Corrole dimers as photosensitizers: synthesis and antimicrobial activity studies

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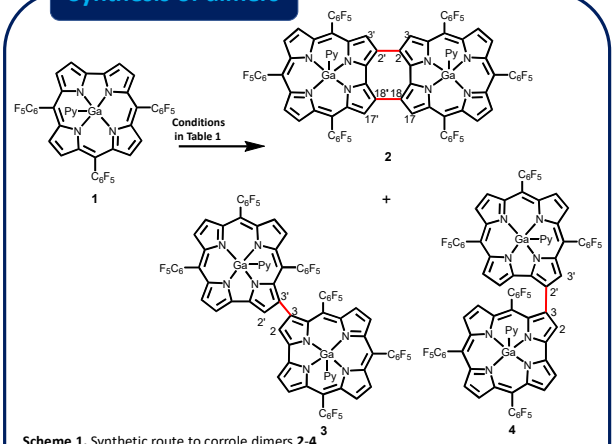
Introduction

Corrole oligomers have emerged as a new class of π-conjugated materials with unique optical, electrical, and magnetic features.[1] Singly linked (*e.g.* **3** and **4**, Figure 1) and doubly linked (*e.g.* **2**, Figure 1) corrole dimers have been synthesized, via a multistep process that relied on regiospecific Pd-catalysed oxidative coupling reactions or by thermo-oxidative conditions.[2] The electronic spectra of corrole dimers such as **2** fall within the PhotoDynamic Therapy (PDT) therapeutic window (600 – 800 nm), which makes them promising candidates to be used as photosensitizers (PS).[2b] To the best of our knowledge the use of corrole dimers as PS has not yet been explored.

Following our interest in the development of new corrole PS to be used in antimicrobial PhotoDynamic Therapy (aPDT),[3] in this communication we will discuss the ability of corrole dimers to photoinactivate a multiresistant *Staphylococcus aureus* strain. Also, a peculiar alternative to the synthesis of dimers **2-4** mediated by acidic conditions will be discussed and their structural, photophysical, and photochemical characterization will also be presented.

Synthesis of dimers



Scheme 1. Synthetic route to corrole dimers **2-4**.

Table 1 - Experimental reaction conditions and its effect on the yield of obtained dimers **2-4**.

Experimental conditions			Yield[a] / %			
Solvent	Temp. (°C)	Time (h)	1	2	3	4
AcOH / TFA / 5% H_2SO_4	100	2	-	15	5	14
AcOH / TFA / 5% H_2SO_4	100	0.5	19	10 (12)	c)	8 (10)
AcOH / TFA / 5% H_2SO_4	40	2	b)	c)	c)	c)
AcOH	100	2	61	c)	10 (26)	3 (8)
AcOH / 5% H_2SO_4	100	2	56	12 (27)	10 (23)	15 (34)

[a] number in brackets refers to yield regarding recovered starting corrole **1**.
[b] recovered
[c] obtained in vestigial amount.

Structural, photophysical, and photochemical characterization

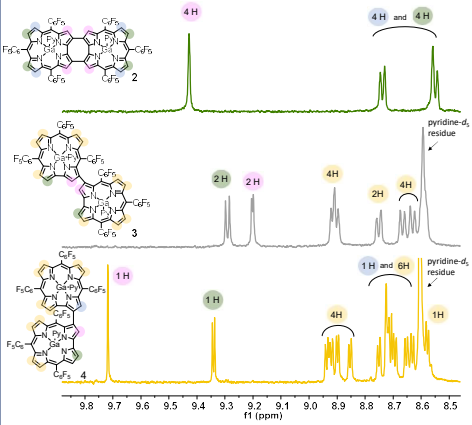


Figure 1. ^{1}H NMR spectra of corrole dimer **2** in $CDCl_3$ and corrole dimers **3** and **4** in $CDCl_3$ + pyridine-d_5.

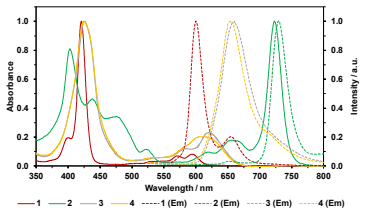


Figure 2. Normalized absorption (—) and fluorescence (---) spectra in DMF of corrole **1** and dimers **2-4** (λ_{exc} = 420 nm).

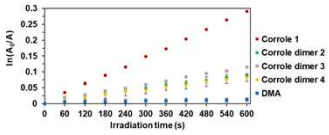


Figure 3. Photo-oxidation of 9,10-dimethylanthracene (DMA 30 μM in DMF) by $^1O_2$ generated by each PS when exposed to monochromatic light (420 nm). Error bars represent standard deviation between two independent experiments.

Antimicrobial activity studies

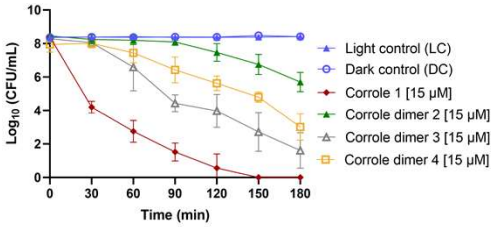


Figure 4. aPDT inactivation of *S. aureus*, in the presence of PS **1-4**, at 15 μM, for a total of 180 min of irradiation with white light (50 mW/cm^2). LC corresponds to the exposure of bacterial cells to white light, with no PS added; DC corresponds to the exposure of bacterial cells to PS at 15 μM in the absence of light. Values are expressed as the mean of three independent experiments with two replicates. Error bars represent standard deviation between experiments.

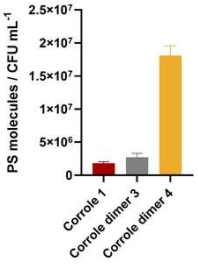


Figure 5. Quantification of adhesion of PS molecules to *S. aureus* bacterial cells after 15 min of dark incubation, at room temperature, at the concentration of 15 μM for each PS tested. Values are expressed as the mean of three independent experiments. Error bars represent standard deviation between experiments.

Conclusions:

☑ Bis-gallium(III) corrole dimers **2-4** were successfully obtained from gallium corrole **1** using a mixture of acids.
☑ The corrole dimers exhibit ability to photoinactivate the Gram(+) bacterium *S. aureus* under white light irradiation, although their photodynamic efficiency is dependent on the position, type of linkage between the monomer units, and aggregation behaviour.

Acknowledgements:

Thanks are due to University of Aveiro and FCT/MCTES for the financial support to CESAM (UIDP/50017/2020 + UIDB/50017/2020), and LAQV-REQUIMTE (UIDB/50006/2020) through national funds and, where applicable, co-financed by the FEDER, within the PT2020 Partnership Agreement, and to the Portuguese NMR Network, which partially support the NMR spectrometers by Infrastructure Project Nº 022161 (co-financed by FEDER through COMPETE 2020, POCI and PORL and FCT through PIDDAC). This work was financially supported by the project Corlutna (POCI-01-0145-FEDER-031523 - PTDC/QUI-ORG/31523/2017) funded by FEDER, through COMPETE2020 - Programa Operacional Competitividade e Internacionalização (POCI), and by national funds (OE), through FCT/MCTES. The research contract of Paula S. S. Lacerda and grant (BI/UI88/49950/2021) of Maria Bartolomeu are supported by project Corlutna.

References

1. S. Ooi, et al., *Chempluschem* **2019**, *84*, 578.
2. a) S. Hiroto, et al., *J. Am. Chem. Soc.* **2006**, *128*, 12380. b) J. F. B. Barata, et al., *Tetrahedron Lett.* **2006**, *47*, 8171. c) S. Bhowmik, et al., *Inorg. Chem.* **2017**, *56*, 2287.
3. T. A. F. Cardote, et al., *An. Acad. Bras. Cienc.* **2018**, *90(1 Suppl. 2)*, 1175.