Fluorinated Phthalocyanines

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Design, Synthesis, and Spectroscopic Investigation of Zinc Dodecakis(trifluoroethoxy)-phthalocyanines Conjugated with Deoxyribonucleosides**

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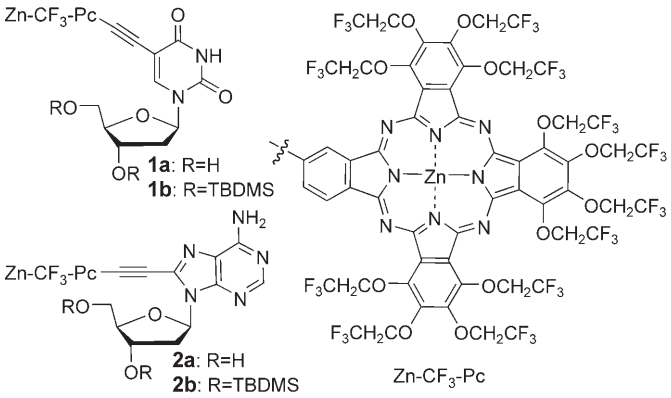
The design and synthesis of an efficient drug carrier that facilitates drug delivery has become a major challenge in drug development, especially for cancer treatment.[1] Among the novel carriers, such as liposome aerosol and fullerene, designed to interact with the tumor cell at specific sites,[2] we are interested in the dyes porphyrins and phthalocyanines.[3] Both are under intensive study in the modern photodynamic therapy (PDT) for cancer.[4] It is well known that these dyes accumulate in the tumor cells and cause localized cellular damage on excitation by visible light; as a result, they act as efficient drug carriers and photoinitiated cancer drugs. A particularly attractive target for such a purpose is phthalocyanines.[5] Although the main absorption of porphyrins is around 400 nm, phthalocyanines display an intense absorption at 600–700 nm. This is particularly favorable because the dyes should be effectively activated by available red light at 630 nm in PDT. Another benefit of phthalocyanines is that the lipophilicity, hydrophilicity, and self-aggregation properties can be biased by altering the substituents on the periphery of the phthalocyanine core. As part of our ongoing research programs directed to the development of a new methodology leading to functionalized phthalocyanines[6] and the synthesis of fluorine-containing biologically active compounds,[7] we describe herein the design, synthesis, and spectroscopic investigations of fluorine-containing phthalocyanine–deoxyribonucleoside conjugates **1** and **2** towards PDT agents. The twelve peripheral trifluoroethoxy substitutions in the phthalocyanine side chains improve the properties of phthalocyanines as phototherapeutic agents such that they have no aggregation properties, higher lipophilicity, a strong absorption band at long wavelength, and acceptable photosensitivity. The nucleoside appendage at one of the benzene units of **1** and **2** would play a key role in binding at the DNA recognition site, which assists radical-induced selective cleavage of the DNA strand in the tumor cell under irradiation.

The structures of the target conjugates, zinc dodecakis-(trifluoroethoxy)phthalocyanines/ethynyluridine (Zn-CF_3-Pc-U, **1**) and zinc dodecakis(trifluoroethoxy)phthalocyanines/ethynyladenosine (Zn-CF_3-Pc-Ad, **2**), are shown in Scheme 1. In addition to the highly specific reasons to make



Scheme 1. Structures of zinc dodecakis(trifluoroethoxy)-phthalocyanines conjugated with deoxyribonucleosides **1** and **2**. TBDMS = *tert*-butyldimethylsilyl.

use of trifluoromethylated functional groups in medicinal chemistry,[8] the fluorinated conjugates would be promising reporter molecules in vivo based on an ^{19}F NMR technique. Although unique properties of per(trifluoroethoxy)phthalocyanines have been revealed,[9] no example of per(trifluoroethoxy)phthalocyanines conjugated with biomolecules has been reported. We therefore considered the introduction of a nucleoside to per(trifluoroethoxy)phthalocyanines. The nucleoside moieties should enhance water solubility and potentially improve the sensitivity towards tumor cells. As tumor cells generally divide faster than normal cells, they require more of the nucleosides. Therefore, the nucleosides conjugated with phthalocyanines would be good substrates for nucleoside transporter proteins responsible for the uptake of natural nucleosides,[10] and they could likely be taken into tumor cells. A deoxyribonucleoside unit is connected with the phthalocyanine ring by an ethynyl linker because 1) ethynylpurine and pyrimidine nucleosides, in particular those tethering the ethynyl moiety to the C8 position in purine nucleosides and the C6 position in pyrimidine nucleosides, are of great interest in view of their potential biological activities,[11] and 2) an ethynyl rigid-rod system would represent a useful way to strengthen the fluorophore properties of phthalocyanines.[12] Moreover, the short spacer length between a nucleoside and a phthalocyanine may be favorable due to the site-selective scission in a DNA strand. Several examples of phthalocyanines conjugated with biomolecules including nucleobases have been reported.[13] Many examples of porphyrin–nucleoside conjugates are also known.[14] However, the phthalocyanines directly conjugated with nucleic acids were rare until we started this chemistry one year ago.[15] It should be pointed out that, in 2006, Sessler et al. reported

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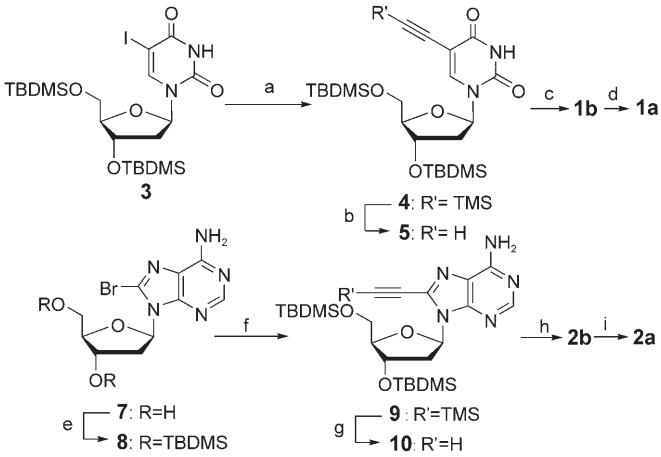
the synthesis of a cytidine-tethered non-fluorinated phthalocyanine under a different concept.[16] This report prompted us to disclose our studies concerning this class of compounds.

The synthesis of Zn-CF_3-Pc-U **1** was accomplished by the use of two palladium-catalyzed Sonogashira cross-couplings of iodides and terminal alkynes as key reactions (Scheme 2).



Scheme 2. a) Trimethylsilylacetylene, [Pd(PPh_3)$_2$$Cl_2$], CuI, Et_3N, THF, RT, 24 h, 94%; b) K_2CO_3, MeOH, RT, 0.5 h, 82%; c) Zinc 23-iodo-1,2,3,4,8,9,10,11,15,16,17,18-dodecakis(2,2,2-trifluoroethoxy)phthalocyaninate (**6**), [Pd(PPh_3)$_2$$Cl_2$], CuI, Et_3N, THF, RT, 36 h, 66%; d) TBAF, THF, 0°C–RT, 0.5 h, 48%; e) TBDMSCl, imidazole, DMF, RT, 24 h, 90%; f) Trimethylsilylacetylene, [Pd(PPh_3)$_2$$Cl_2$], CuI, Et_3N, THF, RT, 24 h, 85%; g) K_2CO_3, MeOH, RT, 0.5 h, 70%; h) **6**, [Pd(PPh_3)$_2$$Cl_2$], CuI, Et_3N, THF, RT, 36 h, 52%; i) TBAF, THF, 0°C–RT, 0.5 h, 64%. TBAF = tetrabutylammonium fluoride.

2′-Deoxy-3′,5′-bis(*O-tert*-butyldimethylsilyl)-5-iodouridine (**3**)[17] was first coupled with trimethylsilylacetylene under Sonogashira cross-coupling conditions ([Pd(PPh_3)$_2$$Cl_2$], CuI, Et_3N in THF) to furnish trisilylated 2′-deoxy-5-ethynyluridine **4** in 94% yield. The trimethylsilyl group on **4** was removed by using K_2CO_3 in MeOH to give 2′-deoxy-3′,5′-bis(*O-tert*-butyldimethylsilyl)-5-ethynyluridine (**5**) in 82% yield. The second Sonogashira coupling reaction was performed between zinc 23-iodo-1,2,3,4,8,9,10,11,15,16,17,18-dodecakis(2,2,2-trifluoroethoxy)phthalocyaninate (**6**)[9b] with terminal acetylene **5** to give TBDMS-protected Zn-CF_3-Pc-U **1b** in 66% yield. Finally, deprotection of all TBDMS groups on **1b** by using TBAF in THF gave Zn-CF_3-Pc-U **1a** in 48% yield as a blue solid.

The phthalocyanine–deoxyadenosine conjugate Zn-CF_3-Pc-Ad **2** was synthesized in a manner similar to that described for the synthesis of Zn-CF_3-Pc-U **1**. TBDMS protection of two hydroxy groups of 2′-deoxy-8-bromoadenosine **7**[18] was done with 2 equivalents of TBDMSCl in *N*,*N*-dimethylformamide (DMF) in the presence of imidazole to give 2′-deoxy-3′,5′-bis(*O-tert*-butyldimethylsilyl)-8-bromoadenosine **8**. This was coupled with trimethylsilylacetylene under Sonogashira coupling conditions to furnish TMS-protected 2′-deoxy-3′,5′-bis(*O-tert*-butyldimethylsilyl)-8-ethynyladenosine **9** in 85% yield, which was then deprotected in the presence of K_2CO_3 in MeOH to give 2′-deoxy-8-ethynyladenosine **10** in 70% yield. The second-round Sonogashira coupling between **10** and the unsymmetrical phthalocyanine **6** gave TBDMS-protected Zn-CF_3-Pc-Ad **2b**, which was then treated with TBAF in THF to give Zn-CF_3-Pc-Ad **2a** in good yield (Scheme 2).

The conjugates **1** and **2** were analyzed by ^{1}H and ^{19}F NMR spectroscopy, UV/Vis spectroscopy, and MALDI-TOF mass spectrometry (see the Supporting Information), clearly proving the expected structures. They have appreciable solubility in both polar and less-polar organic solvents presumably due to the unique character of twelve trifluoroethoxy substituents on the phthalocyanine macrocycle. It should be noted that both the ^{1}H and ^{19}F NMR spectra ([D_6]acetone) of the conjugates **1** and **2** showed extremely resolved, easily assignable signals in accordance with the proposed structures independent of the protective groups (see the Supporting Information). The high resolution in these spectra is indicative of a low degree of aggregation in the solution state. The results are noted because a structurally similar compound reported by Sessler et al. has a high tendency to self-aggregate as judged by UV/Vis spectroscopy.[16] It is quite obvious that the strong repulsion effect of the twelve peripheral trifluoroethoxy groups effectively reduces the chance of self-aggregation.

The UV/Vis spectra of the conjugates in a variety of solvents (acetone, dioxane, 20% CH_2Cl_2/toluene for **1b** and **2b**, acetone, dioxane, and DMF for **1a** and **2a**) with a concentration range of 1×10^{-5} M to 1×10^{-6} M suggest similar conclusions. All the conjugates are present mainly as monomers irrespective of the solvent and characterized by the sharp absorption bands in the B-band region (365 nm) and Q-band region (700 nm). As expected from the previous studies of per(trifluoroethoxy)phthalocyanines,[9] the conjugates display strong absorption bands appearing at longer wavelengths. Figure 1 shows the selected example of absorption

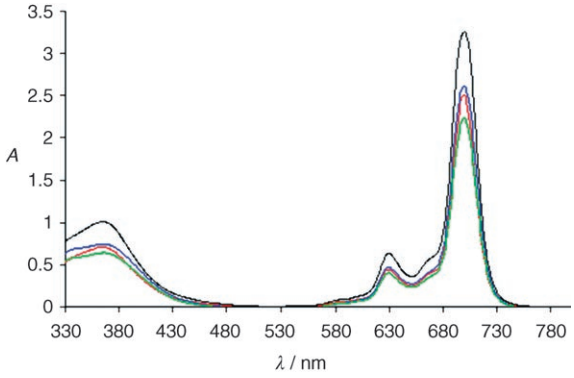


Figure 1. UV/Vis absorption spectra of **1a** (black), **1b** (red), **2a** (green), and **2b** (blue) in acetone (1×10^{-5} M).

spectra of the conjugates in acetone at 1×10^{-5} M, and similar behavior was also found in a variety of solvents at different concentrations (see the Supporting Information). Strong Q- and B-band absorptions at 700 (6.43), 700 (6.41), 700 (6.40), 700 (6.38) and 361 (5.93), 363 (5.90), 362 (5.91), 364 (5.90) for **1a**, **1b**, **2a** and **2b** are observed, respectively. Despite the unsymmetrical structure of **1** and **2**, the Q bands do not split at all, which is different from the observation by Sessler et al.

concerning the alkylated-phthalocyanine–cytidine hybrid.[16] A weak broad blue-shifted absorption centered at 639 nm indicates a cofacial aggregation of phthalocyanines. The strong fluorescence emission at 726 nm (quantum yield (Φ_f) = 0.43 for **1b** and 0.44 for **2b**) in toluene with 1% pyridine also suggests that these compounds are relatively free from aggregation.[19]

We should point out that the conjugate **1** is acceptably stable, but it is sensitive to strong light in CH_2Cl_2. After fluorescence spectroscopy had been recorded in CH_2Cl_2 at 680 nm (see the Supporting Information), conjugates **1b** and **2b** show completely different UV/Vis spectra (see Figure 2,

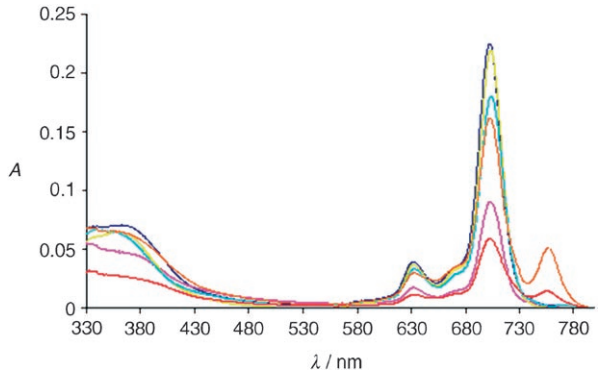


Figure 2. UV/Vis absorption spectra of **1b** in CH_2Cl_2 (blue, 1×10^{-6} M), **1b** in CH_2Cl_2 after fluorescence (orange, 1×10^{-6} M), **1b** in CH_2Cl_2 with pyridine after fluorescence (yellow, 1×10^{-6} M), **2b** in CH_2Cl_2 (pink, 1×10^{-6} M), **2b** in CH_2Cl_2 after fluorescence (red, 1×10^{-6} M), and **2b** in CH_2Cl_2 with pyridine after fluorescence (turquoise, 1×10^{-6} M).

blue versus orange lines and pink versus red lines). This can also be observed as a change in the solution color from green to yellowish green. These observations suggest that the conjugates quickly decompose through photocatalytic generation of highly reactive radicals and/or carbenes from CH_2Cl_2.[20] The decomposition was effectively suppressed by a drop of pyridine (yellow and turquoise lines), presumably through an axial coordination of pyridine with the zinc. To ascertain the sensitivity of **1b** and **2b**, time-dependent fluoresence spectra were recorded both in CH_2Cl_2 and dioxane (Figure 3). Immediate decreases in the fluorescence

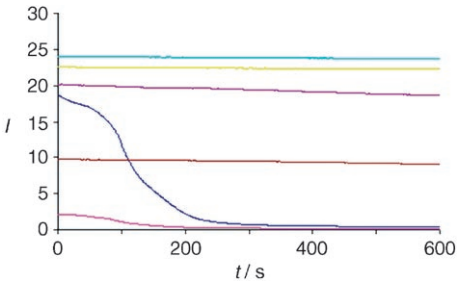


Figure 3. Time-dependent fluorescence spectra of **1b** at 708 nm in CH_2Cl_2 (blue, 1×10^{-6} M), **1b** in dioxane (yellow, 1×10^{-6} M), **1b** in CH_2Cl_2 with pyridine (violet, 1×10^{-6} M), **2b** in CH_2Cl_2 (pink, 1×10^{-6} M), **2b** in dioxane (turquoise, 1×10^{-6} M), and **2b** in CH_2Cl_2 with pyridine (brown, 1×10^{-6} M).

intensity of **1b** and **2b** within 200 s were monitored by fluorescence spectroscopy in CH_2Cl_2 (blue and pink lines). As expected, the decreases of fluorescence were inhibited in the presence of pyridine (violet and brown lines). No decomposition of **1b** and **2b** was observed in dioxane (yellow and turquoise lines). The results presented herein demonstrate that the peripheral twelve trifluoroethoxy groups of phthalocyanines clearly play an important role concerning the photosensitivity in solution state. The strong electron-withdrawing effect of the fluorine atoms enhances the stability of the phthalocyanine conjugates by lowering the energies of the highest occupied molecular orbitals (HOMOs). On the other hand, the sensitivity towards oxidation might be increased by the positive mesomeric effect of the peripheral trifluoroethoxy chains. A balance between an electron-withdrawing fluorine effect, trifluoroethoxy mesomeric effects, solvent effects, and the intrinsic lability of unsymmetrical phthalocyanines can be the main reason for the overall photosensitivity of the conjugates.

In conclusion, the design and synthesis of novel trifluoroethoxy-substituted zinc phthalocyanines conjugated with deoxyribonucleosides, Zn-CF_3-Pc-U **1a**,**b** and Zn-CF_3-Pc-Ad **2a**,**b** have been described through twofold Sonogashira alkynylation protocols in good yields. The effect of twelve peripheral trifluoroethoxy groups in the phthalocyanine core is quite obvious. In contrast with the peripheral *tert*-butylated cytidine–phthalocyanine hybrid,[16] our trifluoromethylated-phthalocyanine hybrids **1** and **2** prefer monomeric forms instead of aggregation, and they show a unique photosensitivity that can be controlled by the addition of base or the solvent used. Although interesting effects of perfluoroalkyl groups at the periphery of phthalocyanines have already been disclosed,[21] this result corresponds to one more possible application of fluorine's unique powers in phthalocyanine chemistry. This strategy will be highly useful in the development of phototherapeutic drugs,[22] especially in further combination with drug-delivery systems. Investigations of whether the conjugates are sufficient and efficient in site-selective cleavage of DNA strand under irradiation will be conducted in due course.

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[22] The conjugates are not sufficiently soluble in water; however, they are soluble in DMF, acetone, dioxane, and alcohols. Therefore, mixed aqueous solution systems such as DMF/water would be helpful for biological application of the conjugates.

