mL, 2.0 N), cooled (0°C) for 75 min, treated with an aqueous NH_4Cl solution (saturated, 40 mL) and extracted with CH_2Cl_2 (3 times, ~ 20 mL each time). The extract was evaporated to dryness by rotary evaporation (room temperature), and the solid was reduced with tri-(*n*-butyl)phosphine (0.025 mL) and CHCl_3 (10 mL) under Ar for 30 min, and evaporated to dryness by rotary evaporation (room temperature). The solid was chromatographed (basic Al_2O_3 V, CH_2Cl_2 -ethyl acetate solution, 10:1), vacuum dried (room temperature), and weighed (61 mg, 80%). UV-vis (toluene) λ_{max} , nm (log ϵ): 678 (5.5). NMR (CDCl_3): δ 9.64 (m, 8H, 1,4-Pc H), 8.34 (m, 8H, 2,3-Pc H), 1.55 (s, 6H, NCH_3), 0.78 (t, 2H, $\text{Si}(\text{CH}_3)_2(\text{CH}_2)_2\text{CH}_2$), -0.14 (q, 2H, $\text{Si}(\text{CH}_2)_2\text{CH}_2$), -0.43 (t, 1H, SH), -1.21 (m, 2H, $\text{Si}(\text{CH}_3)_2\text{CH}_2\text{CH}_2$), -2.37 (t, 2H, $\text{Si}(\text{CH}_3)_2\text{CH}_2$), -2.99 (s, 6H, SiCH_3), -3.67 (m, 2H, SiCH_2CH_2), -6.14 (t, 2H, SiCH_2).

HRMS-ESI (m/z): $[M+H]^+$ calcd for M as $C_{42}H_{41}N_9OSSi_2$, 776.2772; found, 776.2771. **Pc 227** is a green solid. It is soluble in CH_2Cl_2 , dimethylformamide, and toluene, and insoluble in hexanes.

$SiPc[OSi(CH_3)_2(CH_2)_3N(CH_3)_2]$, **Pc 12**. A mixture of $CH_3OSi(CH_3)_2(CH_2)_3N(CH_3)_2$ (711 mg) and a suspension of $SiPc(OH)_2$ (284 mg) and pyridine (170 mL) that had been dried by distillation (~10 mL of distillate) was slowly distilled for 4 h (~10 mL of distillate). The reaction solution was evaporated to dryness by rotary evaporation (40 °C), and the solid was washed with CH_3CN , vacuum dried (40 °C) and weighed (356 mg, 83%). UV-vis (dimethylformamide) λ_{max} , nm (log ϵ): 668 (5.3). NMR ($CDCl_3$): δ 9.63 (m, 8H, 1,4-Pc H), 8.34 (m, 8H, 2,3-Pc H), 1.65 (s, 12H, NCH_3), 0.90 (m, 4H, $Si(CH_3)_2(CH_2)_2CH_2$), -1.10 (m, 4H, $Si(CH_3)_2CH_2CH_2$), -2.26 (m, 4H, $Si(CH_3)_2CH_2$), -2.87 (s, 12H, $SiCH_3$). The compound is a blue solid. It is soluble in CH_2Cl_2 , dimethylformamide, toluene, and insoluble in hexanes.

$SiPc[OH][OSi(CH_3)_2(CH_2)_3N(CH_3)_2]$, **Pc 4**. A solution of unchromatographed **Pc 12** (640 mg), trichloroacetic acid (672 mg) and CH_2Cl_2 (90 mL) was stirred at room temperature for 5 h. The product was mixed with pyridine (90 mL) and then H_2O (90 mL) and the mixture was separated. The aqueous layer was washed with CH_2Cl_2 , the washings were filtered, and the residue was washed with CH_2Cl_2 . The organic layer was filtered and the filtrate and CH_2Cl_2 washings were combined and evaporated to dryness by rotary evaporation (40 °C). The solid was vacuum dried (40 °C) and weighed (638 mg). A solution of this product (630 mg) and CH_2Cl_2 was chromatographed (Al_2O_3 V, CH_2Cl_2 -ethyl acetate solution, 5:1) and the eluate was evaporated to dryness by rotary evaporation (40 °C). The solid was washed with CH_3CN , vacuum dried (40 °C), and weighed (392 mg, 61% based on $SiPc(OH)_2$ used). UV-vis (CH_2Cl_2) λ_{max} , nm (log ϵ): 669 (5.3). NMR ($CDCl_3$): δ 9.11 (m, 8H, 1,4-Pc H), 8.18 (m, 8H, 2,3-Pc H), 1.35 (s, 6H, NCH_3), 0.60 (m, 2H, $Si(CH_3)_2(CH_2)_2CH_2$), -1.36 (m, 2H, $Si(CH_3)_2CH_2CH_2$), -2.49 (m, 2H, $Si(CH_3)_2CH_2$), -3.10 (s, 6H, $SiCH_3$). HRMS-FAB (m/z): $[M+H]^+$ calcd for M as $C_{39}H_{35}N_9O_2Si_2$, 717.2452; found, 717.2422. The compound is a blue solid. It is soluble in CH_2Cl_2 , dimethylformamide, toluene, and insoluble in hexanes.

$SiPc[OCH_3][OSi(CH_3)_2(CH_2)_3N(CH_3)_2]$, **Pc 233**. A mixture of **Pc 4** (60 mg), CH_3OH (900 mg), and pyridine (30 mL) was refluxed for 30 min and concentrated by rotary evaporation (room temperature). The solid was chromatographed (neutral Al_2O_3 III, CH_2Cl_2 -ethyl acetate solution, 2:1), evaporated to dryness by rotary evaporation (room temperature), vacuum dried (room temperature), and weighed (49 mg, 80%). UV-vis (toluene) λ_{max} , nm, (log ϵ): 671 (5.4). NMR($CDCl_3$): δ 9.63 (m, 8H, 1,4-Pc H), 8.33 (m, 8H, 2,3-Pc H), 1.63 (s, 6H, NCH_3), 0.88 (t, 2H, γ - CH_2), -1.10 (m, 2H, β - CH_2), -1.82 (s, 3H, OCH_3), -2.27 (t, 2H, α - CH_2), -2.87 (s, 6H, $SiCH_3$). HRMS-FAB (m/z): $[M+H]^+$ calcd for $C_{40}H_{37}N_9O_2Si_2$,

732.2687: found 732.2690. **Pc 233** is a purple solid. It is soluble in CH₂Cl₂, dimethylformamide and toluene and insoluble in hexanes.

SiPc(CH₃)Cl, **Pc 310**. A mixture of 1,3-diiminoisoindoline (2.02 g, 13.9 mmol), methyltrichlorosilane (1.15 mL, 9.79 mmol) and quinoline (19 mL) was refluxed for 90 min, filtered while hot, washed (acetone, ether, toluene). The filtrate was cooled, refiltered and the solid was washed. The two solids were combined and weighed (1.50g, 73% based on diiminoisoindoline). **Pc 310** is a purple solid. It is insoluble in CH₂Cl₂, dimethylformamide, toluene and hexanes.

SiPc[CH₃][(OSi(CH₂CH₃)₃)], **Pc 311**. A mixture of **Pc 310** (222 mg, 0.376 mmol), triethylsilanol (0.228 mL, 1.49 mmol), chlorobenzene (68 mL) and pyridine (10 mL) was refluxed for 20 min, filtered and evaporated to dryness by rotary evaporation (40 °C). The solid was chromatographed (basic alumina III, CH₂Cl₂-hexanes, 1:1), washed (acetonitrile), vacuum dried (60 °C), and weighed (157 mg, 61%). UV-vis (toluene) λ_{max}, nm (log ε): 675 (5.4). NMR (CDCl₃): δ 9.63 (m, 1,4-Pc H), 8.32 (m, 2,3-Pc H), -1.28 (t, CH₂CH₃), -2.51 (q, CH₂CH₃), -6.40 (s, SiCH₃). **Pc 311** is a purple solid. It is soluble in CH₂Cl₂, dimethylformamide and toluene, and insoluble in hexanes.

SiNc(CH₃)Cl, **Nc 1** (Nc represents a naphthalocyanine macrocycle). A mixture of SiCH₃Cl₃ (1.2 mL), 1,3-diiminobenz(*f*)isoquinoline (2.24g) and dry quinolone (35 mL) was heated (185 °C) for 60 min, refluxed for 75 min, and filtered. The solid was washed (CH₃OH, pyridine, CH₃OH), vacuum dried 80 °C and weighed (1.56 g, 69%). IR (Nujol, cm⁻¹): 1377 (s), 1370 (s), 1343 (s), 1255 (w, Si-CH₃), 1081 (s), 1014 (w), 886 (m), 756 (s), 723 (m), 468 (m, Si-Cl). The product is green-brown. It is insoluble in common organic solvents.

SiNc(CH₃)(OH), **Nc 2**. A mixture of **Nc 1** (529 mg) and concentrated H₂SO₄ (10 mL) was stirred for 2.6 h, poured onto ice (70 g) and filtered. The solid was washed (H₂O, 3N NH₄OH), air dried and combined with a solution of 3N NH₄OH and pyridine (3:35). The suspension formed was refluxed for 1 h and filtered. The solid was washed (pyridine, CH₃OH), vacuum dried (~80 °C) and weighed (479 mg, 93%). IR (mineral oil, cm⁻¹): 3440 (w br, O-H), 1377 (s), 1370 (s), 1349 (m), 1341 (m), 1253 (w, Si-CH₃), 1089 (s), 1079 (s), 1042 (s), 884 (m), 802 (m, Si-OH), 757 (m), 721 (m). The product is dark green. It is insoluble in common organic solvents.

SiNc[CH₃][OSi((CH₂)₅CH₃)₃], **Nc 3**. A mixture of **Nc 2** (389 mg), tri-*n*-hexylchlorosilane (2.0 mL), tri-*n*-butylamine (2.0 mL) and dry pyridine (30 mL) was refluxed for 2.6 h, filtered while hot, vacuum concentrated (~60°C), diluted with CH₃OH (30mL) and filtered. The solid was washed (CH₃OH, pentane), vacuum dried (~80°C) and weighed (404 mg, 76%). Some of the solid (171 mg) was

recrystallized (toluene), washed (CH₃OH), vacuum dried (~90°C), and weighed (118 mg, 69%). Mp (°C) 239; IR (Nujol, cm⁻¹) 1376 (s), 1370 (s), 1349 (s), 1341 (s), 1254 (w, Si-CH₃), 1082 (s), 1041 (m), 1026 (m, Si-O-Si), 1016 (m), 802 (m, Si-OH), 761 (s), 721 (m); NMR (C₆D₆): δ 10.19 (s, 5,36-NcH), 8.34 (m, 1,4- NcH), 7.59 (m, 2,3-NcH), 0.73 (m, ε-CH₂), 0.48 (t, *t*-CH₂), 0.40 (m, γ, δ-CH₂), -0.65 (m, β-CH₂), -1.76 (m, α-CH₂), -4.89 (s, SiNc-CH₃). Anal Calcd for C₆₇H₆₆N₈Si₂O: C, 76.24; H 6.30; Si, 5.32. Found: C, 76.26; H, 6.26; Si, 5.40. The compound is bright blue-green. It is soluble in toluene, benzene, and CHCl₃, and insoluble in CH₃OH and hexanes.

SiNc[OH][OSi((CH₂)₅CH₃)₃], **Nc 4**. A cooled (0 °C) mixture of **Nc 3** (593 mg) and toluene (750 mL) was stirred in direct sunlight for 1.5 h. The solution was filtered and the filtrate was evaporated to dryness by rotary evaporation (~60 °C), vacuum dried (~90°C) and weighed (84 mg, 40%). Some of the solid (209 mg) was recrystallized (toluene), vacuum dried (~90°C) and weighed (84 mg, 40%). Mp (°C) ~370; IR (Nujol) 3440 (w br, O-H), 1378 (s), 1366 (s), 1353 (s), 1342 (m), 1096 (s), 1079 (s), 1041 (m), 1036 (m, Si-O-Si), 1015 (m), 760 (m), 723 (m). NMR (C₆D₅CD₃, 91 °C): δ 9.22 (s, 5,36-NcH), 8.17 (m, 1,4- NcH), 7.74 (m, 2,3-NcH), 0.43 (m, ε-CH₂), 0.24 (t, *t*-CH₂), 0.00 (m, γ, δ-CH₂), -0.95 (m, β-CH₂), -2.01 (m, α-CH₂); Anal Calcd for C₆₆H₆₄N₈SiO₂: C, 74.97; H, 6.10; Si, 5.31. Found: C, 74.54; H, 5.88; Si, 5.63. The compound is blue-green. It is slightly soluble in toluene and CHCl₃, and insoluble in CH₃OH.

Computations. The geometry optimization of the model species used in the computations was carried out with the Gaussian 09 package.²¹ All optimized stationary points were confirmed to be energy minima on the corresponding potential energy surfaces through vibrational frequency analyses (i.e., by verifying the lack of imaginary frequencies). The spin-restricted method was used for the singlet states and the spin-unrestricted method was used for the doublet states, i.e., the open-shell systems.

Results and Discussion

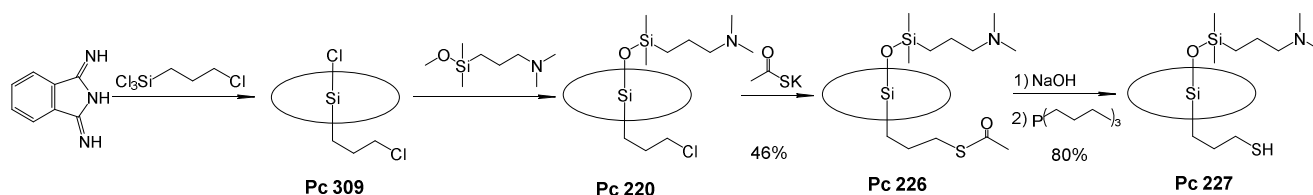
Syntheses. The **Pc 309** synthesized, Scheme 1, was very impure. This prohibited giving a meaningful yield of it. No way was found to improve its yield. The low yield of **Pc 309** was the primary cause of the low overall yield of **Pc 227**.

The fourth step in the synthesis of **Pc 227**, the NaOH-thioacetate hydrolysis step, produced a reaction mixture containing both **Pc 227** and its disulfide oxidation dimer, **Pc 228**, even when care was taken to exclude air. This led to the use of tributylphosphine in the last step.

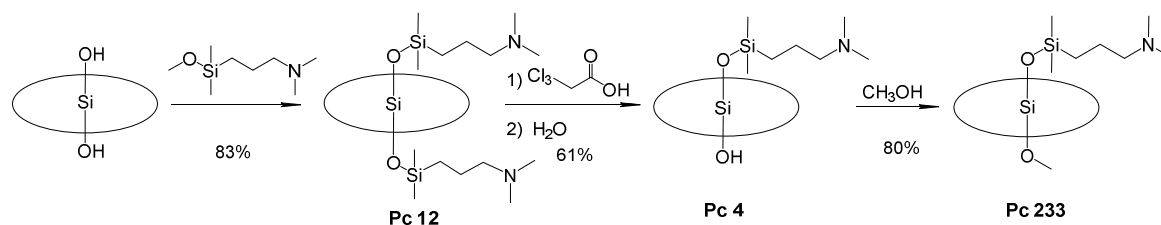
The synthesis used for **Pc 4** via **Pc 12**, Scheme 2, has been described earlier in the patent literature.²² The similarity of the synthesis of the pair of compounds SiPc(CH₃)[OSi(CH₂CH₃)₃], **Pc 311**, and

$\text{SiNc}(\text{CH}_3)[\text{OSi}(\text{CH}_2)_5\text{CH}_3]_3$, **Nc 3**, Schemes 3 and 4, illustrates again the close (but not identical) relationship between corresponding pairs of silicon phthalocyanines and naphthalocyanines.

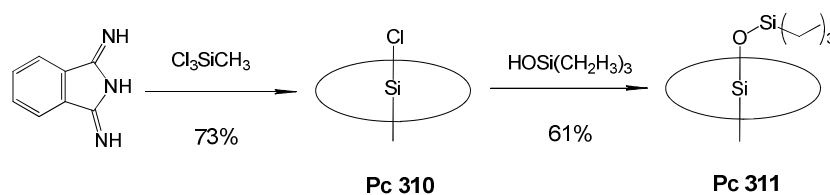
Scheme 1. The synthesis of **Pc 220**, **Pc 226** and **Pc 227**



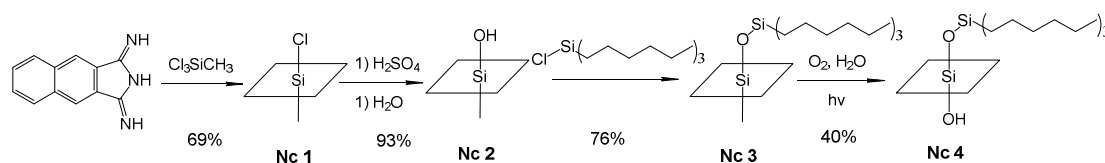
Scheme 2. The synthesis of **Pc 12**, **Pc 4** and **Pc 233**



Scheme 3. The synthesis of **Pc 310** and **Pc 311**



Scheme 4. The synthesis of **Nc 1**, **Nc 2**, **Nc 3** and **Nc 4**



NMR Spectra. As expected, the NMR spectra of **Pc 227** and **Pc 233** in CDCl_3 show large ring-current effects, Figure 2. The resonance at ~ 6 ppm in the spectrum of **Pc 227** and its absence in that of **Pc 233** provides unambiguous evidence for the presence of an $\text{Si}_{\text{Pc}}\text{-C}$ bond in **Pc 227**.

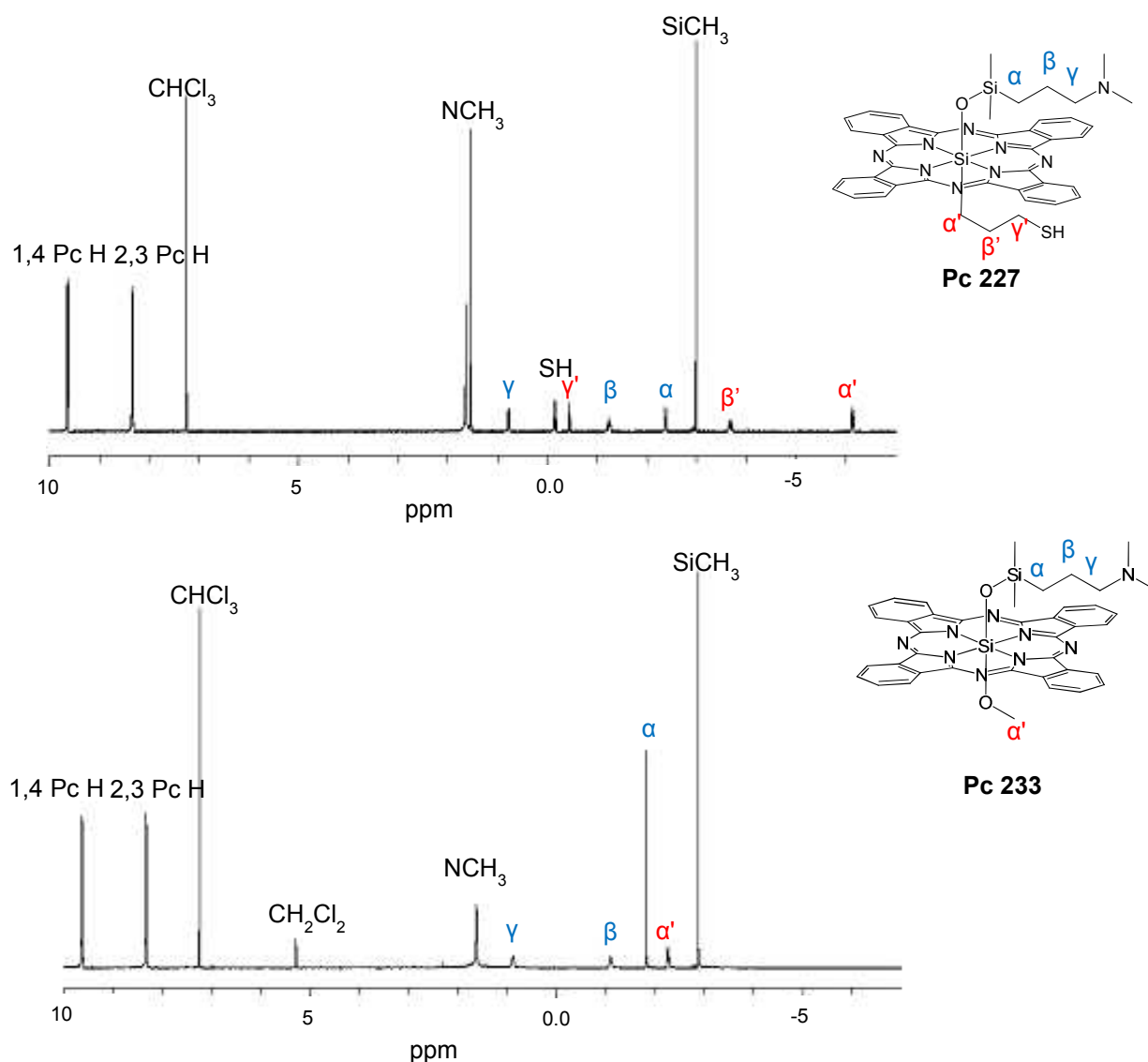


Figure 2. The NMR spectra of **Pc 227** and **Pc 233**.

Bond Dissociation Energy of the Si-C bond in $\text{SiPc}(\text{OH})(\text{CH}_3)$, Model 1. The bond dissociation energy (BDE) of the $\text{Si}_{\text{Pc}}\text{-C}$ bond in $\text{SiPc}(\text{OH})(\text{CH}_3)$, **Model 1**, was determined using the B3LYP and BP86 density functionals at the DFT/6-31G(d) level. BP86 is a generalized gradient approximation

(GGA) method²³⁻²⁴ and B3LYP is a hybrid GGA with 20% exact exchange.²⁵⁻²⁶ Values for both heterolytic cleavage of the bond to SiPc⁺ and L⁻ and homolytic cleavage of it to SiPc•, and L• were determined, Table 1. As is seen, the values given by the two functionals are quite similar.

Table 1. The BDEs of the SiPc-C and SiPc-O Bonds in **Model 1**, SiPc(OH)(CH₃) (kcal/mol)

	bond	cleavage	E ₁ ¹	ZPE ²	E ₂ ³
B3LYP	SiPc-C	hetero	187	-5	182
		homo	42	-5	37
	SiPc-O	hetero	196	-3	193
		homo	79	-4	75
BP86	SiPc-C	hetero	190	-5	185
		homo	45	-5	40
	SiPc-O	hetero	199	-3	196
		homo	84	-4	79

¹E₁, electronic energy. ²ZPE, zero-point correction. ³E₂, sum of E₁ and ZPE.

The BDEs for heterolytic cleavage of the SiPc-C bond are high as expected, but those for its homolytic cleavage are ~50 kcal/mol lower than those that are typical for this bond, ~90 kcal/mol.²⁷ This is attributed to delocalization of the unpaired electron of the phthalocyanine π radical generated by the homolysis of the bond and the consequent stability of it.

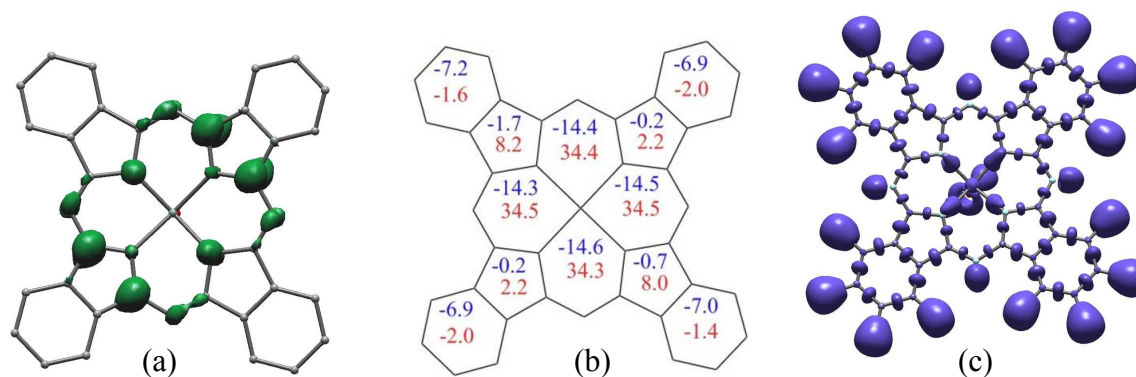
NBO Charges of Models 1 and 2. A NBO analysis of the charge distribution of **Model 1**, SiPc(OH)(CH₃), and **Model 2**, SiPc(OH)•, was carried out with NBO version 3²⁸ implemented in Gaussian 09 with at the B3LYP/6-31G(d) level. Only the B3LYP functional was used in this work since both it and the BP86 functional gave similar BDE values.

The NBO data show that the negative charge on the phthalocyanine ring is considerably larger in the case of **Model 2** than **Model 1**, Table 2 and Figure 3. This result is consistent with the presence of a delocalized electron in the ring of **Model 2**. Support for the postulated presence of a delocalized electron in the SiPc• π radical is found in an earlier EPR study of the photolysis of silicon porphyrins in which a species was found which under Ar retained 95% of its signal intensity after 1 day and 86% after 50 days.²⁹

Spin Densities of Model 2. The spin densities for **Model 2** are given in Figure 3a. The results indicate that the unpaired electron of this model is delocalized largely over its inner 16-membered ring.

Table 2. The NBO Charges in **Model 1**, SiPc(OH)(CH₃), and **Model 2**, SiPc(OH)•

	Si	Me	Pc	OH
model 1	2.20	-0.49	-1.09	-0.62
model 2	2.32	0.00	-1.73	-0.60

**Figure 3.** The (a) spin density distribution in **Model 2** (isovalue = 0.004), (b) NICS shifts in **Model 1** (blue) and **Model 2** (red), and (c) ELF domains in **Model 2**, ($f = 0.84$).

NICS Shifts in Models 1 and 2. Nucleus-independent chemical shifts (NICS)³⁰⁻³¹ of **Model 1** SiPc(OH)(CH₃), and **Model 2**, SiPc(OH)•, were determined with the gauge independent atomic orbital (GIAO) method³² at the B3LYP/6-311+G(2d,p) level with geometries optimized at the B3LYP/6-31G(d) level. The negative sign of all the NICS values in **Model 1** are consistent with the ring-current effects observed in the NMR spectra of **Pc 227** and **Pc 309**, Figure 2. The negative sign of the values for the benzo rings and the positive sign of the values for the inner, nonbenzo rings of **Model 2** indicate that its benzo rings are aromatic and its nonbenzo rings are antiaromatic. This is consistent with the conclusion that the number of electrons in the macrocycle of **Model 2** is odd.³³⁻³⁴

The fact that the NICS values for the inner nonbenzo rings of **Model 2** become more positive relative to those of the benzo rings (when compared to **Model 1**), can be rationalized by noting that the spin density distribution results indicate that the unpaired electron is delocalized largely over the inner rings.

ELF Domains in Model 2. Spatial grids of the electron localization function (ELF) domains of **Model 2** were generated with Checkden³⁵ and a topological analysis of its ELF basins was conducted with Topmod³⁶ both with a wave function generated at the B3LYP/6-31G(d) level, Figure 3c (ELF is a function which gives a quantitative Lewis description of a molecule). The results reveal the ELF domains expected for the bonding and lone-pair electrons. No nonbonding localization domain is shown near the central silicon as would be expected if the unpaired electron were localized on it. Topological analysis of the ELF data shows a division of the molecular space into 117 basins with 42 being core, 5 monosynaptic and 70 disynaptic. These basins correspond to 42 non-hydrogen atom cores and 5 lone pairs (4 aza-nitrogen pairs and 1 oxygen pair), and 70 bonds (32 C-C bonds, 16 C-H bonds 16 C-N bonds, 4 Si-C bonds, 1 O-H bond and 1 Si-O bond). No ELF attractor corresponding to a localized unpaired electron near the silicon is evident. This is consonant with the delocalization of the unpaired electron over the macrocycle.³³⁻³⁴

Si-O Bond Dissociation Energies for Model 1. Calculated Si_{Pc}-O BDEs of **Model 1** were determined in the same way as those for its Si_{Pc}-C BDEs, Table 1. The calculated BDEs for the heterolytic cleavage of the Si_{Pc}-O bond are high. Those for the homolytic cleavage of it are about ~50 kcal/mol lower than those typical for the homolytic cleavage of such bonds, ~125 kcal/mol.²⁷ While substantial, this reduction is not enough to lead to homolytic cleavage of the Si_{Pc}-O bond by red light or by ambient temperatures, and it is this that allows the selective cleavage of the Si_{Pc}-C bond by red light in the presence of the Si_{Pc}-O bond.

Irradiation of Nc 3 with Red Light. The irradiation of a toluene solution of SiNc(CH₃)[OSi(C₆H₁₃)₃], **Nc 3**, over a period of two days with sunlight from which wavelengths shorter than 660 nm had been filtered did not alter its NMR spectrum. This shows that the Si_{Nc}-C bond, in contrast with the Si_{Pc}-C bond, resists photolysis by red light. This is as expected since the Q-band of silicon naphthalocyanines is at ~775 nm,³⁷ and light of this wavelength probably cannot provide enough energy to homolytically cleave the Si_{Nc}-C bond. (The irradiation of a toluene solution of **Nc 3** with unfiltered sunlight gave **Nc 4**, Scheme 4. The photolytic sensitivity of **Nc 3** under these conditions is attributable to absorption of more energetic light by its Soret band.)

Essential Elements in the Selective Photolysis of Alkylsiloxysilicon Phthalocyanines by Red Light. The essential elements making possible the selective photolysis of the Si_{Pc}-C bond of alkyl-alkylsiloxysilicon phthalocyanines such as **Pc 227** by red light are: (1) a Q-band absorption near 670 nm, (2) an Si_{Pc}-C bond which is weak as a result of the Si being embedded in the macrocycle, and (3) an

Si_{Pc}-O bond which is still relatively strong (although its Si is thus embedded). These elements probably can also be found in alkylsilicon phthalocyanines with *trans* alkoxy or aryloxy ligands instead of siloxy ligands, i.e., RSiPcOR or RSiPcOAr. However, they cannot be expected in alkyl-alkylsiloxysilicon tetrapyrroles as a whole because most do not have strong red absorptions.

Applications of the Photolytic Sensitivity of the Si_{Pc}-C Bond to Red Light. The selective cleavage of the Si_{Pc}-C bond has already proven useful for the preparation of **Pc 4** from **Pc 3**, SiPc[CH₃][OSi(CH₂)₃N(CH₃)₂],³ of **Pc 233** (the methoxy analogue of **Pc 4**¹⁹) from **Pc 227** and of other silicon phthalocyanines.³⁸⁻³⁹ These results make it apparent that a variety of target compounds can be prepared by treating **Pc 227** and other alkyl-alkylsiloxysilicon phthalocyanines with red light in the presence of nucleophiles, Figure 4. This approach probably can be further extended to some ring-substituted alkyl-alkylsiloxysilicon phthalocyanines, and thus offers considerable flexibility.

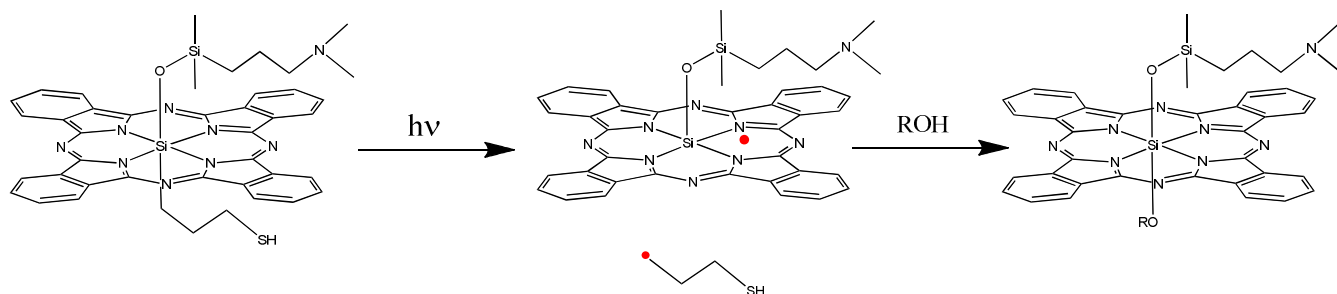


Figure 4. Selective cleavage of the Si_{Pc}-C bond and formation of the Si_{Pc}-O bond in the presence of nucleophiles.

A possible use of the selective photolytic cleavage of the Si_{Pc}-C bond is the intravenous release in biological systems of silicon phthalocyanine drugs from prodrug silicon phthalocyanine-nanoparticle conjugates by irradiation with red light.¹⁹⁻²⁰ Since this approach does not use blue or ultraviolet light, it is suited to systems in which hemoglobin is present. Precedent for the use of prodrugs which can be photocleaved is found in the work of Rotello et. al..⁴⁰⁻⁴² Another possible use of the selective photolytic cleavage of the Si_{Pc}-C bond is the topical release of silicon phthalocyanine drugs from prodrug nonconjugated alkyl-alkylsiloxysilicon phthalocyanines.²⁰

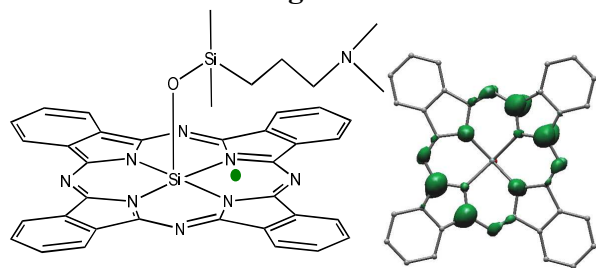
Summary and Conclusions

The compounds SiPc[(CH₂)₃SH][OSi(CH₃)₂(CH₂)₃N(CH₃)₂], **Pc 227**, and SiNc[CH₃][OSi((CH₂)₅CH₃)₃], **Nc 3**, have been prepared, purified and characterized. The Si_{Pc}-C bond

in **Pc 227** is photolyzed by red light when the compound is in solution, while the Si_{Nc}-C bond of **Nc 3** is not. Calculations on the model compound SiPc(CH₃)(OH), **Model 1**, and π radical SiPcOH•, **Model 2**, show that the homolytic bond dissociation energy of the Si_{Pc}-C bond of **Model 1** is reduced from the value typical for an ordinary Si-C bond by about 50 kcal/mol. This reduction is due in large part to a delocalization of the unpaired electron of an intermediate silicon phthalocyanine π radical, SiPc[OSi(CH₃)₂(CH₂)₃N(CH₃)₂]•, in the reaction pathway. While the lowering of the bond energy of the Si_{Pc}-C bond leads to its photochemical instability it is insufficient to cause to its thermal instability at ambient temperatures. The lowered bond energy of the Si_{Pc}-C bond makes a variety of photochemically labile but chemically and thermally stable synthetic intermediates accessible. It also makes possible intravenous silicon phthalocyanine-nanoparticle conjugate prodrugs that can be activated by low-energy visible light. This light does not cause the deleterious side effects that blue light or ultraviolet light can. The lowered bond energy also makes possible topical nonconjugated silicon phthalocyanine prodrugs that can be activated by red light. The Si_{Nc}-C bond of **Nc 3** is not photolyzed by red light because the Q-band of silicon naphthalocyanines is shifted by about 100 nm to the red relative to the band of phthalocyanines, and the energy of the light absorbed by this band is insufficient to cause homolytic cleavage of the Si_{Nc}-C bond.

Acknowledgments. Professor Clemens Burda and Dr. Tennyson L. Doane are thanked for helpful conversations. This work was supported in part by allocations of computing resources from the Case High Performance Computing System and the Ohio Supercomputer Center.

Table of Contents Figure and Text



The photolysis yields the extensively studied photodynamic therapy drug **Pc 4**. The pathway is a homolysis involving a phthalocyanine π radical and low bond dissociation energy.

References

- 1 J. N. Esposito, J. E. Lloyd and M. E. Kenney, The Synthesis and Physical Properties of Some Organo- and Organosiloxysilicon Phthalocyanines, *Inorg. Chem.*, 1966, **5**, 1979-1984.
- 2 CAS Registry Number: 135719-28-7. Silicon, [[3-(dimethylamino)propyl]dimethylsilanolato- κO]hydroxy[29H,31H-phthalocyaninato(2-)- $\kappa N^{29}, \kappa N^{30}, \kappa N^{31}, \kappa N^{32}$]-, (OC-6-23)- (9CI).
- 3 N. L. Oleinick, A. R. Antunez, M. E. Clay, B. D. Richter and M. E. Kenney, New Phthalocyanine Photosensitizers for Photodynamic Therapy, *Photochem. Photobiol.*, 1993, **57**, 242-247.
- 4 E. BenHur, M. M. Zuk, M. E. Kenney, N. L. Oleinick and J. Mulvihill, Action Spectra (660-700 nm) for Virus Inactivation and Red Cell Damage Photosensitized by the Silicon Phthalocyanine Pc 4, *Lasers Med. Sci.*, 1996, **11**, 221-225.
- 5 V. C. Colussi, D. K. Feyes, J. W. Mulvihill, Y. S. Li, M. E. Kenney, C. A. Elmets, N. L. Oleinick and H. Mukhtar, Phthalocyanine 4 (Pc 4) Photodynamic Therapy of Human OVCAR-3 Tumor Xenografts, *Photochem. Photobiol.*, 1999, **69**, 236-241.
- 6 M. E. Kenney, Y. S. Li, N. L. Oleinick, H. Mukhtar and M. A. J. Rodgers, PDT Structure-Activity Study of Two Homologous Series of Compounds Related to Pc 4, *Photochem. Photobiol.*, 1999, **69**, 38S-38S.
- 7 R. L. Morris, M. E. Varnes, M. E. Kenney, Y. S. Li, K. Azizuddin, M. W. McEnery and N. L. Oleinick, The Peripheral Benzodiazepine Receptor in Photodynamic Therapy with the Phthalocyanine Photosensitizer Pc 4, *Photochem. Photobiol.*, 2002, **75**, 652-661.
- 8 J. E. George, Y. Ahmad, D. Varghai, X. L. Li, J. Berlin, D. Jackowe, M. Jungermann, M. S. Wolfe, L. Lilge, A. Totonchi, R. L. Morris, A. Peterson, W. D. Lust, M. E. Kenney, C. L. Hoppel, J. Y. Sun, N. L. Oleinick and D. Dean, Pc 4 Photodynamic Therapy of U87-Derived Human Glioma in the Nude Rat, *Lasers Surg. Med.*, 2005, **36**, 383-389.
- 9 J. D. Miller, E. D. Baron, H. Scull, A. Hsia, J. C. Berlin, T. McConnick, V. Colussi, M. E. Kenney, K. D. Cooper and N. L. Oleinick, Photodynamic Therapy with the Phthalocyanine Photosensitizer Pc 4: The Case Experience with Preclinical Mechanistic and Early Clinical-Translational Studies, *Toxicol. Appl. Pharmacol.*, 2007, **224**, 290-299.
- 10 K. K.-H. Wang, J. D. Wilson, M. E. Kenney, S. Mitra and T. H. Foster, Irradiation-Induced Enhancement of Pc 4 Fluorescence and Changes in Light Scattering Are Potential Dosimeters for Pc 4-PDT, *Photochem. Photobiol.*, 2007, **83**, 1056-1062.
- 11 T. H. Foster, B. R. Giesselman, R. Hu, M. E. Kenney and S. Mitra, Intratumor Administration of the Photosensitizer Pc 4 Affords Photodynamic Therapy Efficacy and Selectivity at Short Drug-Light Intervals, *Transl. Oncol.*, 2010, **3**, 135-141.
- 12 A. M. Master, M. E. Rodriguez, M. E. Kenney, N. L. Oleinick and A. Sen Gupta, Delivery of the Photosensitizer Pc 4 in PEG-PCL Micelles for in Vitro PDT Studies, *J. Pharm. Sci.*, 2010, **99**, 2386-2398.
- 13 M. E. Rodriguez, J. Kim, G. B. D. Santos, K. Azizuddin, J. Berlin, V. E. Anderson, M. E. Kenney and N. L. Oleinick, Binding to and Photo-Oxidation of Cardiolipin by the Phthalocyanine Photosensitizer Pc 4, *J. Biomed. Opt.*, 2010, **15**, 051604.
- 14 M. Lam, A. H. Hsia, Y. Liu, M. Guo, A. R. Swick, J. C. Berlin, T. S. McCormick, M. E. Kenney, N. L. Oleinick, K. D. Cooper and E. D. Baron, Successful Cutaneous Delivery of the Photosensitizer Silicon Phthalocyanine 4 for Photodynamic Therapy, *Clin. Exp. Dermatol.*, 2011, **36**, 645-651.

- 15 M. D. Maree, T. Nyokong, K. Suhling and D. Phillips, Effects of Axial Ligands on the Photophysical Properties of Silicon Octaphenoxypthalocyanine, *J. Porphyrins Phthalocyanines*, 2002, **6**, 373-376.
- 16 M. Durmus and T. Nyokong, Synthesis, Photophysical and Photochemical Studies of New Water-Soluble Indium(III) Phthalocyanines, *Photochem. Photobiol. Sci.*, 2007, **6**, 659-668.
- 17 N. Masilela, E. Antunes and T. Nyokong, Axial Coordination of Zinc and Silicon Phthalocyanines to Silver and Gold Nanoparticles: An Investigation of Their Photophysicochemical and Antimicrobial Behavior, *J. Porphyrins Phthalocyanines*, 2013, **17**, 417-430.
- 18 Z. Iqbal, N. Masilela, T. Nyokong, A. Lyubimtsev, M. Hanack and T. Ziegler, Spectral, Photophysical and Photochemical Properties of Tetra- and Octaglycosylated Zinc Phthalocyanines, *Photochem. Photobiol. Sci.*, 2012, **11**, 679-686.
- 19 Y. Cheng, T. L. Doane, C.-H. Chuang, A. Ziady and C. Burda, Near Infrared Light-Triggered Drug Generation and Release from Gold Nanoparticle Carriers for Photodynamic Therapy, *Small*, 2014, **10**, 1799-1804.
- 20 J. Li, Silicon Phthalocyanines for Photodynamic Therapy Studies, Ph.D. Dissertation, Case Western Reserve University, Cleveland, 2008.
- 21 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, Gaussian 09, Revision A.02, Gaussian, Inc., Wallingford, CT, USA, 2009.
- 22 Y. S. Li and M. E. Kenney, Novel Methods of Syntheses of Phthalocyanine Compounds, U.S. Patent 5,763,602, 1998.
- 23 J. P. Perdew, Density Functional Approximation for the Correlation Energy of the Inhomogeneous Electron Gas, *Phys. Rev. B*, 1986, **33**, 8822-8824.
- 24 A. D. Becke, Density Functional Exchange Energy Approximation with Correct Asymptotic Behavior, *Phys. Rev. A*, 1988, **38**, 3098-3100.
- 25 C. Lee, W. Yang and R. G. Parr, Development of the Colle-Salvetti Correlation-Energy Formula into a Functional of the Electron Density, *Phys. Rev. B*, 1988, **37**, 785-789.
- 26 A. D. Becke, Density Functional Thermochemistry. III. The Role of Exact Exchange, *J. Chem. Phys.*, 1993, **98**, 5648-5652.
- 27 R. Walsh, Bond Dissociation Energy Values in Silicon-Containing Compounds and Some of Their Implications, *Acc. Chem. Res.*, 1981, **14**, 246-252.
- 28 E. D. Glendening, A. E. Reed, J. E. Carpenter and F. Weinhold, *NBO, version 3.1*.
- 29 J.-Y. Zheng, K. Konishi and T. Aida, A Photoresponsive Silicon Radical within a Porphyrin π -Cloud: Photolysis of Organo- and Nitroxysilicon Porphyrins with Visible Light, *J. Am. Chem. Soc.*, 1998, **120**, 9838-9843.
- 30 P. V. Schleyer, C. Maerker, A. Dransfeld, H. J. Jiao and N. Hommes, Nucleus-Independent Chemical Shifts: A Simple and Efficient Aromaticity Probe, *J. Am. Chem. Soc.*, 1996, **118**, 6317-6318.

- 31 Z. F. Chen, C. S. Wannere, C. Corminboeuf, R. Puchta and P. V. Schleyer, Nucleus-Independent Chemical Shifts (NICS) as an Aromaticity Criterion, *Chem. Rev.*, 2005, **105**, 3842-3888.
- 32 J. R. Cheeseman, G. W. Trucks, T. A. Keith and M. J. Frisch, A Comparison of Models for Calculating Nuclear Magnetic Resonance Shielding Tensors, *J. Chem. Phys.*, 1996, **104**, 5497-5509.
- 33 Y. Yang, Electron Localization in Nonplanar Conjugated Macrocycles: Failure of Electron Buffers to Delocalize Electrons, *Chem. Phys. Lett.*, 2011, **516**, 268-271.
- 34 Y. Yang, Pyrrolic Macrocycles with Stabilized Triplet States: Metal-Centered and Ligand-Centered Separation of Unpaired Electrons, *Polyhedron*, 2012, **42**, 249-257.
- 35 L. F. Pacios and A. Fernandez, CheckDen, A Program to Compute Quantum Molecular Properties on Spatial Grids, *J. Mol. Graphics Modell.*, 2009, **28**, 102-112.
- 36 S. Noury, X. Krokidis, F. Fuster and B. Silvi, Computational Tools for the Electron Localization Function Topological Analysis, *Comput. Chem.*, 1999, **23**, 597-604.
- 37 J. R. Sounik, Synthesis and Characterization of Group IV Naphthalocyanines, Ph.D. Dissertation, Case Western Reserve University, Cleveland, 1988.
- 38 D. W. DeWulf, J. K. Leland, B. L. Wheeler, A. J. Bard, D. A. Batzel, D. R. Dininny and M. Kenney, Isolation, Spectroscopic Properties, and Electrochemical Properties of Two Oligomeric Silicon Phthalocyanines, *Inorg. Chem.*, 1987, **26**, 266-270.
- 39 X.-J. Zhao, S. Lustigman, M. E. Kenney and E. Ben-Hur, Structure-Activity and Mechanism Studies on Silicon Phthalocyanines with Plasmodium Falciparum in the Dark and Under Red Light, *Photochem. Photobiol.*, 1997, **66**, 282-287.
- 40 G. Y. Tonga, K. Saha and V. M. Rotello, 25th Anniversary Article: Interfacing Nanoparticles and Biology: New Strategies for Biomedicine, *Adv. Mater.*, 2014, **26**, 359-370.
- 41 B. Duncan, C. Kim and V. M. Rotello, Gold Nanoparticle Platforms as Drug and Biomacromolecule Delivery Systems, *J. Control. Release*, 2010, **148**, 122-127.
- 42 S. S. Agasti, A. Chomposor, C.-C. You, P. Ghosh, C. K. Kim and V. M. Rotello, Photoregulated Release of Caged Anticancer Drugs from Gold Nanoparticles, *J. Am. Chem. Soc.*, 2009, **131**, 5728-5729.