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Porphyrins in 1,3-Dipolar Cycloaddition Reactions. Synthesis of New Porphyrin−Chlorin and Porphyrin−Tetraazachlorin Dyads

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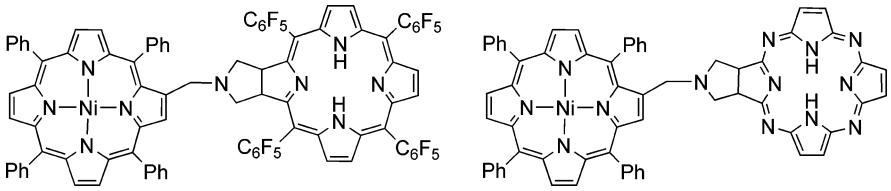

N-(Porphyrin-2-ylmethyl)glycine was synthesized and used as precursor of azomethine ylide, which was trapped with several dipolarophiles. The reaction of that azomethine ylide with dimethyl fumarate afforded the expected adduct. However, with 1,4-benzo- and 1,4-naphthoquinones only dehydrogenated adducts were isolated. Also, the reaction of that ylide with *meso*-tetrakis(pentafluorophenyl)porphyrin and tetraazaporphine allowed access to novel porphyrin−chlorin and porphyrin−tetraazachlorin dyads.

Introduction

During the past decade, various synthetic strategies have been developed in order to make different multiporphyrin systems where the porphyrin units are directly linked by *meso*-*meso*, *meso*-β, and β-β positions, oligoporphyrins with fused π-systems and arrays bearing rigid and flexible spacers.[1] In such a way, a large range of multiporphyrin systems with linear, cyclic, and cross-linked geometries have been synthesized. The interest in the synthesis of multiporphyrin materials[2] (dimers and other oligomers) arise from their potential application as models in light harvesting,[3] as molecular photonic and electronic wires,[4] as catalysts,[5] and as photosensitizers for photodynamic therapy (PDT).[6]

In the past few years, we have shown that porphyrins can participate in 1,3-dipolar cycloadditions in two different ways: they react as dipolarophiles with azomethine ylide **2**, generated from *N*-methylglycine and formaldehyde, to give pyrrolidine-fused chlorins **3** (route **I**, Scheme 1),[7] and they can be used as precursors of the porphyrinic azomethine ylide **5**, which reacts with dipolarophiles to give β-pyrrolidine-*meso*-tetraphenylporphyrins **7** (route **II**, Scheme 1).[8] In the absence of dipolarophiles,

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(1) Lacerda, P. S. S.; Silva, A. M. G.; Tomé, A. C.; Neves, M. G. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S.; Llamas-Saiz, A. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 5487 and references cited therein.

(2) Recent review: Elemans, J. A. A. W.; van Hameren, R.; Nolte, R. J. M.; Rowan, A. E. *Adv. Mater.* **2006**, *18*, 1251.

(3) Recent review: Kobuke, Y. *Eur. J. Inorg. Chem.* **2006**, *12*, 2333. Recent examples: (a) Hori, T.; Aratani, N.; Takagi, A.; Matsumoto, T.; Kawai, T.; Yoon, M.-C.; Yoon, Z. S.; Cho, S.; Kim, D.; Osuka, A. *Chem. Eur. J.* **2006**, *12*, 1319. (b) Hajjaj, F.; Yoon, Z. S.; Yoon, M.-C.; Park, J.; Satake, A.; Kim, D.; Kobuke, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4612. (c) Maes, W.; Vanderhaeghen, J.; Smeets, S.; Asokan, C. V.; Van Renterghem, L. M.; Du Prez, F. E.; Smet, M.; Dehaen, W. *J. Org. Chem.* **2006**, *71*, 2987.

(4) Recent example: Thamyongkit, P.; Yu, L.; Padmaja, K.; Jiao, J.; Bocian, D. F.; Lindsey, J. S. *J. Org. Chem.* **2006**, *71*, 1156.

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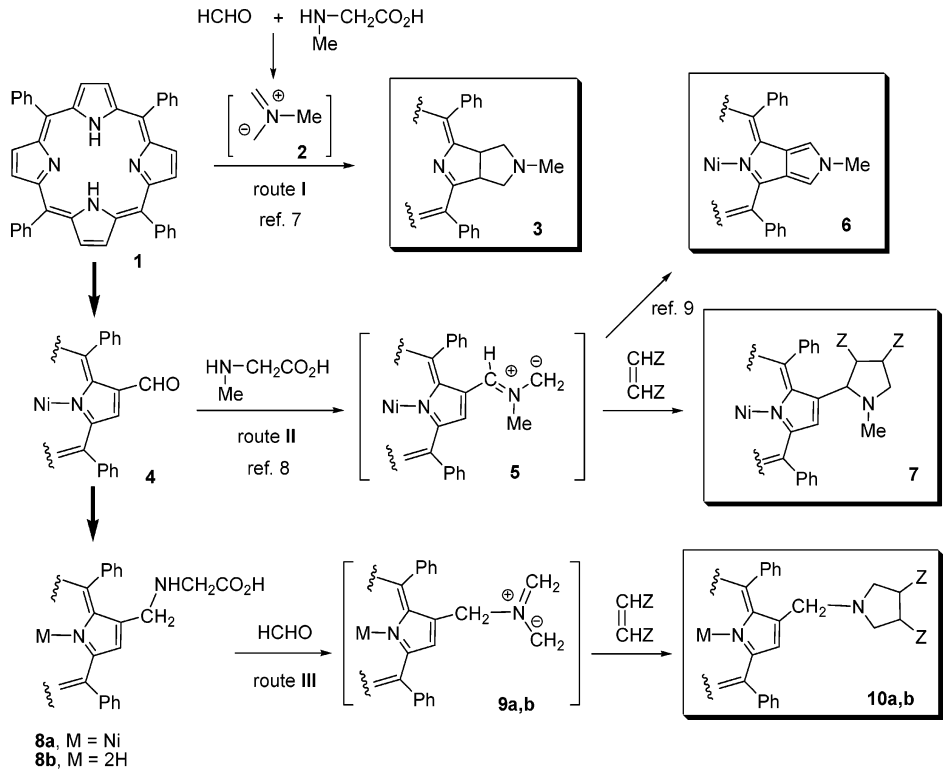
SCHEME 1



porphyrinic azomethine ylide **5** gives 1,5-electrocyclization to yield pyrroloporphyrin **6**.[9]

Along these lines, we synthesized the new *N*-(porphyrin-2-ylmethyl)glycine derivative to be used as an azomethine ylide precursor. With this compound, a range of porphyrin derivatives of type **10** were prepared (route **III**, Scheme 1). Thus, in this report we describe the conversion of (*β*-formyl-*meso*-tetraphenylporphyrinato)nickel(II) **4** into *N*-(porphyrin-2-ylmethyl)-glycines **8a,b** and the corresponding methyl ester **12** (Scheme 2) and their use as precursors of the porphyrinic azomethine ylides **9a,b** and **S1** (Supporting Information, Scheme S1), which react with dipolarophiles to give *β*-pyrrolidinemethyl-*meso*-tetraphenylporphyrins (route **III**, Scheme 1 and Scheme S1). From those ylides, some porphyrin−chlorin dyads and a porphyrin−tetraazachlorin dyad were prepared. Although porphyrin−porphyrin dyads have been extensively investigated,[10] porphyrin−chlorin dyads have received scarce attention.[11]

In this report we describe, for the first time, the use of porphyrins in 1,3-dipolar cycloaddition reactions simultaneously as dipoles and as dipolarophiles. New porphyrin−chlorin and porphyrin−tetraazachlorin dyads were obtained from those reactions.

Results and Discussion

The synthesis of the *N*-(porphyrin-2-ylmethyl)glycine **8a** involves a three-step process (Scheme 2). First, the Ni(II) complex of *β*-formyl-*meso*-tetraphenylporphyrin (**4**) was treated with an excess of glycine methyl ester hydrochloride in the presence of potassium carbonate and lanthanum(III) triflate. The subsequent reduction of imine **11** with sodium borohydride gave pure methyl glycinate **12** in 66% yield (two steps), after chromatographic purification. The alkaline hydrolysis of compound **12** gave the Ni(II) complex of *N*-(porphyrin-2-ylmethyl)-glycine **8a** in 98% yield. Demetalation of **8a** with 10% H_2SO_4 in dichloromethane afforded derivative **8b** in quantitative yield.

The reactivity of azomethine ylide **9a** in 1,3-dipolar cycloadditions with several dipolarophiles, namely, dimethyl fumarate, 1,4-naphthoquinone, 1,4-benzoquinone, *meso*-tetrakis(pentafluorophenyl)porphyrin **17**, and tetraazaporphine **19**, was then studied (Schemes 3 and 5). Typically, the cycloaddition reactions were performed by refluxing a toluene solution of porphyrin **8a**, paraformaldehyde (excess), and the desired dipolarophile (excess) for 1 h. Because of the low solubility of tetraazaporphine in toluene, the reaction with this dipolarophile was carried out in 1,2-dichlorobenzene, at 120 °C.

In the reaction with dimethyl fumarate, the expected adduct **13** was isolated in 74% yield. With 1,4-benzoquinone, the adduct **14** was not isolated; the ^{1}H NMR and mass spectra of the reaction product showed that it was a mixture of di- and tetradehydrogenated derivatives of adduct **14**. Because during

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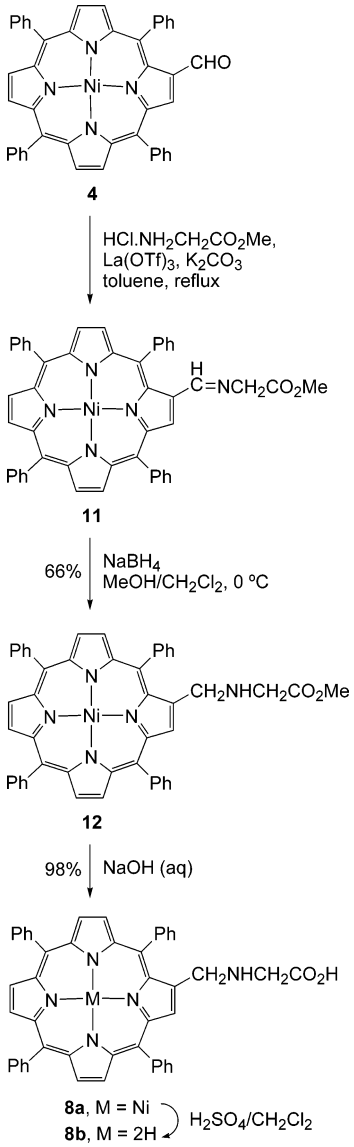
SCHEME 2



the purification step the didehydrogenated derivative was converting to the tetradehydrogenated one, we decided to treat the reaction mixture with DDQ. In that way, compound **15** was obtained in 44% yield. When the reaction was performed with an excess of **8a**, compound **15.1** was also isolated, indicating that a second azomethine ylide **9a** reacted with **15** (Scheme 4). The attempted oxidation of **15.1** to **15.2** was unsuccessful: treatment of **15.1** with an excess of 1,4-benzoquinone (in refluxing toluene) gave the starting material; treatment of **15.1** with a stronger oxidant (DDQ at room temperature) afforded only decomposition products.

From the reaction of **8a** with paraformaldehyde and 1,4-naphthoquinone, two products were isolated: compound **16.1** (56% yield, higher R_f on silica gel) and compound **16.2** (small amount, smaller R_f on silica gel). These compounds resulted from di- and tetradehydrogenation of the initial adduct. Compound **16.1** was found to be quite unstable, and it slowly converts into **16.2** during the chromatographic process or when it is left in solution.

Due to the low dipolarophile character of *meso*-tetrakis(pentafluorophenyl)porphyrin,[7] its reaction with azomethine ylide **9a** to form the porphyrin−chlorin dyad **18a** required a bigger excess of porphyrin **17** (3 equiv) and a longer reaction period (3 h) (Scheme 5). Under these conditions, dyad **18a** was obtained in 42% yield. Demetallation of dyad **18a** afforded **18b** in quantitative yield. Dyad **18b** was also obtained in 35% yield from the reaction of *N*-(porphyrin-2-ylmethyl)glycine **8b** with paraformaldehyde and porphyrin **17**. These results contrast with those obtained when we tried to synthesize porphyrin−chlorin dyads from the 1,3-dipolar cycloaddition reaction of ylide **5** with *meso*-tetraarylporphyrins; in those cases only pyrroloporphyrin **6** was obtained (Scheme 1).

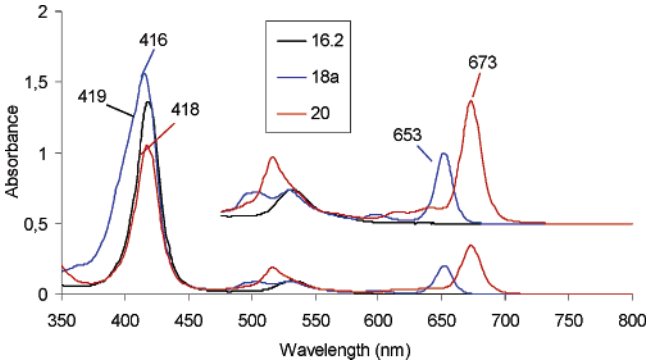


FIGURE 1. Electronic absorption spectra of compounds **16.2**, **18a**, and **20**, at equimolar concentrations (5 μM) in dichloromethane.

The reactivity of tetraazaporphine **19** was found to be similar to that of porphyrin **17**. In fact, the reaction of ylide **9a** with **19** (3 equiv), in 1,2-diclorobenzene at 120 °C, afforded the porphyrin−tetraazachlorin dyad **20** in 30% yield (Scheme 5).

Methyl glycinate **12** was also used as precursor of an azomethine ylide that was trapped with dimethyl fumarate and *meso*-tetrakis(pentafluorophenyl)porphyrin **17**. In these cases, methyl pyrrolidine-2-carboxylate derivatives were obtained (see Scheme S1 in Supporting Information).

Note that in all of these cycloaddition reactions the formation of minor products resulting from the degradation of the glycine derivative **8a**, namely β-formylporphyrin **4**, is observed. This thermal degradation was confirmed by refluxing a toluene solution of porphyrin **8a**.

Structural Characterization of the New Compounds. All synthesized compounds were characterized by nuclear magnetic resonance, UV−vis spectroscopy, and mass spectrometry or elemental analyses (see Supporting Information).

Figure 1 shows the electronic absorption spectra of compounds **16.2**, **18a**, and **20**, measured in dichloromethane, at equimolar concentrations. The spectrum of compound **16.2** shows a typical metalated porphyrin profile (Soret band at 419 nm and a broad Q-band at 532 nm). The spectrum of porphyrin−chlorin dyad **18a** exhibits a characteristic chlorin band at 653 nm, whereas the spectrum of porphyrin−tetraazachlorin dyad **20** shows a strong band at 673 nm and two small bands at 616 and 641 nm, typical of tetraazachlorin derivatives. It is interesting to note the lower intensity of the Soret band of the porphyrin−tetraazachlorin dyad when compared with that of the porphyrin−chlorin dyad. This is due to the fact that the tetraazachlorin macrocycle has no relevant absorption in this region (tetraazachlorins show a Soret band typically at 320−345 nm).[12]

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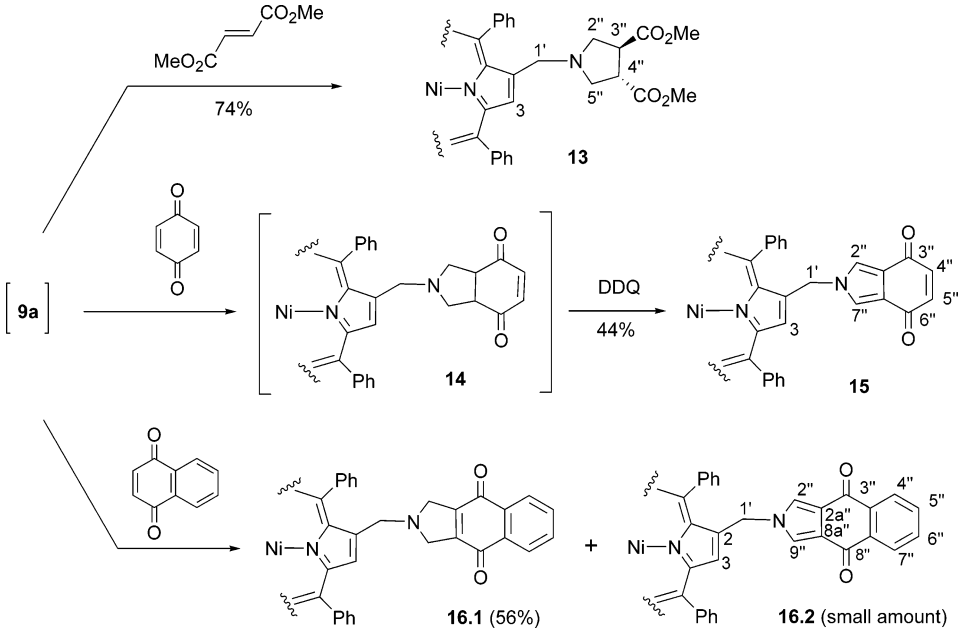
SCHEME 3



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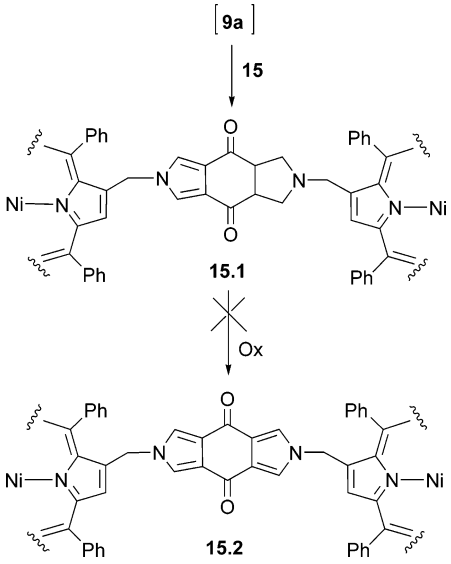

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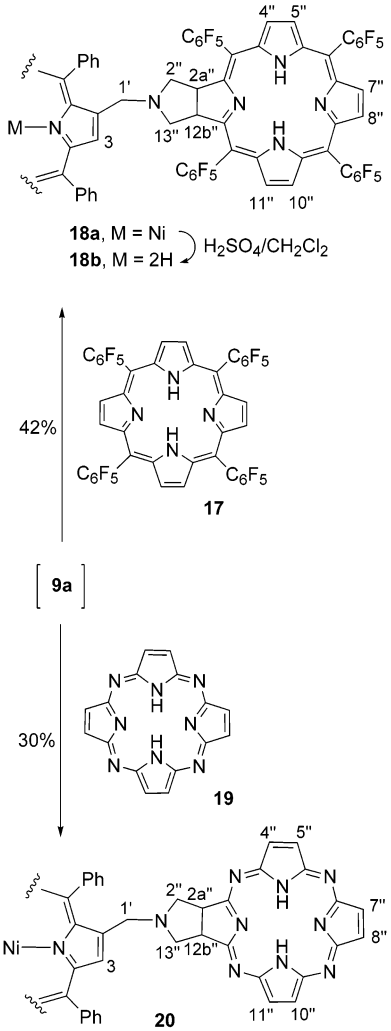

The NMR spectra were crucial for the structural elucidation of the synthesized compounds. In fact, the structure of compound **13** was confirmed by the presence in its ^{1}H NMR spectrum of a singlet at 3.63 ppm (corresponding to the two methoxy groups), two multiplets at 2.63−2.72 and 3.32−3.39 ppm (corresponding to the six pyrrolidine protons), and an AB system at 3.48 and 3.73 ppm (J = 14.9 Hz) corresponding to the H-1′ protons.

The ^{1}H, ^{13}C, and 2D NMR spectra of **15** are consistent with a tetradehydrogenated derivative. Indeed, the ^{1}H NMR spectrum shows, in addition to the porphyrin protons, three singlets at 5.27, 6.60, and 6.86 ppm corresponding to H-1′, H-4″,5″, and H-2″,7″, respectively. The ^{13}C NMR spectrum shows only one signal corresponding to a sp^3 carbon (signal at 49.6 ppm due to C-1′). The signals due to the carbons of the dioxoisoindole group appear in the aromatic region: at 120.9 ppm due to C-2a″,6a″; at 124.3 ppm due to C-2″,7″; at 139.7 ppm due to C-4″,5″; and at 182.0 ppm due to C-3″,6″. The unequivocal assignments were established by HMBC and HSQC.

TABLE 1. ^{1}H NMR Spectral Data for Aliphatic Protons of Dyads 18a and 20

	18a	20
H-2a″,12b″	5.10−5.12 (m)	5.07 (d, *J* 6.5 Hz)
H-2″,13″	2.40−2.44 (m)	2.96−3.00 (m, H_{cis})
	2.94−2.98 (m)	3.75 (d, *J* 10.0 Hz, H_{trans})
H−1′	3.45 (s)	3.62 (s)
NH	−1.82 (s)	−0.81 (s)

The ^{1}H NMR spectrum of compound **16.2** shows, in the aliphatic region, only one singlet at 5.33 ppm, due to H-1′. In the aromatic region, in addition to the signals corresponding to the porphyrin protons, it reveals a singlet at 7.03 ppm due to the H-2″,9″, a multiplet at 8.16−8.22 ppm due to H-4″,7″, and a multiplet at 7.55−7.75 ppm due to H-5″,6″ (overlapped with the H_{ortho}-Ph protons).

The NMR spectra of dyads **18a** and **20** show a pattern much more complex than the previous ones, in particular in the aromatic region, due to the overlap of the proton resonances of both macrocycles. From the analysis of Table 1, it is interesting to note that there are differences in the chemical shift and multiplicity of some signals. The inner NH protons are more deprotected in porphyrin−tetraazaporphine dyad **20** than in porphyrin−chlorin dyad **18a**, as expected from the literature data.[13]

Conclusions

The synthesis of *N*-(porphyrin-2-yl-methyl)glycines **8a,b**, precursors of the porphyrinic azomethine ylides **9a,b**, is described. Ylide **9a** was trapped in 1,3-dipolar cycloaddition reactions with dimethyl fumarate, 1,4-benzoquinone, 1,4-naphthoquinone, porphyrin **17**, and tetraazaporphine **19**. Each reaction afforded the expected adducts; in the case of quinones, the dehydrogenated derivatives were obtained instead. Ylide **9b** was trapped only with porphyrin **17**; the expected dyad porphyrin−chlorin was obtained. Bisaddition of ylide **9a** to 1,4-benzoquinone was accomplished when an excess of the ylide precursor was used.

The synthetic route now presented (route III, Scheme 1) is more versatile than the previously reported one (route II, Scheme 1)[8] because less reactive dipolarophiles can also be used. This new route allows the simultaneous use of porphyrin derivatives as 1,3-dipoles and as dipolarophiles in 1,3-dipolar cycloaddition reactions.

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Supporting Information Available: Complete experimental section, including the synthesis of *N*-(porphyrin-2-ylmethyl)glycine, and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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