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Synthesis of Phthalocyanines−ALA Conjugates: Water-Soluble Compounds with Low Aggregation

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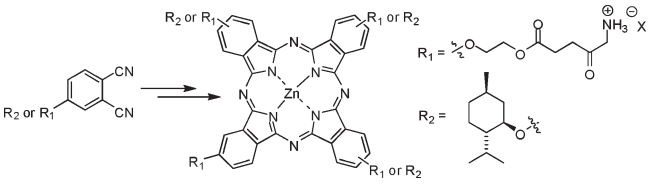

Syntheses of two water-soluble phthalocyanines (Pc) containing 5-aminolevulinic acid (ALA) linked to the core structure are described. These compounds were prepared by using original functionalizations, and they present remarkable structural and photophysical features, indicating that they could be applied to photodynamic therapy (PDT).

The chemistry of new water-soluble photosensitizers has caught the attention of several research groups wordwide.[1] The use of such compounds in PDT has been considered a promising and efficient treatment against superficial dermatological diseases and malignant tumors, not to mention that they can also function as bactericidal agents and antivirus agents and in many other applications.[2] Fundamentally, the treatment utilizes the combined action of a photosensitizer, light, and molecular oxygen to cause cellular and tissue damage, in which singlet oxygen, generated through a series of photoinduced processes, is believed to be the major cytotoxic agent.[2] In this sense, phthalocyanines (Pc) fulfill certain photophysical PDT requirements. However, one important issue related to phthalocyanine derivatives is their low solubility in several organic media and in water.[3] In addition, aggregation phenomena are observed and may have a strong influence on the bioavailability and on the efficiency of singlet oxygen production.[4]

A large number of papers about tetrasubstituted phthalocyanines obtained as a mixture of regioisomers (with C_{4h}, D_{2h}, C_{2v}, and C_s symmetry) have been published.[3,5] For many applications, the enhanced solubility provided by the mixture of isomers is beneficial.[3,5] Statistical condensations in order to obtain phthalocyanines composed of three identical and one different isoindole subunits (A_3B type) have been used to produce low-symmetry derivatives[3c,6] to be applied in nonlinear optical studies.[3c,7] Also, these compounds (A_3B type) can be adequately used to produce amphiphilic phthalocyanines; in general, amphiphilic photosensitizers are considered to be the most potent ones for use in PDT treatments.[8]

Synthetical strategies to produce phthalocyanine derivatives with good solubility and low aggregation have been undertaken.[9]

(1) (a) Li, H.; Jensen, T. J.; Fronczek, F. R.; Vicente, M. G. H. *J. Med. Chem.* **2008**, *51*, 502–511. (b) Sesalan, B. S.; Koca, A.; Gül, A. *Dyes Pigm.* **2008**, *79*, 259–264. (c) Moreira, L. M.; dos Santos, F. V.; Lyon, J. P.; Costa, M. M.; Soares, C. P.; da Silva, N. S. *Aust. J. Chem.* **2008**, *61*, 741–754. (d) Mantareva, V.; Kussovski, V.; Angelov, I.; Borisova, E.; Avramov, L.; Schnurpfeild, G.; Wöhrled, D. *Bioorg. Med. Chem.* **2007**, *15*, 4829–4835. (e) Lo, P. C.; Zhao, B.; Duan, W.; Fong, W. P.; Ko̧c, W. H.; Nga, D. K. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1073–1077. (f) Álvarez-Micó, X.; Calvete, M. J. F.; Hanack, M.; Ziegler, T. *Synthesis* **2007**, *14*, 2186–2192. (g) Reddy, M. R.; Shibata, N.; Kondo, Y.; Nakamura, S.; Toru, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 8163–8166.

(2) (a) Morton, K. E.; McKenna, C. A.; Rhodes, L. E. *Br. J. Dermatol.* **2008**, *159*, 1245–1266. (b) Kessel, D. *J. Porphyrins Phthalocyanines* **2008**, *12*, 877–880. (c) Calzavara−Pinton, P. G.; Venturini, M.; Sala, R. *J. Eur. Acad. Dermatol. Venerol.* **2007**, *21*, 293. (d) Calzavara−Pinton, P. G.; Venturini, M.; Sala, R. *J. Eur. Acad. Dermatol. Venerol.* **2007**, *21*, 439. (e) Juzeniene, A.; Moan, J. *Photodiag. Photodyn. Ther.* **2007**, *4*, 3. (f) Detty, M. R.; Gibson, S. L.; Wagner, S. J. *J. Med. Chem.* **2004**, *47*, 3897–3915.

(3) (a) Suchan, A.; Nackiewicz, J.; Hnatejko, Z.; Waclawek, W.; Lis, S. *Dyes Pigm.* **2009**, *80*, 239–244. (b) Li, Z.; Huang, X.; Xu, S.; Chen, Z.; Zhang, Z.; Zhang, F.; Kasatani, K. *J. Photochem. Photobiol. A* **2007**, *188*, 311–316. (c) *The Porphyrin Handbook−Phthalocyanines: Synthesis*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, 2003; Vol. 15. (d) *The Porphyrin Handbook−Phthalocyanines: Proprieties and Materials*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, 2003; Vol. 17. (e) *The Porphyrin Handbook−Applications of Phthalocyanines*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, 2003; Vol. 19.

(4) (a) Komagoe, K.; Tamagake, K.; Katsu, T. *Chem. Pharm. Bull.* **2006**, *54*, 1004–1009. (b) Henderson, B. W.; Dougherty, T. J. *Photochem. Photobiol.* **1992**, *55*, 145–157.

(5) (a) Nyokong, T. *Coord. Chem. Rev.* **2007**, *251*, 1707–1722. (b) Lo, P. C.; Leng, X.; Ng, D. K. P. *Coord. Chem. Rev.* **2007**, *251*, 2334–2353. (c) Tedesco, A. C.; Rotta, J. C. G.; Lunardi, C. N. *Curr. Org. Chem.* **2003**, *7*, 187–196.

(6) Martínez-Díaz, M. V.; Rodrígues-Morga, M. S.; Feiters, M. C.; van Kan, P. J.; Nolte, R. J. M.; Stoddart, J. F.; Torres, T. *Org. Lett.* **2000**, *2*, 1057–1060.

(7) Maya, E. M.; Garcia, C.; García-Frutos, E. M.; Vázquez, P.; Torres, T. *J. Org. Chem.* **2000**, *65*, 2733–2739.

(8) (a) Boch, R.; Canaan, A. J.; Cho, A.; Dolphin, D. D.; Hong, L.; Jain, A. K.; North, J. R.; Richter, A. M.; Smits, C.; Sternberg, E. D. *Photochem. Photobiol.* **2006**, *82*, 219–224. (b) Boyle, R. W.; Dolphin, D. *Photochem. Photobiol.* **1996**, *64*, 469–485.

(9) (a) Durmus, M.; Ahsen, V.; Nyokong, T. *J. Photochem. Photobiol. A* **2007**, *186*, 323–329. (b) Atilla, D.; Saydan, N.; Durmus, M.; Gül Gürek, A.; Khan, T.; Rück, A.; Walt, H.; Nyokong, T.; Ahsen, V. *J. Photochem. Photobiol. A* **2007**, *186*, 298–307. (c) McKeown, N. B.; Helliwell, M.; Hassan, B. M.; Hayhurst, D.; Hong, L.; Thompson, N.; Teat, S. J. *Chem.—Eur. J.* **2007**, *13*, 228–234. (d) Ribeiro, A. O.; Tomé, J. P. C.; Neves, M. G. P. M. S.; Tomé, A. C.; Cavaleiro, J. A. S.; Serra, O. A.; Torres, T. *Tetrahedron Lett.* **2006**, *47*, 6129–6132. (e) Ribeiro, A. O.; Tomé, J. P. C.; Neves, M. G. P. M. S.; Tomé, A. C.; Cavaleiro, J. A. S.; Iamamoto, Y.; Torres, T. *Tetrahedron Lett.* **2006**, *47*, 9177–9180.

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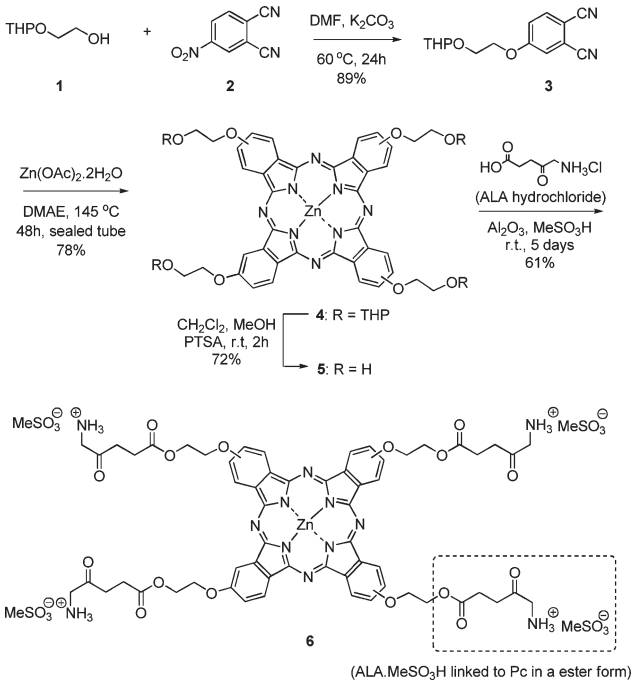
SCHEME 1. Synthesis of Tetrasubstituted Phthalocyanine 6



Some papers have reported the use of nonsymmetrical *tert*-butylated phthalocyanines containing a polar fragment such as peptides and ammonium salts,[10] which resulted in products with good solubility and amphiphilicity. These compounds have been studied in the cellular environment and led to attachment, but aggregation is still high, probably affecting singlet oxygen production.[10]

In this work we report the syntheses and the photophysical evaluation of new phthalocyanines with remarkable features. The first is the presence of 5-aminolevulinic acid (ALA) in the ester form linked to the core structure of phthalocyanines. It is expected that these peripheral ALA will be easily released in a cellular environment by hydrolysis as in the case of ALA esters, which have been widely used in PDT treatments.[11] A synergistic effect is also possible because protoporphyrin IX can be produced by the cell, consequently both photosensitizers will be able to act in the process of singlet oxygen production. The other feature is the presence of menthyl groups in a core structure of one phthalocyanine. As is known in the chemistry of phthalocyanines, bulky peripheral substitutions can be used for enhancing the solubility in organic and aqueous media and for changing the aggregation behavior.[3c−e,12] Therefore, the menthyl group can be considered as an adequate and original functionalization to phthalocyanines, since it is a bulky[13] organic group.

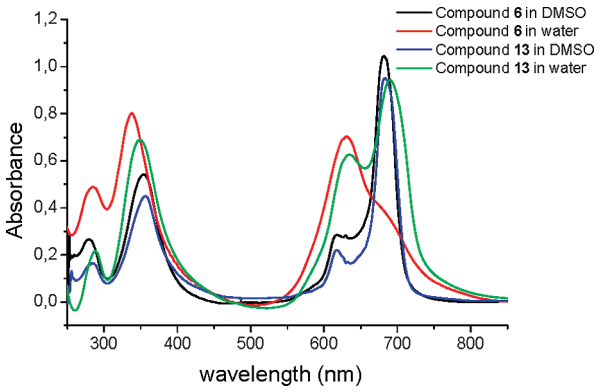


FIGURE 1. UV−vis spectra of phthalocyanines **6** and **13**.

Then, the synthesis of phthalocyanine **6** was carried out in 3 steps, starting from the phthalonitrile **3** (Scheme 1).[14] The isomeric mixture of phthalocyanine **4** was synthesized under appropriated conditions by using $Zn(OAC)_2 \cdot 2H_2O$, DMAE (*N*,*N*-dimethylethanolamine) in a sealed tube, with 78% yield after purification in silica and subsequent crystallization. Deprotection of **4**[15] and esterification with 5-aminolevulinic acid (ALA)[16] under mild conditions[17] yielded the tetrasubstituted phthalocyanine **6** (44% yield—two steps) after crystallization with methanol/ethyl ether. In this case, the use of acidic conditions is mandatory due to the nature of ALA, an ammonium salt that decomposes in basic environment. Yet, this esterification step was also tested by using other acidic conditions such as the reaction via the acyl chloride ALA derivative. However, in all attempts the phthalocyanine−ALA conjugate **6** was not obtained; instead decomposition of phthalocyanine **5** was observed.

Then, the solubility of the tetra-ALA-substituted phthalocyanine **6** was tested and we could observe that this compound is highly soluble in water and DMSO besides other solvents such as methanol, ethanol, and acetonitrile. Compound **6** gives well-defined UV−vis spectra in DMSO (Figure 1), with sharp Q-bands centered at 682 nm, indicating monomeric species in solution.[3d,18] However, the optical features of this compound in water differ remarkably from those in DMSO, indicating the occurrence of aggregation.

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Publication Date (Web): September 11, 2009 | doi: 10.1021/jo901633a

(10) (a) Dubuc, C.; Langlois, R.; Bénard, F.; Cauchon, N.; Klarskov, K.; Tonec, P.; van Liera, J. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2424–2427. (b) Sibrian-Vazquez, M.; Ortiz, J.; Nesterova, I. V.; Fernández-Lázaro, F.; Sastre-Santos, A.; Soper, S. A.; Vicente, M. G. H. *Bioconjugate Chem.* **2007**, *18*, 410–420.

(11) (a) Di Venosa, G.; Fukuda, H.; Batlle, A.; MacRobert, A.; Casas, A. *J. Photochem. Photobiol., B* **2006**, *83*, 129–136. (b) Fotinos, N.; Campo, M. A.; Popowycz, F.; Gurny, R.; Lange, N. *Photochem. Photobiol.* **2006**, *82*, 994–1015. (c) Lopez, R. F. V.; Lange, N.; Guy, R.; Bentley, M. V. L. B. *Adv. Drug Delivery Rev.* **2004**, *56*, 77. (d) Brunner, H.; Hausmann, F.; Knuechel, R. *Photochem. Photobiol.* **2003**, *78*, 481–486.

(12) (a) Agírtas, M. S. *Dyes Pigm.* **2007**, *74*, 490–493. (b) Kimura, M.; Nakada, K.; Yamaguchi, Y.; Hanabusa, K.; Shiraia, H.; Kobayashi, N. *Chem. Commun.* **1997**, 1215–1216. (c) Rihter, B. D.; Bohorquez, M. D.; Rodgers, M. A. J.; Kenney, M. E. *Photochem. Photobiol.* **1992**, *55*, 677–680.

(13) (a) Bałczewski, P.; Szadowiak, A.; Bodzioch, A.; Białas, T.; Wieczorek, W. M.; Szyrej, M. *J. Organomet. Chem.* **2007**, *692*, 997–1009. (b) Salvatella, L.; Mokrane, A.; Cartier, A.; Ruiz-López, M. F. *J. Org. Chem.* **1998**, *63*, 4664–4670.

(14) (a) Meder, M.; Galba, C. H.; Gade, L. H. *Monatsh. Chem.* **2005**, *136*, 1693–1706. (b) Li, K.; Ran, L.; Yu, Y. H.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 3986–3989.

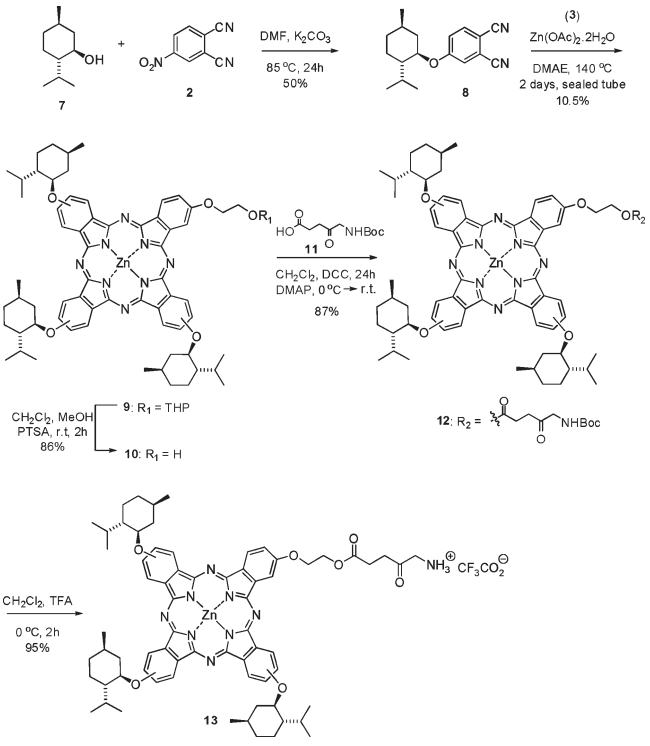
(15) Kimura, M.; Kuroda, T.; Ohta, K.; Hanabusa, K.; Shirai, H.; Kobayashi, N. *Langmuir* **2003**, *19*, 4824–4830.

(16) (a) Drabrowski, Z.; Kwasny, M.; Kaminsky, J.; Beldowicz, M.; Lewicka, L.; Obukowicz, B.; Kaliszewski, M.; Pirozynska, E. *Acta Pol. Pharm.* **2003**, *60*, 219–224. (b) Ha, H. J.; Lee, S. K.; Ha, Y. J.; Park, J. W. *Synth. Commun.* **1994**, *24*, 2557–2562.

(17) Sharghi, H.; Sarvari, M. H. *Tetrahedron* **2003**, *59*, 3627–3633.

(18) (a) Durmus, M.; Ayhan, M. M.; Gürek, A. G.; Ahsen, V. *Dyes Pigm.* **2008**, *77*, 570–577. (b) Schutte, W. J.; Sluyters-Rehbach, M.; Sluiters, J. H. *J. Phys. Chem.* **1993**, *97*, 6069–6073. (c) Stillman M. J.; Nyokong T. *Phthalocyanines: Properties and Applications*; Leznoff, C. C., Lever A. B. P., Eds.; VCH Publishers: New York, 1989; Vol. 1. (d) Anderson, A. B.; Gorden, T. L.; Kenney, M. E. *J. Am. Chem. Soc.* **1985**, *107*, 192–195.

SCHEME 2. Synthesis of Tetrasubstituted Phthalocyanine 13



In aqueous media, phthalocyanine **6** probably forms H-type aggregate as seen by the Q-band broadening in the UV−vis spectra (Figure 1).[1a,3d,19]

To reduce this aggregation phenomenon in water we proposed the synthesis of a nonsymmetrical phthalocyanine containing a new substituent such as the menthyl group. The reason for this other synthesis was based on the large bulk of this group,[13] which can avoid a strong π-stacking interaction among macrocycles in solution.[20] In addition, some studies involving the use of menthol derivatives as additive in formulations for use in PDT treatments have been published.[21] In particular, the ester derivatives have promoted good improvement in the penetration of ALA into tumor cells.[21] The new phthalonitrile **8** was prepared by the nucleophilic aromatic substitution such as the one carried out for the synthesis of **3** (Scheme 2).[14] Then, the synthesis of phthalocyanine **9** was performed by the statistical tetramerization of 1 equiv of phthalonitrile **3** and 3 equiv of phthalonitrile **8**. The nonsymmetrical phthalocyanine **9** was isolated by purification in silica (10.5% yield).

Deprotection of **9** was performed by using MeOH/PTSA (*p*-toluenesulfonic acid) in CH_2Cl_2, which furnished phthalocyanine **10** in 86% yield after crystallization with methanol. Attempts of esterification of **10** with ALA by using Sharghi's methodology[17] were made; however, even under mild conditions and low temperature the expected compound was not obtained.

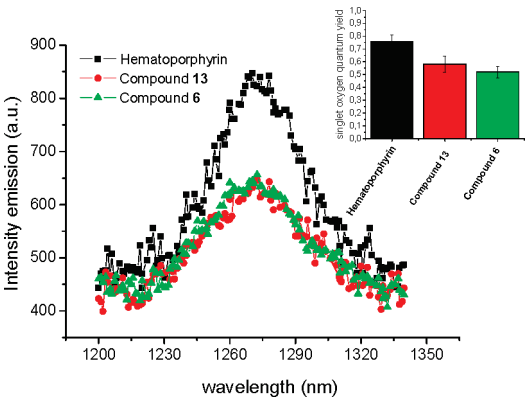


FIGURE 2. Emission spectra of singlet oxygen and singlet oxygen quantum yield (Φ_Δ). Comparison between phthalocyanines **6** and **13** in acetonitrile.

Through the ^{1}H NMR analysis of the obtained product we could confirm that the menthyl groups were totally or partially removed during the reactions. To avoid this problem, we decided to protect the 5-aminolevulinic acid with Boc_2O[22] and then carry out the esterification with DCC.[23] In this way, phthalocyanine **12** was successfully obtained after purification on silica, with 87% yield. Deprotection of **12**[10b] with TFA in CH_2Cl_2 at 0 °C afforded phthalocyanine **13** with 95% yield after crystallizations with ethyl ether and hexanes. The solubility of **13** was evaluated in several organic environments such as methanol, ethanol, DMSO, and water, and this compound was very soluble in all these solvents. We observed that in water the aggregation phenomenon is lower than that observed for compound **6**, probably due to the peripheral substituent (see UV−vis spectra—Figure 1).

The direct measurement of the singlet oxygen quantum yield (Φ_Δ)[24] was carried out in order to quantify the ability of compounds **6** and **13** to generate $^1O_2$ (Figure 2).

The analysis was performed by time-resolved near-infrared luminescence technique (NIR), and the photoexcitation experiments of **6** and **13** were performed with laser pulses at 320 nm (10 mJ/pulse, 1−10 Hz). The measurements were performed by using acetonitrile as solvent and adjusting the absorbance to 0.2 (10 spectra in triplicate). The reference was hematoporphyrin (Φ_Δ = 0.76).[25] The emission wavelength (1270 nm) was selected by using a silicon cutoff filter and a monochromator.

The Φ_Δ values obtained for **6** and **13** were 0.52 and 0.58, respectively, indicating that these new water-soluble phthalocyanines are good candidates for PDT treatments.[1a,26]

Aggregation and singlet oxygen emissions were also studied in deuterated water (Figure 3) in the presence and absence of SDS (sodium dodecyl sulfate). As described in

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(19) (a) Makhseed, S.; Samuel, J. *Dyes Pigm.* **2009**, *82*, 1–5. (b) Nikolaitchik, A. V.; Korth, O.; Rodgers, M. A. J. *J. Phys. Chem. A* **1999**, *103*, 7587–7596.
(20) Chen, Z.; Lohr, A.; Saha-Möller, C. R.; Würthner, F. *Chem. Soc. Rev.* **2009**, *38*, 564–584.
(21) Tokuoka, Y.; Suzuki, M.; Ohsawa, Y.; Ochiai, A.; Ishizuka, M.; Kawashima, N. *Drug Dev. Ind. Pharm.* **2008**, *34*, 595–601.
(22) Battah, S. H.; Chee, C. E.; Nakanishi, H.; Gerscher, S.; MacRobert, A. J.; Edwards, C. *Bioconjugate Chem* **2001**, *12*, 980–988.
(23) Vallinayagam, R.; Bertschy, H.; Berger, Y.; Wenger, V.; Neier, R. *Synthesis* **2007**, *23*, 3731–3735.
(24) (a) Uchoa, A. F.; Knox, P. P.; Turchielle, R.; Seifullina, N. Kh.; Baptista, M. S. *Eur. Biophys. J.* **2008**, *37*, 843. (b) Spiller, W.; Kliesch, H.; Wöhrle, D.; Hackbarth, S.; Roder, B.; Schnurpfeil, G. *J. Porphyrins Phthalocyanines* **1998**, *2*, 145. (c) de Oliveira, K. T.; Silva, A. M. S.; Tomé, A. C.; Neves, M. G. P. M. S.; Neri, C. R.; Garcia, V. S.; Serra, O. A.; Iamamoto, Y.; Cavaleiro, J. A. S. *Tetrahedron* **2008**, *64*, 8709–8715.
(25) Wilkinson, F.; Helman, W. P.; Ross, R. B. *J. Phys. Chem. Ref. Data* **1993**, *22*, 13.
(26) Ke, M. R.; Huanga, J. D.; Weng, S. M. *J. Photochem. Photobiol., A* **2009**, *201*, 23–31.

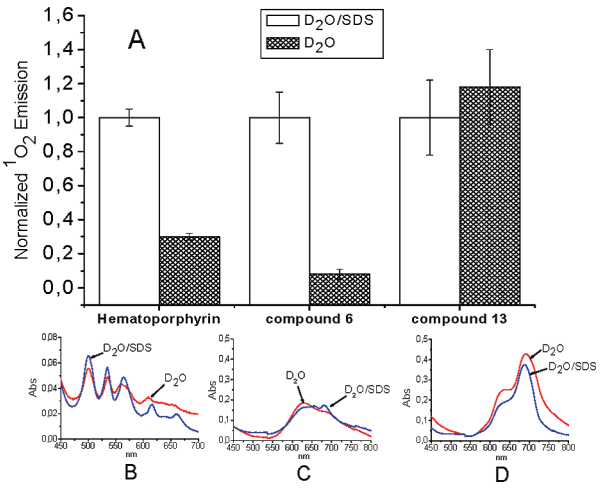

FIGURE 3. (A) Normalized emission at 1270 nm of hematoporphyrin, **6**, and **13** in D_2O in the presence and absence of 30 mM SDS. (B−D) Absorption spectra of hematoporphyrin, **6**, and **13**, respectively, in D_2O in the presence and absence of 30 mM SDS.

the literature,[27] SDS induces disassembly of photosensitizer aggregates, favoring the emission of singlet oxygen, and the fact that the singlet oxygen emission from photossensitizers is not influenced by SDS indicates that it was not aggregated prior to the addition of SDS.

In the case of hematoporphyrin and compound **6**, the presence of SDS greatly increases the yield of singlet oxygen emission and changes the absorption spectra favoring monomer species. On the other hand, for compound **13** the presence of SDS does not change significantly either the yield of singlet oxygen or the absorption spectra, demonstrating that **13** was in the monomer state already,[27] and proving that the presence of the menthyl group as the peripheral substituent promotes lower aggregation and improves the photosensitizer activity. This is important information because photosensitizer aggregation is the main issue to be considered in the development of new photosensitizer agents.

Thus, these photophysical studies are only preliminary; however, they are positive in terms of PDT application. Also, these studies give importance to the new synthesized ALA derivatives **6** and **13**.

Regarding the characterizations, the intermediates and products were elucidated by spectroscopic and spectrometric techniques including ^1H and ^{13}C NMR (if adequate), UV, and HRMS (ESI and MALDI). An intriguing result was observed during the ESI and MALDI analysis, where ionization through metal oxidation was obtained in the absence of a protonation process. In electrospray ionization mass spectrometry (ESI-MS), charge formation is proposed to occur as a result of acid−base reactions or coordination with metal cations. However, an increasing number of papers and reviews have reported the formation of radical ions (molecular ions) as a result of loss of one or two electrons.[28,29]

The metallophthalocyanine compounds can be included in this class of ionization exception in ESI, and the molecular ion is more prone to be formed than protonated or cationizated compounds.[30,31] These results stimulate the MALDI analysis of this series of compounds, to confirm the possible induction of molecular ion formation by the laser source. As expected, all the compounds afforded molecular ions, and these data were useful to confirm the proposed structures and also to furnish more evidence of the molecular ion formation in ESI and MALDI sources.

Experimental Section

Representative Procedure: {Tetrakis-[2-(5-ammonio-4-oxapentanoyloxy)ethoxy]phthalocyaninato}zinc(II) Tetramethanesulfonate (6). To a mixture containing 5-aminolevulinic acid (126 mg, 0.75 mmol), acidic alumina (Al_2O_3, 230 mg, 2.25 mmol), and CH_3SO_3H (1.4 mL) at room temperature and under argon atmosphere was added the phthalocyanine **5** (20.6 mg, 25.0 μmol), maintaining under stirring and protection from light for 5 days. Then, the reaction mixture was treated with DMSO (1 mL) and filtered, to remove the residual alumina. The resulting solution was treated with 1 mL of methanol and 10 mL of ethyl ether, yielding a dark-green precipitate that was filtered off. This purification procedure was performed twice again, and the resulting powder was recrystallized with methanol/ethyl ether, furnishing the phthalocyanine **6** (22 mg, 15.6 μmol, 61%). Mp >300 °C ; UV−vis (DMSO) λ_{max} (log ε) 354 (4.67), 618 (4.35), 629 (4.33), 682 (4.91); ^1H NMR (DMSO-d_6, 500.13 MHz) δ (ppm) 2.30 (br s, 12H), 2.77 (br s, 8H), 2.92 (br s, 8H), 4.05 (br s, 8H), 4.68 (br s, 8H), 4.82 (br s, 8H), 7.74−7.89 (m, 4H), 8.07 (br s, 12H), 8.78−8.99 (m, 4H), 9.16−9.37 (m, 4H); HRMS-ESI-TOF m/z calcd for $C_{60}H_{60}N_{12}O_{16}Zn^+$ $(M)^+$ 1268.3542, found 1268.3601.

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Supporting Information Available: All experimental details and the syntheses of compounds **ALA**, **1**, **3**, **4**, **5**, **8**, **9**, **10**, **11**, **12**, and **13** are described, and the NMR (^1H and ^{13}C) and MALDI analyses are included. This material is available free of charge via the Internet at http://pubs.acs.org.

(27) Junqueira, H. C.; Severino, D.; Dias, L. G.; Gugliotti, M.; Baptista, M. S. *Phys. Chem. Chem. Phys.* **2002**, *4*, 2320–2328.

(28) Vessecchi, R. L.; Galembeck, S. E.; Lopes, N. P.; Nascimento, P. G. B. D.; Crotti, A. E. M. *Quím. Nova* **2008**, *31*, 840–853.

(29) Vessecchi, R. L.; Crotti, A. E. M.; Guaratini, T.; Colepicolo, P.; Galembeck, S. E.; Lopes, N. P. *Mini-Rev. Org. Chem.* **2007**, *4*, 75–87.

(30) Guarantini, T.; Gates, P. J.; Pinto, E.; Colepicolo, P.; Lopes, N. P. *Rapid Commun. Mass Spectrom.* **2007**, *21*, 3842–3848.

(31) Guarantini, T.; Vessecchi, R. L.; Lavarda, F. C.; Maia, P. M. B. G.; Naal, Z.; Gates, P. J.; Lopes, N. P. *Analyst* **2004**, *129*, 1223–1226.

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