

DOI: 10.1002/open.201402001

# Corroles: Synthesis, Functionalization and Application as Chemosensors

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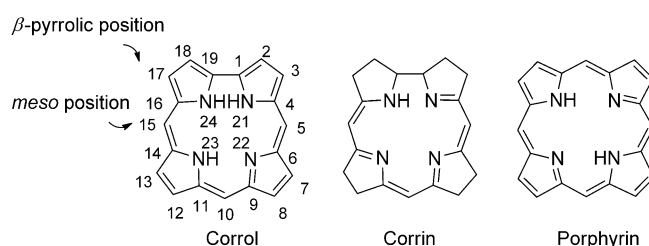
**Date Awarded:** December 13, 2013

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In recent years, the design and development of new fluorescent chemosensors has received great attention due to its important applications in fields such as materials sciences, biomedical analysis, environmental sciences and analytical chemistry, where molecular probes are often useful tools for monitoring relevant analytes either *in vitro* or *in vivo*. According to the literature a fluorescent chemosensor is obtained by merging two fundamental moieties: the recognition site (receptor) and the signaling source (fluorophore). Through the control of these two moieties it is possible to design a specific fluorescent chemosensor for analytical sensing. However, to provide an efficient detection, these units must have a high selectivity or specificity for the analyte and a stable luminescent signal.

Tetrapyrrolic macrocycles like porphyrins and analogues have useful properties to be considered as fluorophores in this type of application. From the porphyrinoid family, corroles have merited special attention in recent years since the discovery of facile methodologies to obtain synthetic triarylcorroles and the corresponding metal complexes. These contracted macrocycles, that maintain the skeletal structure of corrins, the aromaticity of porphyrins and that owe their name to the cobalt-chelating corrin of vitamin B<sub>12</sub> (Figure 1), exhibit rich spectroscopic features including: 1) high molar extinction coefficients, 2) high fluorescence quantum yields, and 3) the corrole core can accommodate a broad array of metal ions which in turn can act as active centers. In addition, corroles can be functionalized at the structural periphery to enhance binding specificity. A corrole macrocycle is susceptible to react at the inner nitrogen atoms, at the  $\beta$ -pyrrolic positions (2,3,7,8,12,13,17,18), at the *meso*-positions (5,10,15) or at its aryl substituents.

Having these properties in mind, this dissertation focused on the synthesis of *meso*-triarylcorroles and their functionalization for later use as chemosensors. The work was divided into five chapters. In the first chapter, the general features of corroles, synthetic methodologies, the functionalization proce-



**Figure 1.** Structures of corrole, corrin and porphyrin core.

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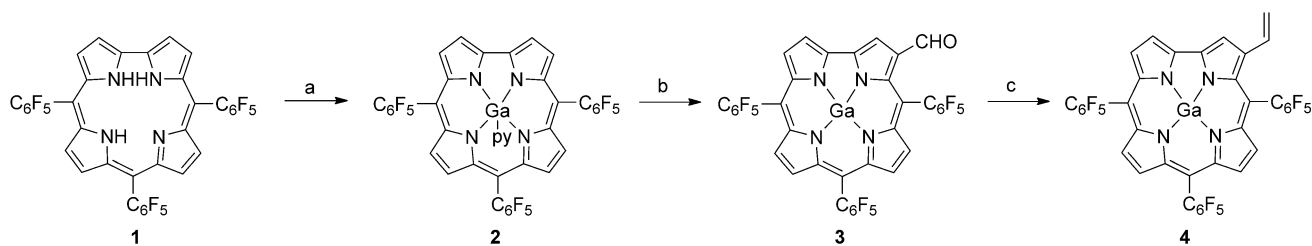
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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/open.201402001>.

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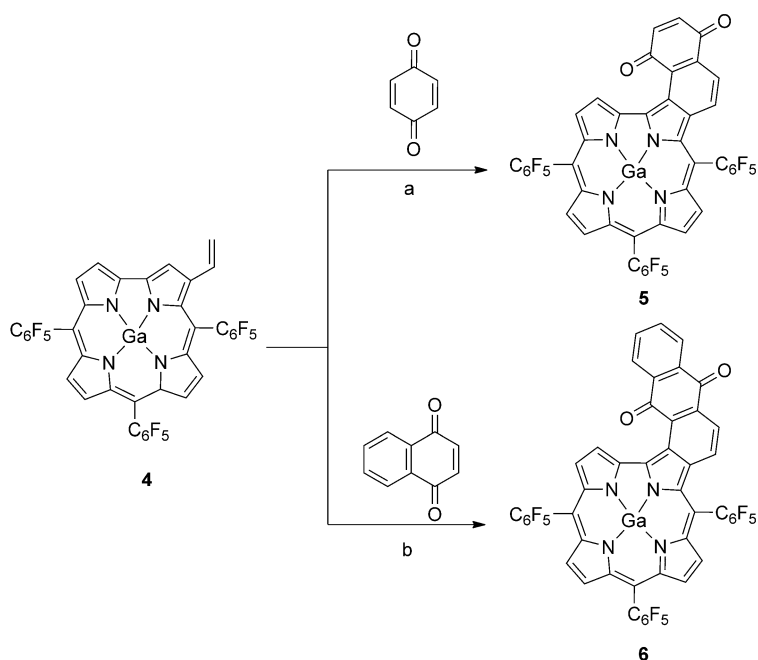
**Scheme 1.** Reagents and conditions: a) i) GaCl<sub>3</sub>, py, reflux, ii) 1. HCl 36%, 2. NaHCO<sub>3(aq)</sub>; b) Vilsmeier–Haack reagent; c) CH<sub>3</sub>PPh<sub>3</sub>Br, NaH in THF, RT, N<sub>2</sub>.

dures and the several potential applications of this kind of macrocycles is described. Additionally, some considerations about chemosensors and the importance of analytes that will be evaluated are also discussed. In the second chapter, the Wittig and Diels–Alder reactions were chosen as post-functionalization procedures to apply to corroles. In this way, by the use of a Wittig reaction, the derivative 3-vinyl-5,10,15-tris(pentafluorophenyl)corrole was synthesized from the corresponding 3-formylcorrole.

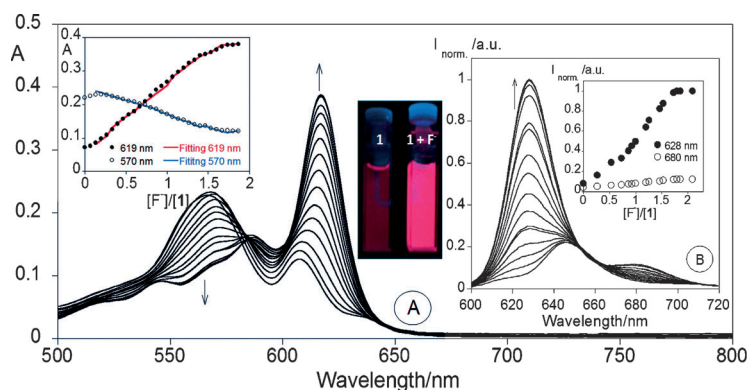
The starting materials, 5,10,15-tris(pentafluorophenyl)corrole (1), 5,10,15-tris(pentafluorophenyl)corrolatogallium(III)(pyridine) (2), 3-formyl-5,10,15-tris(pentafluorophenyl)corrolatogallium(III) (3) were synthesized according to procedures described in literature: the free base by condensation of pyrrole with pentafluorobenzaldehyde using Gryko and Koszarna's method, the gallium(III) complex by refluxing corrole 1 in pyridine with GaCl<sub>3</sub>, and the 3-formylcorrole through a Vilsmeier–Haack reaction involving corrole 2 (Scheme 1).

The reactivity of 3-vinyl-5,10,15-tris(pentafluorophenyl)corrole (4) as diene in Diels–Alder reactions was also evaluated in the presence of the dienophiles 1,4-benzoquinone and 1,4-naphthoquinone (Scheme 2). These studies afforded two Diels–Alder adducts (5 and 6) whose sensorial ability, as well as of their precursors, was studied in solution in the presence of spherical (F<sup>-</sup>, Br<sup>-</sup>, Cl<sup>-</sup>), linear (CN<sup>-</sup>) and bulky (CH<sub>3</sub>COO<sup>-</sup>, H<sub>2</sub>PO<sub>4</sub><sup>-</sup>) biologically and environmentally relevant anions.

The 5,10,15-tris(pentafluorophenyl)corrole (1) showed to be the most sensitive macrocycle to the F<sup>-</sup> (Figure 2). The addition of F<sup>-</sup> to 1 is responsible, in the absorption spectrum (Figure 2A), for a decrease of the intensity of the band centered at 570 nm and for an increase at 606 nm, accompanied by a red-shift from 606 nm to 619 nm ( $\Delta\lambda = 13$  nm). An isosbestic point at 586 nm is also observed. Considering the emission spectrum of 1 (Figure 2B), the titration with F<sup>-</sup> is responsible for an enhancement of intensity of about 91% at 628 nm.



**Scheme 2.** Reagents and conditions: a) Reflux, toluene, N<sub>2</sub>; b) Reflux, toluene, N<sub>2</sub>.



**Figure 2.** A) Spectrophotometric and B) spectrofluorimetric titration of compound **1** with the addition of  $F^-$  in toluene. The inset represents the absorption (A) and the emission intensity (B) as a function of  $[F^-]/[1]$  at 570 nm, 619 nm for (A) and 628 nm, 680 nm for (B). ( $[1] = 1 \times 10^{-5}$  M,  $\lambda_{exc} = 565$  nm,  $T = 298$  K).

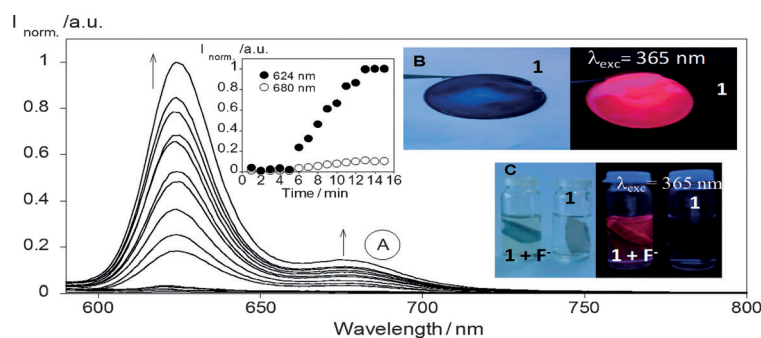
Although all derivatives interacted with this anion, the coordination of the corrole core with gallium(III) decreased their affinity for this anion, and consequently lower association constants were observed.

In general, all compounds showed interaction with  $CN^-$ . Two low-cost polymers based on polymethylmethacrylate (PMMA) and polyacrylamide were prepared and used in the detection of the anions  $F^-$  and  $CN^-$ . The PMMA polymers doped with compounds **1** and **5** show a purple color, and a strong red emission under UV lamp irradiation ( $\lambda = 365$  nm) or when excited in the spectrofluorimeter at 565 nm. However, the system did not show significant changes to the naked eye in the presence of the analytes. On the other hand, the acrylamide gel based on the same derivative **1** that in the absence of the analyte was not emissive was able to switch on the emission after being submerged in a fluoride solution. The reason of this enhancement in emission intensity is probably due to the large pores in the acrylamide gel that allow the entry of fluoride anions into the gel. The enhancement in the emission intensity with time of submersion in a fluoride solution was performed with this polymer, and the main results are shown in Figure 3. With cyanide a similar behavior was observed.

These studies were also extended to water samples. A polyacrylamide gel doped with corrole **1** was introduced in water previously doped with different concentrations of cyanide, such as, 0, 0.5, 1.0, 2.0 and 4.0 ppm. Overall, corrole **1** in a solid support is able to detect a maximum of 1 ppm of cyanide in water and a minimal amount of 70.0 ppb in water.

In the third chapter, the reactivity of the 3-vinylcorrole as a diene was extended to dimethyl acetylenedicarboxylate as dienophile. This study afforded the two new corrole derivatives **7** and **8** (Figure 4). The sensorial ability of the new macrocycles towards fluoride, cyanide, acetate and phosphate anions was carried out by absorption and emission spectroscopy. Compound **7** showed to be colorimetric to cyanide, where a change of color from green to colorless was visualized (Figure 5).

For in vivo applications, fluorescent chemosensors must to be water soluble. The change in the solubility of the corrole macrocycle resulting from the insertion of coumarin-type units in its structure is the subject of the fourth chapter. Two new corrole-coumarin derivatives were obtained from hetero-



**Figure 3.** A) Emission spectra of polyacrylamide gel doped with corrole **1** in the presence of  $F^-$  as a function of time ( $T = 298$  K,  $\lambda_{exc} = 570$  nm). B) PMMA film with **1** and C) polyacrylamide gel of **1** in the presence  $F^-$ .

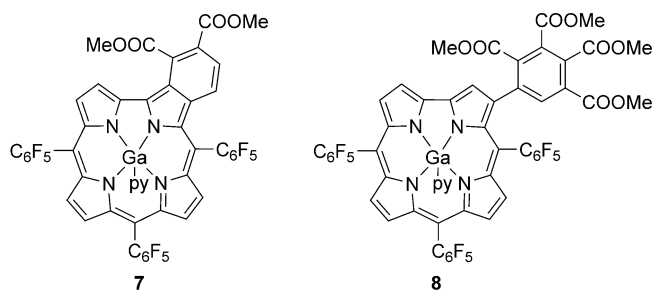


Figure 4. Structures of the derivatives 7 and 8.

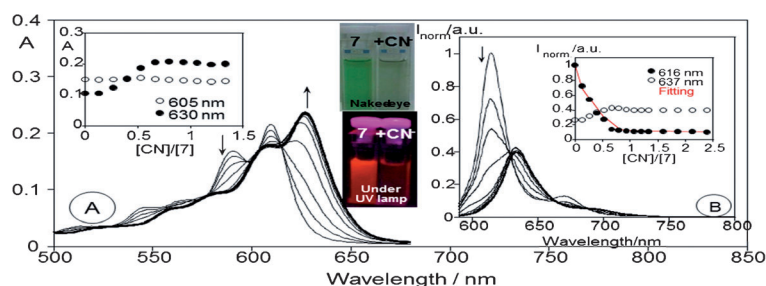
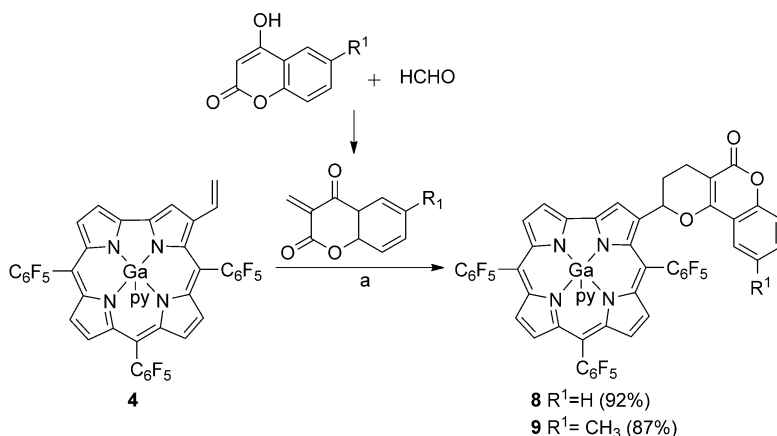


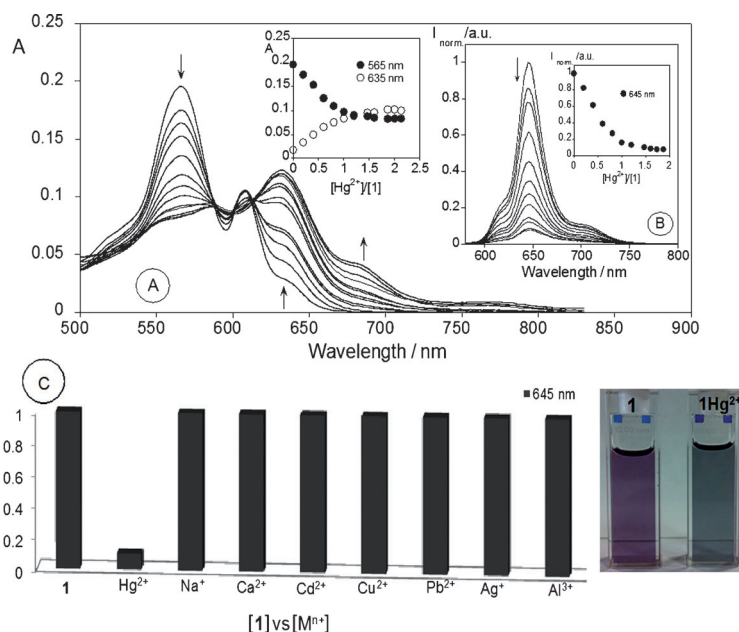
Figure 5. A) Spectrophotometric and B) spectrofluorimetric titration of compound 7 with the addition of  $\text{CN}^-$  in toluene.

Diels–Alder reactions between the 3-vinylcorrole and *o*-quinone methides (*o*-QM) generated in situ from Knoevenagel reactions of coumarins with paraformaldehyde (Scheme 3). The introduction of the coumarin moiety conferred an unusual solubility of these conjugates in ethanol and in ethanol/water (50:50) mixtures. The sensing ability of the resulting compounds was studied in the presence of different anions. All corrole-coumarin conjugates interacted with cyanide anions. These sensorial studies were extended to porphyrin-coumarin analogues. Porphyrin free-base conjugates were fully studied in a mixture of ethanol/water (50:50), showing a colorimetric effect (color change from purple to yellow) and an unprecedented selectivity for  $\text{Hg}^{2+}$ . Having in mind the biological and environmental application of these conjugates, non-expensive solid supports, like agarose and natural cellulose polymers were developed. In the cellulose support material (filter paper) the colorimetric effect for  $\text{Hg}^{2+}$  reveals a similar behavior as in solution.

The last chapter shows the sensorial ability of 5,10,15-tris(pentafluorophenyl)corrole (**1**) and of its monoanionic species  $1^-$  towards  $\text{Na}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Hg}^{2+}$ ,  $\text{Ag}^+$ ,  $\text{Al}^{3+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Cr}^{3+}$ ,  $\text{Ga}^{3+}$ ,  $\text{Fe}^{3+}$  metal ions in toluene and acetonitrile. The photophysical studies towards metal ions were carried out by absorption and emission spectroscopy. These corroles showed to be selective and colorimetric for  $\text{Hg}^{2+}$  (Figure 6). In addition, a new  $\beta$ -imine corrole was successfully synthesized and further function-



Scheme 3. Reagents and conditions: a) Dioxane, reflux,



**Figure 6.** A) Spectrophotometric and B) spectrofluorimetric titration of **1** with the addition of  $\text{Hg}^{2+}$  in acetonitrile. C) Normalized fluorescence at 645 nm of corrole **1** with addition of 0.5 equivalents of metal ions in acetonitrile [ $(\text{Na}^+, \text{Ca}^{2+}, \text{Cd}^{2+}, \text{Cu}^{2+}, \text{Pb}^{2+}, \text{Hg}^{2+}, \text{Ag}^+$  and  $\text{Al}^{3+}) = \text{M}^{n+}$ ]; and picture with a color change from purple to green-blue with the addition  $\text{Hg}^{2+}$  in acetonitrile.

alized with 3-isocyanatopropyl-trimethoxysilane resulting in an alkoxy silane derivative. Knowing that the incorporation of organic ligands in silica nanoparticles could improve the affinity, versatility and sensitivity of the chromophores to the guests, the grafting of the alkoxy silane derivative with optically transparent silica nanoparticles (SiNPs) was performed. The new, coated silica nanoparticles with corrole were studied in the presence of  $\text{Cu}^{2+}$ ,  $\text{Hg}^{2+}$  and  $\text{Ag}^+$  as metal ion probes. In the presence of  $\text{Ag}^+$  a change of color from green to yellow was observed.

The scientific work performed in this thesis allowed to obtain new knowledge on the corrole chemistry. Currently it is known that is possible to introduce a vinyl group in a  $\beta$ -pyrrolic position of the corrole core, through a Wittig reaction, and that the resulting  $\beta$ -vinylcorrole can participate as diene in Diels–Alder reactions or as dienophile in the presence of reactive *o*-quinone methides.

In terms of sensorial behavior, the 5,10,15-trisubstituted corrole showed to be highly sensitive to fluoride anions, and exhibited the highest value of fluorescence quantum yield. It was also observed that the insertion of a substituent at position 3 of the corrole unit leads to a decrease of the luminescent quantum yield. This decrease can probably be attributed to conformation issues.

Although the coordination with gallium(III) and the functionalization at 3-position have originated less emissive compounds, these derivatives have found application as colorimetric chemosensors and as solid support sensors.

**Keywords:** chemosensors · corroles · cycloaddition reactions · nanoparticles

#### Publications arising from this work:

- C. I. M. Santos, E. Oliveira, J. F. B. Barata, M. A. F. Faustino, J. A. S. Cavaleiro, M. G. P. M. S. Neves, C. Lodeiro, *Inorg. Chim. Acta* **2013**, *in press*, DOI: 10.1016/j.ica.2013.09.049.
- C. I. M. Santos, E. Oliveira, J. C. J. M. D. S. Menezes, J. F. B. Barata, M. A. F. Faustino, V. F. Ferreira, J. A. S. Cavaleiro, M. G. P. M. S. Neves, C. Lodeiro, *Tetrahedron* **2013**, *in press*, DOI: 10.1016/j.tet.2013.07.022.
- C. I. M. Santos, E. Oliveira, J. F. Lodeiro, J. F. B. Barata, S. M. Santos, M. A. F. Faustino, J. A. S. Cavaleiro, M. G. P. M. S. Neves, C. Lodeiro, *Inorg. Chem.* **2013**, *52*, 8564–8572.
- C. I. M. Santos, E. Oliveira, J. F. B. Barata, M. A. F. Faustino, J. A. S. Cavaleiro, M. G. P. M. S. Neves, C. Lodeiro, *J. Mater. Chem.* **2012**, *22*, 13811–13820.

Received: February 27, 2014  
Published online on April 11, 2014