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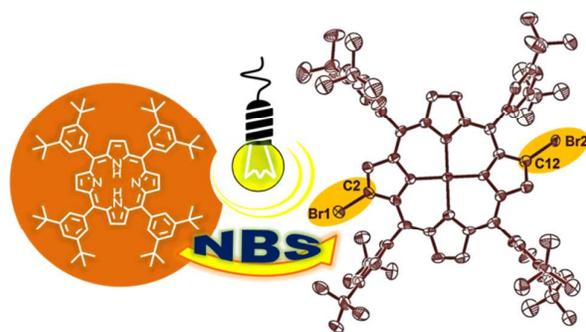
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GRAPHICAL ABSTRACT



A Schematic Representation of the Light-Induced Regiospecific Functionalization of *meso*-Tetra(3,5-Di-*tert*-butylphenyl)Porphyrinic Core by NBS-mediated Bromination.

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3 KEYWORDS: Porphyrins, Regioselective Bromination, X-Ray Structure Determination, DFT
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5 Calculations
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10 ABSTRACT

11 The antipodal introduction of two bromine atoms on 2,12 β -pyrrolic position of 5,10,15,20-
12 tetra(3,5-di-*tert*-butylphenyl)porphyrin was successfully achieved by a light-induced reaction of the
13 substrate with excess NBS. Complexation with Ni^{II} of the major regioisomer led to good quality
14 crystals, suitable for X-ray structure determination with unprecedented probability levels. The
15 regiospecific character of the synthetic procedure and the exactness of the bromine atom position
16 assignment were thus confirmed, suggesting also an unexpected electrophilic aromatic substitution
17 pathway rather than a free-radical halogenation process. A QTAIM topological analysis on the DFT
18 optimized wavefunction of the mono-substituted free-base porphyrin intermediate carrying a
19 bromine atom in C2 β -pyrrolic position confirmed the largest negative charge for the C12 carbon
20 atom in antipodal position, in agreement with the proposed electrophilic aromatic substitution
21 mechanism.
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3 INTRODUCTION
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5 Porphyrins are one of the most widely investigated classes of molecules in chemistry,¹ because they
6 are featured by high chemical stability, interesting optical and photophysical properties and
7 catalytic activities, all of which are being used in a wide range of research fields such as medicine,²
8 biology,³ catalysis,⁴ optoelectronics⁵⁻⁷ and green energy engineering.⁸⁻¹⁰ Porphyrins can also be
9 subjected to a modulation of their chemical structure resulting in rational control of their electronic
10 properties. In particular, chemical functionalization of porphyrinic core *via* a bromination strategy¹¹
11 followed by cross-coupling reactions¹² or nucleophilic aromatic substitutions^{13,14} appears to be
12 beneficial in tuning the properties of macrocyclic systems in accordance with the structural
13 requirements necessary for a specific application. In fact it was recently reported by some of us that
14 the properties of β -functionalized Zn^{II}-porphyrinates are strongly influenced by introducing π -
15 delocalized systems to the macrocyclic core.^{5,15} These substituents directly linked on pyrrolic
16 positions exert strong steric and electronic effects on the porphyrinic rings¹⁶ resulting in a dramatic
17 alteration of their optical, electrochemical and spectroelectrochemical properties.¹⁷ For these
18 reasons brominated porphyrinic intermediates are considered extremely important building-blocks
19 to synthesize more complex and extended structures and thus numerous synthetic approaches have
20 been proposed in order to selectively functionalize the macrocyclic ring on its different positions.¹¹
21 Owing to the large number of delocalized π -electrons, the porphyrinic core is highly sensitive to
22 electrophilic aromatic substitution reactions which can occur on two different receptive positions.
23 The carbon atoms at the *meso* positions, consisting of four methenyl bridges on the porphyrinic
24 core, exhibit excellent reactivity to the substitution of a hydrogen with a bromine atom, so that their
25 functionalization occurs with high yields under relatively mild conditions.^{18,19} On the contrary β -
26 positions, comprising the eight carbon atoms of the four pyrrolic rings, are less responsive to the
27 bromination reaction requiring stricter settings.^{20,21} These severe reaction conditions strongly
28 influence the substitution degree of the porphyrinic core which is difficult to control. Hence a
29 mixture of poly-brominated derivatives and several regioisomers are typically obtained by various
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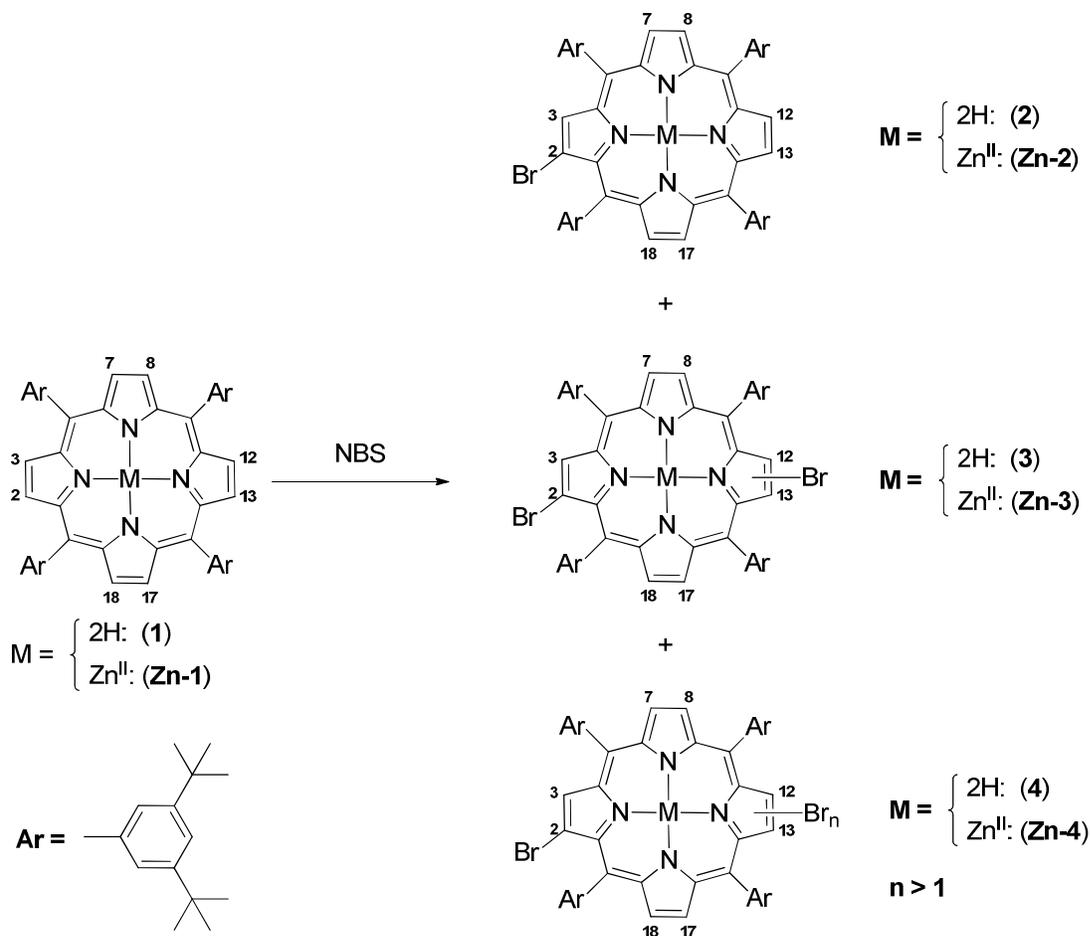
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3 β -bromination procedures.¹¹ Furthermore hard purification steps of the reaction mixture are
4 required inducing, in turn, a decrease of the overall yield of a single specifically brominated species.
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6 Since the 70s, several bromination procedures have been investigated in order to obtain various β -
7 functionalized tetraarylporphyrinic structures, in particular *via* synthetic pathways involving N-
8 Bromosuccinimide (NBS). Among all of the reported approaches the method first proposed by
9 Callot,^{20,21} which requires to reflux a solution of tetraphenylporphyrin (TPP) in CHCl₃ with
10 appropriate equivalents of NBS, is still the most commonly used. Thanks to this approach, it has
11 been possible to functionalize the porphyrinic core with a range of bromine atoms from one to
12 eight. Numerous authors have employed this procedure to brominate either TPP or other different
13 tetraarylporphyrins.²²⁻²⁴ Subsequently, other NBS mediated bromination procedures^{12,25} were
14 proposed to attain poly-functionalized porphyrins,²⁶⁻²⁸ however only in a few cases the reaction
15 mechanism was investigated in detail. Consequently, factors and reaction conditions which drive
16 the regiochemistry of these substitutions,¹³ especially when various bromine atoms should be
17 introduced in specific positions of the porphyrinic ring, are still quite unknown.

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34 A particularly unclear topic remains the partial bromination of the antipodal positions, indeed
35 several attempts to selectively introduce only two bromine atoms on opposite pyrrolic residues in a
36 well defined arrangement failed. Bhyrappa et al.²⁹ have achieved the antipodal introduction of two
37 bromine atoms on free base TPP by controlling the concentration of NBS working at room
38 temperature obtaining a mixture of 2,12/2,13/2,3 dibromo regioisomers. An alternative bromination
39 procedure of free-base non-planar porphyrins involving two equivalents of NBS in refluxing
40 chloroform was reported by Senge et al.³⁰ to give a small portion of 2,13-dibromo isomer in a pure
41 form after repeated purification steps of the complex reaction mixture.

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Despite the difficulties in obtaining porphyrinic rings specifically dibrominated on the antipodal
pyrrolic positions with significant yields and in pure forms, these structures have emerged as
fundamental precursors for the synthesis of specific asymmetric push-pull systems.¹⁰ These latter, in
fact, showing highly defined architectures, play an extremely important role as chromophores both

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3 in non-linear optics (NLO)^{5,6} and in Dye Sensitized Solar Cell (DSSC)¹⁰ applications. The
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5 regiospecific functionalization of opposite pyrrolic units is thus considered the focal step to obtain
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7 the key building-blocks for the synthesis of attractive push-pull porphyrinic systems. Therefore it
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9 has become of great interest to develop a facile and effective synthetic procedure to successfully
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11 introduce two bromine atoms on specific antipodal positions thus reducing the formation of
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13 regioisomers and increasing the overall synthetic yield of such specific porphyrinic systems.

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16 As the electronic distribution of the π -delocalized porphyrinic core is strongly influenced by the
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18 four *meso* aryl substituents, which then affect the pyrrolic substitution degree and consequently the
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20 functionalization yields, it is unrealistic to design a general bromination procedure suitable for all
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22 tetraarylporphyrinic systems. For these reason, in this work, we have focused our attention on a
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24 specific substrate consisting of the free-base 5,10,15,20-tetra(3,5-di-*tert*-butylphenyl) porphyrinic
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26 core **1** and on its Zn^{II}-complex **Zn-1** (Scheme 1).
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Scheme 1. Schematic NBS-mediated bromination of the free-base porphyrin (**1**) and the Zn^{II} -porphyrinate (**Zn-1**) on β -pyrrolic positions. The positions of substituents in dibrominated (**3** and **Zn-3**) and in polybrominated (**4** and **Zn-4**) porphyrinic structures depend on bromination conditions.

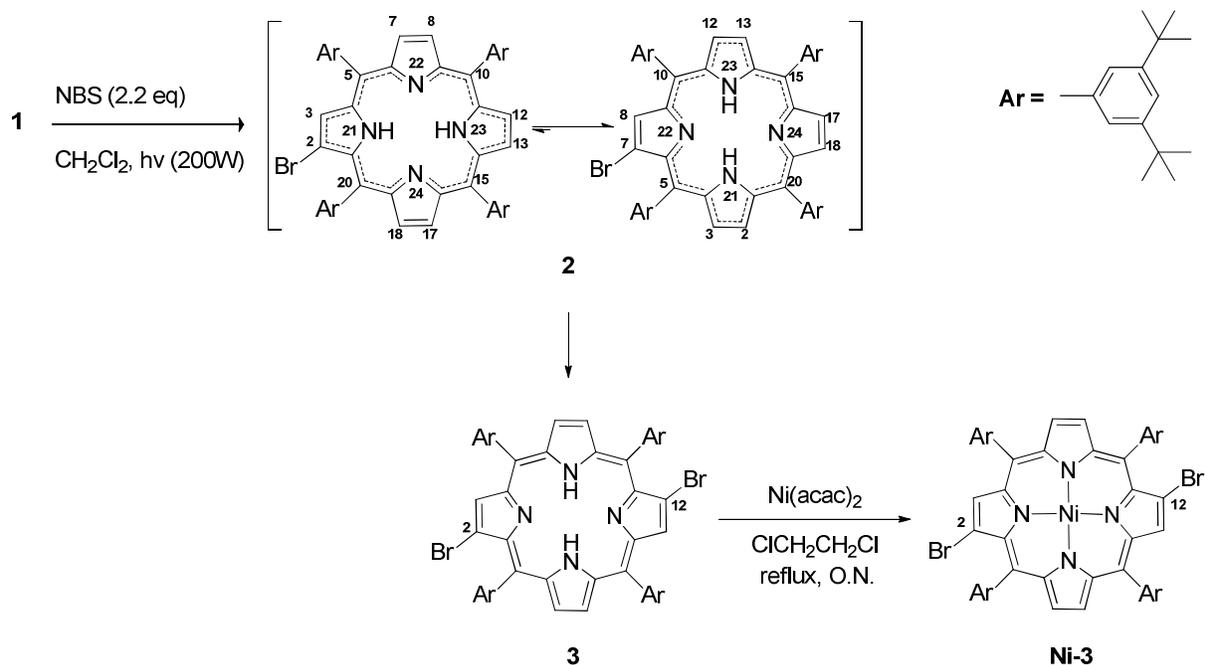
With the aim to compare the efficiency and the selectivity of various bromination procedures on substrates **1** and **Zn-1**, the relative amounts of monobromo substituted porphyrins (**2** and **Zn-2**), dibromo substituted porphyrins (**3** and **Zn-3**) and polybrominated derivatives will be also reported (Table 1).

Table 1. Set of Various Synthetic Attempts; “X” Is the Relative Amount of Products in the Crude of Reaction.

Entries	Free-Base Porphyrin (1)	Zn-Complex Porphyrin (Zn-1)	NBS Equivalents	Reaction Conditions	Unreacted Porphyrin (1 or Zn-1)	Mono-Bromo Derivative (2 or Zn-2)	Di-Bromo Derivatives ^a (3 or Zn-3)	Poly-Bromo Derivatives ^a (4 or Zn-4)
a ^{20,21}	•		1.7	CHCl ₃ ; 1h reflux	XX	X	X	XX
b ³¹	•		1.1	Py; CHCl ₃ , 1h r.t.	XX	XX	X	X
c ³²	•		1.1	CH ₂ Cl ₂ /CH ₃ OH; 10 min reflux	XX	X	X	XX
d ³³	•		1.7	CHCl ₃ ; 18h reflux	X	X	X	XXX
e ¹²		•	1.1	CH ₃ OH; 1h reflux	XXX	-	-	-
f ^{10,17}		•	1.8	CCl ₄ ; 2h reflux	-	XXX	XXX	-
g	•		2.1	CCl ₄ ; 2h reflux	X	XXX	XX	-
h	•		2.1	CCl ₄ ; 200W lamp 4h	X	XX	XX	X
i	•		2.2	CH ₂ Cl ₂ ; 200W lamp 4h	X	XX	XXX	-
j		•	2.2	CH ₂ Cl ₂ ; 200W lamp 4h	-	XXX	XX	X
k	•		2.2	CH ₂ Cl ₂ ; 4h reflux	X	X	XX	XX

^amixtures of regioisomers

Furthermore, the rational optimization of the reaction conditions has allowed us to develop a regioselective synthetic procedure to unquestionably obtain the 2,12-dibromo substituted regioisomer **3** (Scheme 2).



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Scheme 2. Schematic representation of the tautomeric equilibrium of the 18- π -annulene system in the monobromo intermediate **2** and the assignment variation of the bromine substituent according to the different ways of fixing the inner hydrogens. Regiospecific synthesis of the free-base 2,12-dibromo substituted porphyrin (**3**) and its Ni^{II}-porphyrinate (**Ni-3**).

In particular, this specific antipodal pyrrolic functionalization occurred with good yields on the free-base porphyrinic core by a light-induced reaction with N-bromosuccinimide (NBS) in dichloromethane. The complexation of the regioisomeric product gave the Ni^{II} complex **Ni-3** (Scheme 2) in pure form providing good quality crystals for X-ray structure determination (Figure 1) which confirmed the accuracy of the substituents assignment and the high regiospecificity of the proposed synthetic procedure. Crystallographic details of the data collection and refinement parameters (Table S1) as well as selected bond lengths [\AA] and angles [$^\circ$] for compound **Ni-3** (Table S2) are reported in the Supporting Information.

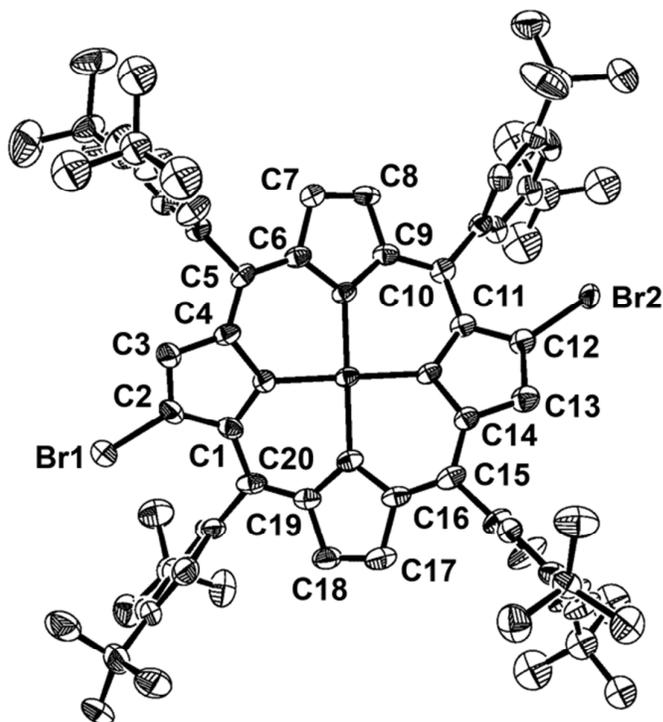
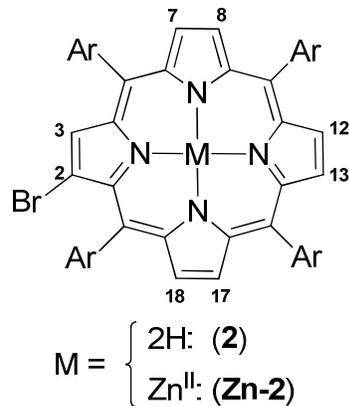


Figure 1. A view of the molecular structure of **Ni-3** with the atom-numbering scheme. *Thermal ellipsoids* are represented at the 50% probability level. Hydrogen atoms and disorder are omitted for clarity. Only one set of rotationally disordered bromine substituents is shown.

The selective introduction of bromine atoms on the specific 2,12 β -pyrrolic positions has also suggested that this light-induced bromination procedure occurred by an unexpected electrophilic aromatic substitution pathway rather than *via* a free-radical halogenation process. The substitution mechanism has been rationalized by means of quantum-mechanical calculations on both monobromo derivative **2** and its metal complex **Zn-2** (Table 2), *in vacuo* and in solvent, aimed at determining the net atomic charges of the pyrrolic carbons after introduction of the first bromine atom on a pyrrolic position of the porphyrinic ring. These calculations allowed us to determine the electronic effect of the halogen substituent on the remaining pyrrolic carbons, thus predicting the more reactive sites for electrophilic substitution.

Table 2. M06/6-311G(d) Integrated Net Charges q (e) of the Atomic Basins of Mono-Brominated Free-Base (**2**), *in vacuo* and CH_2Cl_2 , and its Zn^{II} Complex (**Zn-2**) *in vacuo* and CCl_4 , Computed by QTAIM Partitioning

Atom	Free-Base (2)		Zn^{II} -Complex (Zn-2)	
	<i>vacuum</i>	CH_2Cl_2	<i>vacuum</i>	CCl_4
C3	-0.0421	-0.0464	-0.0345	-0.0379
C7	-0.0477	-0.0482	-0.0654	-0.0693
C8	-0.0482	-0.0489	-0.0656	-0.0692
C12	-0.0776	-0.0817	-0.0678	-0.0714
C13	-0.0769	-0.0813	-0.0659	-0.0698
C17	-0.0487	-0.0496	-0.0659	-0.0699
C18	-0.0461	-0.0486	-0.0633	-0.0678



RESULTS AND DISCUSSION

In the last decades several efforts were devoted to optimize the conditions to regioselectively brominate the pyrrolic rings of porphyrinic core.^{11-13,34} Up to now the reported synthetic procedures led mainly to complex mixtures of variously substituted porphyrins providing by purification only crystals with disordered structures wherein bromine atoms were arranged in several β -pyrrolic positions with different probabilities.^{29,30}

Crossley et al.³⁵ first observed the regioselective introduction of 4 bromine atoms at the antipodal positions of a tetraarylporphyrin. The driving force of such a selective functionalization was suggested to be due to the degenerate aromatic systems of the porphyrinic core. The aromatic delocalization, defined by a $18\text{-}\pi$ -annulene system with two isolated double bonds on the porphyrinic periphery, involved two distinct tautomeric forms (Scheme 2). When a substituent was introduced in a β -pyrrolic position, the aromatic delocalization pathway was altered shifting the equilibrium to the tautomeric form with a localized double bond arranged on the pyrrolic ring opposite to that bearing the substituent. Hence a more susceptible site to electrophilic attack resulted on the antipodal pyrrolic position compared to the $18\text{-}\pi$ -annulene system with a more

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3 prominent aromatic character. Subsequently, Crossley et al.¹³ have also shown that the reaction of
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5 free-base porphyrins with 4.3 equivalents of NBS in boiling ethanol-free chloroform afforded the
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7 7,8,17,18 tetrabromo substituted porphyrin rather than the misassigned 2,7,12,17 tetrabromo isomer
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9 as previously proposed by Callot.^{20,21} Moreover, Smith et al.³⁶ have described a further attractive
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11 synthetic approach to drive a dibromination of porphyrins regiospecifically on C2 and C3 pyrrolic
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13 positions. A suitable electron-withdrawing moiety, such as a nitro group, previously introduced in a
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15 β -pyrrolic site, was able to impose the electrophilic attack at both carbons of the antipodal pyrrolic
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17 ring.
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21 Here, we focused our attention on the specific porphyrinic core **1** consisting of four 3,5-di-*tert*-
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23 butylphenyl units directly linked on 5,10,15,20 *meso*-positions (Scheme 1). This substrate was
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25 previously selected, by some of us, as a suitable precursor to synthesize various β -substituted
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27 porphyrinic Zn^{II} complexes as promising sensitizers to assemble highly performing DSSCs.^{10,15,37}
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29 The bulky aryl substituents were evidenced to confer a great sterical hindrance to the dye structures
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31 thus suppressing the undesired aggregation among porphyrinic systems and simultaneously
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33 inducing excellent passivation of the TiO₂ photoanode³⁷ thanks to its intrinsic shielding character.
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37 With the aim to optimize the selective β -pyrrolic functionalization of the porphyrinic core on
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39 specific antipodal sites, we have performed several NBS-mediated bromination procedures both on
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41 free-base porphyrin **1** and on its Zn^{II}-complex **Zn-1**. An overview of the tested methods is
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43 schematically reported in Table 1. The entries **a-f**^{10,12,17,20,21,31-33} have already been investigated for
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45 TPP or similar porphyrinic molecules, thus, by using **1** and **Zn-1** as substrates, some differences can
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47 be noticed in the reaction results when compared to those earlier reported. Finally, the conditions of
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49 procedures **g-k** have been rationally optimized specifically for our substrates, **1** and **Zn-1**, in order
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51 to improve both regioselectivity and reaction yield. It was observed that **a-e** bromination procedures
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53 yielded a complex mixture of products consisting of the unreacted porphyrin (**1** or **Zn-1**), the mono-
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55 bromo derivative (**2** or **Zn-2**), dibrominated regioisomers (**3** or **Zn-3**) and the poly-functionalized
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57 derivatives (**4** or **Zn-4**), resulting in a hard purification of the crude. The mono-functionalization of
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3 the core was observed to successfully occur in good yield by optimizing the procedure proposed by
4 D'Souza.¹⁷ In particular a solution of the Zn^{II}-porphyrinate **Zn-1** in CCl₄ was refluxed in presence
5 of a slight excess of NBS (1.1 equivalents), as previously reported by some of us,¹⁰ while 1.8
6 equivalents were necessary to give the di-brominated Zn^{II}-porphyrinate **Zn-3**. This latter was
7 obtained with good yield (60%) as major component of reaction mixture following the procedure **f**
8 but we failed in the first attempts to discriminate which of the dibrominated regioisomers are
9 mainly formed as previously suggested.¹⁰ Only the slow evaporation at low temperature of a THF
10 solution of **Zn-3** has allowed us to obtain crystals good enough for an X-ray crystallographic
11 structure determination (see Figure S1 in the Supporting Information). The crystallographic
12 investigation has revealed the presence of the 2,13 di-bromo derivative as the major component in
13 a crystal containing at least 3 di-substituted regioisomers. In fact, the **Zn-3** X-ray structure has
14 shown a disorder similar to those previously reported,^{29,30} thus it was necessary to refine the crystal
15 structure by using a site-occupancy disorder model. The bromine substituents were located in the
16 Fourier difference map and were refined with free occupancy variables and fixed B-factors. The
17 similarity in the resulting occupancies has allowed the identification of the three regioisomers
18 although problems related to poor quality of the crystal and the low intensity of the diffraction
19 pattern have not led to satisfactory R values. Despite these limitations the occupancy of the 2,13
20 disubstituted isomer has been found to be 50%, whereas the occupancies of the 2,7 and 2,3 isomers
21 have been 33% and 17% respectively. These findings have suggested a reduced selectivity of the
22 bromination of a metallo-porphyrinate that could be rationalized by the loss of localized double-
23 bond character in the macrocyclic π system after metallation of the porphyrinic core.¹³ Nevertheless
24 it is noteworthy that no unreacted product has been recovered by bromination of **Zn-1** using **f** and **j**
25 procedures suggesting an increased reaction yield when the reaction takes place on the Zn^{II}-
26 porphyrinate, with the exception of procedure **e** which resulted ineffective due to the low solubility
27 of the porphyrinate in methanol. The observations reported in Table 1 have also suggested that at
28 least 1.8 equivalents of NBS (entries **f-k**) are necessary to obtain appreciable amount of β di-
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3 brominated porphyrins. Moreover, in order to reduce the formation of poly-brominated products
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5 and to improve the regiospecific functionalization of the pyrrolic rings of porphyrinic core, mild
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7 reaction conditions are mandatory (entries **h-j**). Finally, the synthetic procedure **i** has been
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9 appointed as an effective route to unquestionably provide a specific antipodal di-bromo
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11 regioisomer. In this procedure the light-induced bromination approach has specifically provided the
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13 pure 2,12 di-bromo isomer **3** with 42% yield starting from the free-base 5,10,15,20 tetra(3,5-
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15 ditertbutylphenyl) porphyrin **1** as summarized in Scheme 2. This regiospecific functionalization
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17 process takes place in the presence of 2.2 equivalents NBS by irradiating the reaction mixture with
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19 a 200W lamp which maintains a slight reflux in dichloromethane. Hence, with the aim to validate
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21 the positive effect of the light irradiation on regioselectivity, we have also performed the
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23 bromination step of the free-base porphyrin **1** by refluxing the reaction vessel in dark conditions
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25 (entry **k**, Table 1). This latter method has provided a complex mixture of regioisomers hard to
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27 purify, similar to that achieved by Callot procedure,^{20,21} thus confirming our assumptions.

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31 The β disubstituted porphyrinic regioisomer **3**, obtained as major component by the light-induced
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33 procedure **i**, after chromatographic purification has successfully reacted overnight, in a 1,2-
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35 dichloroethane refluxing solution, with Nickel(II) acetylacetonate ($\text{Ni}(\text{acac})_2$) giving quantitatively
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37 the pure Ni^{II} -porphyrinate **Ni-3**, as shown in Scheme 2. This latter step has given crystals of very
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39 good quality thus allowing an X-ray structure determination with unprecedented probability levels.
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41 The **Ni-3** molecular structure, reported in Figure 1, presents a bromine distribution and a rotational
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43 disorder very similar to those reported for the molecular structure of 2,12-dibromo-5,10,15,20-
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45 tetraphenylporphyrin,³⁰ wherein half of the molecule, and therefore only one bromine, was present
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47 in the asymmetric unit. The second antipodal substituent was generated by symmetry leading to one
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49 specific regioisomer. Actually, in that structure, the bromine atoms were disordered over three
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51 different positions, refined with different occupancies, generating a clear and well defined rotational
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53 disorder. On the contrary, in the **Ni-3** crystal structure there is only one crystallographically
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55 independent molecule which shows four disordered bromine atoms in 2,3 and 12,13 positions.
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3 However, the rotational disorder is well resolved because it is limited to the two specific positions
4 and the high quality of the data has allowed us to couple the bromine atoms in 2,12 antipodal
5 positions. Thus the nature and the purity of **Ni-3** regioisomer, and consequently of its free-base
6 precursor **3**, have been confirmed.
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11 It is noteworthy that a di-bromo derivative, very similar to the porphyrin **3**, was previously
12 identified by Crossley et al.^{13,35} as a 7,17 rather than a 2,12 disubstituted regioisomer. This
13 particular attribution was ascribed to the introduction of bromine atoms on β pyrrolic carbons with
14 the inner hydrogens at the porphyrinic ring fixed in N-21 and N-23 positions (Scheme 2) thus
15 imposing the character of double bonds in $\Delta^{7,8}$ and $\Delta^{17,18}$. On the other hand, metal-complexation
16 reverts the attribution to the 2,12-dibromo regioisomer since no tautomeric forms are allowed due to
17 the lack of inner hydrogens. Such effect on the assignment of the substituents position could make
18 the comparison of the free-base porphyrinic derivatives with their metal complex forms rather
19 unclear. Hence, for a better comprehension of our results, we have arbitrarily assigned the
20 substituents position starting from C2 even for the free-base porphyrin **3**. Consequently, the free-
21 base porphyrin **3** will be referred as to the 2,12 dibrominated regioisomer (Table 2) rather than to its
22 7,17 tautomeric form.
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38 With the aim to gain deeper insight about geometrical characteristics of the 2,12 dibrominated Ni^{II} -
39 porphyrinate, the distances among atoms within the porphyrinic core and the resulting distortion of
40 structure were further investigated. The Ni(II) metal center adopts a quasi-ideal square planar
41 coordination geometry with the N-Ni-N angles near 90° (89.33- 90.74°) and a maximum deviation
42 of 0.003 Å from the NiN4 mean plane. The average Ni-N distance of 1.909 Å is quite similar to that
43 found in other analogous complexes³⁸ though the bond lengths in the case of the two nitrogen of the
44 brominated pyrrolic rings result slightly longer (1.898-1.896 Å; 1.911-1.932 Å). This is due
45 essentially to the distortion of the porphyrinic core that results in a different transannular distance
46 for the two N ··· N couples. Thus the macrocyclic hole results *stretched* in the direction of the two
47 substituted rings as frequently observed in the distortion pattern of metal complexed
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3 porphyrins.^{30,36,39} The significant distortion of the porphyrin core can be described as a mixing of
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5 saddle and ruffle distortion modes with a maximum displacements from the 24-core atoms mean
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7 plane of 0.64 and 0.40 Å for the meso-carbons (ruffle-shaped distortion) and β -pyrrolic positions
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9 (saddle-shaped distortion) respectively. The noteworthy contribution of the ruffling distortion to the
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11 macrocycle deformation is stressed by the value of the dihedral angles between the planes of the
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13 opposite pyrrolic rings (38.9° and 37.6°). Instead, the dihedral angles between the phenyl rings and
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15 the mean plane formed by the 24-atoms core, lie in the range 73.5°- 89.1° that suggest only weak
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17 steric interactions between the phenyl rings and the adjacent antipodal bromine substituents.
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21 With the aim to rationalize the impressive regioselectivity obtained by the light-induced NBS-
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23 mediated bromination of **1** we were interested in figuring out the mechanism which drives the
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25 introduction of the two bromine atoms on 2,12 pyrrolic positions of the porphyrinic core. As
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27 previously reported⁴⁰ and now confirmed by our results, the free-base porphyrinic ring **1** results to
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29 be less reactive to the bromine aromatic substitutions than the Zn^{II}-porphyrinate **Zn-1**, thus the light
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31 irradiation has been initially employed to improve the reaction rates. At first this approach was
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33 reasonably expected to promote a radical pathway involving a homolytic bond cleavage of NBS.
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35 With the light irradiation, instead, the NBS-mediated bromination has specifically provided the 2,12
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37 di-bromo regioisomer **3** as major product, the mono-bromo derivative **2** as minor component and
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39 only small traces of other di-bromo regioisomers and poly-brominated derivatives (**4**). Even if it is
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41 known that NBS can react both by radical mechanisms in the case of non-delocalized double-
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43 bonds⁴¹ or by electrophilic aromatic substitution in polar⁴² and in non polar solvents,⁴³ the observed
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45 remarkable regioselectivity by a light-induced bromination was unexpected. However similar
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47 findings were earlier reported by Gruter et al.⁴⁴ who evidenced that the nuclear bromination of
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49 anisole took place *via* an electrophilic aromatic substitution mechanism under irradiation
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51 conditions.
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56 Consequently an in-depth theoretical investigation has been performed to support and rationalize
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58 the electrophilic aromatic substitution process. The results of a QTAIM topological analysis on the
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3 charge density distribution of the free-base mono-brominated porphyrin **2**, as determined by M06/6-
4 311G(d) DFT calculations both in *vacuo* and in the same solvent used for the synthesis (CH_2Cl_2),
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6 are summarized in Table 2. In this Table, we report the net atomic charges obtained by integration
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8 over the volume of atomic basins as defined within QTAIM. It can be noticed that the carbon atoms
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10 C12 and C13, in antipodal position with respect to the pyrrolic unit bearing the bromine atom, show
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12 the largest negative charges, while the carbon atom C3, adjacent to the bromine substituted carbon,
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14 is the less negative one. By comparing the net charges on C12 and C13 very small differences can
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16 be observed, with the former showing slightly more negative charge than the latter. This trend is
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18 confirmed to be the same both in *vacuo* and in CH_2Cl_2 solvent and also by varying the
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20 computational methodology (see Table S3), thus suggesting a slight preference of an electrophilic
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22 aromatic substitution on C12 position rather than on C13, as experimentally observed.
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27 In order to better understand the influence of the metal complexation on the electrophilicity of
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29 porphyrinic core, the atomic net charges on the pyrrolic carbons of the porphyrinic intermediate **Zn-**
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31 **2** have been also determined *in vacuo* and in CCl_4 , the solvent used for the synthesis (see Table 2).
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33 A slightly more negative charge was obtained for the C12 carbon atom on the opposite side of
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35 pyrrolic ring bearing the bromine substituent. Nevertheless in this case the charge values are much
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37 more homogeneous within the different carbon atoms, except for the C3 position which shows a
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39 significantly less negative net charge. Therefore the computational investigation has evidenced that
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41 (i) the electrophilic aromatic substitution is prevented on C3 position, as experimentally observed,
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43 almost certainly due to the inductive effect of the bromine atom linked to the C2 carbon; (ii) the
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45 selective introduction of a second bromine atom on a specific carbon atom of the opposite pyrrolic
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47 ring appears to be much more pronounced on the mono functionalized free-base porphyrin **2** rather
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49 than on its Zn^{II} -complex counterpart **Zn-2**, confirming the loss of regioselectivity in the
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51 bromination reaction after metal complexation step of the porphyrinic core; and (iii) our QTAIM
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53 findings are consistent with an electrophilic aromatic substitution mechanism which drives the
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55 introduction of the second bromine atom specifically on the pyrrolic sites having the most
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3 electronegative character. On the other hand, calculations on all the possible cationic intermediates
4 approximating the transition state from the mono- to the di-brominated free-base derivatives
5 provided essentially, in the more stable configuration, the same energies for the species leading to
6 the 2,12 and the 2,13 regioisomers. The former emerged to be more stable than the latter for less
7 than 0.1 kcal/mol, and slightly higher energies (up to 1.9 kcal/mol) were obtained for the other
8 possible intermediates (see SI for details). Despite a free radical halogenation mechanism cannot
9 therefore be ruled out entirely, all the experimental evidences suggested an electrophilic aromatic
10 substitution process.
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20 21 22 CONCLUSIONS

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25 In this work we have tested and compared some of the most used NBS-mediated bromination
26 procedures on both the free-base 5,10,15,20 tetra(3,5-ditertbutylphenyl) porphyrin **1** and on its Zn^{II}-
27 complex **Zn-1**. Furthermore some alternative synthetic procedures have been also reported for the
28 same substrates. We have found that the light-induced bromination of **1**, under rather controlled
29 conditions, occurs regiospecifically on the 2,12 antipodal positions giving the 2,12 dibrominated
30 porphyrin **3** as major component with remarkable reaction yields. The subsequent complexation
31 step of **3** with Ni(acac)₂ has provided suitable crystals of the Ni^{II}-porphyrinate **Ni-3** for an in-depth
32 crystallographic investigation. The 2,12 dibromo regioisomer, thus obtained, has been identified
33 with an unprecedented confidence degree due to the impressive probability levels of the X-ray
34 analysis confirming the high regiospecificity of the light-induced bromination of the porphyrinic
35 core by NBS. Interestingly some differences have been observed in the behaviour of the **Zn-1**
36 complex. In this latter case the NBS-mediated bromination occurs rapidly and with high yields but
37 with a limited regioselectivity, although the 2,13 disubstituted regioisomer was evidenced as the
38 major component.⁴⁵
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56 Finally, a computational investigation has been performed to gain mechanistic information about
57 NBS-mediated bromination of porphyrinic substrates and to support the findings concerning the
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3 regiospecificity of such reaction. In particular, after introducing a first bromine atom in C2 position,
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5 significant differences between the free-base porphyrin **2** and its Zn^{II} complex **Zn-2** have been
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7 evidenced as far as the relative values of negative net charges on the pyrrolic carbons were
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9 concerned. Such charges have been found to be quite different in the free-base porphyrin **2** and
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11 rather homogenous in Zn^{II}-porphyrinate **Zn-2**, except for the C3 position adjacent to bromine
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13 substituted carbon atom. In the case of **2**, the higher negative charges have been located respectively
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15 on carbons in antipodal position, in agreement with the observed significant reactivity of these
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17 positions to electrophilic substitution reaction. Conversely, in the case of **Zn-2**, the reduced
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19 differences in the net charges of the β-pyrrolic carbons fully support the limited regioselectivity
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21 observed for the complexed porphyrin. This different behaviour is rationally explained by the loss
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23 of localized double-bond character of the antipodal pyrrolic ring, as previously suggested by
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25 Crossley et al.¹³ for metal-complexed porphyrins.
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30 In conclusion, the reported results have shed some more light on the dibromination reaction of the
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32 porphyrinic ring. They have also shown that the regiospecific introduction of two bromine atoms on
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34 the opposite pyrrolic rings is in good agreement with an electrophilic aromatic substitution
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36 mechanism, although further mechanistic studies would be needed to confirm this hypothesis.
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39 EXPERIMENTAL SECTION

40 *Materials*

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42 All reagents and solvents used in the synthesis were purchased by Sigma Aldrich and used as
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44 received, except N-Bromosuccinimide (freshly crystallized in boiling water). The **Zn-2** and **Zn-3**
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46 porphyrins were synthesized as reported elsewhere¹⁰ and a schematic synthetic pathway is
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48 illustrated in scheme 1. Silica gel for gravimetric chromatography (Geduran Si 60, 63-200 μm) and
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50 for flash chromatography (Geduran Si 60, 40-63 μm) were purchased by Merck. Glassware was
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52 flame-dried under vacuum before use when necessary. A 200 W commercial tungsten light bulb
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54 was adopted for the light source.
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¹H NMR spectra were recorded at 25°C in CDCl₃ as solvent with addition, when necessary, of a drop of pyridine-d₅ or in THF-d₈ (Cambridge Isotope Laboratories, Inc.). Mass spectra were obtained by a magnetic mass spectrometer with a LSIMS ionic source.

Synthesis of 2,12-dibromo-5,10,15,20-tetra(3,5-di-tert-butylphenyl)porphyrin (3)

In a 250 mL two-neck round-bottom flask a solution of porphyrin **1** (200 mg, 0.19 mmol) in CH₂Cl₂ (75 mL) and NBS (73 mg, 0.41 mmol) were introduced. Afterwards, a light source consisted of a 200W lamp, was placed at about 10 cm distance from the reaction vessel so that a slightly reflux was maintained. The mixture was allowed to react and after 4 hours the complete disappearance of the starting porphyrin was evidenced by TLC (CH₂Cl₂/n-hexane = 2/8). The reaction was quenched by adding acetone and, after removal of the solvent in *vacuo*, the crude was purified by flash chromatography (SiO₂; column diameter = 3.5 cm; column height = 30 cm; CH₂Cl₂/n-hexane = 12/88). The major product, consisting of di-bromo porphyrin **3**, was collected in the first eluted fraction as a deep pink powder (96 mg, 42% yield) whilst the minor product **2** obtained by incomplete bromination of the porphyrinic core was contained in the second eluted fraction.

¹H-NMR (400 MHz, CDCl₃, 25°C) δ, ppm 8.95-8.88 (m, 6H), 8.05 (s, 4H), 7.95 (s, 4H), 7.83 (s, 2H), 7.82 (s, 2H), 1.55 (s, 36H), 1.53 (s, 36H), -2.89 (s, 2H) . MS-FAB(+): m/z: 1220 [M+H]⁺. Anal. Calcd for C₇₆H₉₂Br₂N₄: C, 74.74; H, 7.59; N, 4.59. Found: C, 75.01; H, 7.57; N, 4.60.

Synthesis of 2,12-dibromo-5,10,15,20-tetra(3,5-di-tert-butylphenyl)porphyrinate Ni^{II} (Ni-3)

In a two-neck round-bottom flask a solution of **3** (20 mg, 0.016 mmol) in 1,2-dichloroethane (5 mL) was slightly warmed and, whilst stirring, then Ni(acac)₂ (12 mg, 0.047 mmol) was added portionwise. The resulting mixture was refluxed overnight and after removal of the solvent in *vacuo*, the pure product **Ni-3** was obtained as a reddish powder in quantitative yield by washing and filtering the crude with H₂O milliQ.

¹H-NMR (400 MHz, CDCl₃, 25°C) δ, ppm 8.91-8.87 (m, 2H) 8.82 (s, 2H), 8.73-8.71 (m, 2H), 7.81 (s, 4H), 7.72 (s, 2H), 7.68 (s, 2H), 7.66 (s, 4H), 1.47 (s, 36H), 1.44 (s, 36H). MS-FAB(+): m/z: 1278 [M+H]⁺. Anal. Calcd for C₇₆H₉₀Br₂N₄Ni: C, 71.42; H, 7.10; N, 4.38. Found: C, 71.68; H, 7.07; N, 4.40.

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Supporting Information: Experimental procedures for X-ray Crystal Structure Determination and Computational Details are described in the Supporting Information. Crystallographic details of the data collection and refinement parameters for **Ni-3** (Table S1), X-ray molecular structure of compound **Zn-3** (Figure S1), Hypothetical cationic intermediates (Figure S2) Integrated Net Charges of **2** and **Zn2** computed by QTAIM Partitioning (Table S3), Selected bond lengths and angles for compound **Ni-3** measured (Table S2) and computed (Table S4) as well as M06/6-311G(d) relative energies (kcal/mol) of the hypothetical cationic intermediates (Table S5) and Cartesian coordinates of the modelled compounds (Table S6) are reported on Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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14 (45) In a previous work,¹⁰ we have arbitrarily reported the main dibrominated Zn^{II}-
15 porphyrinate as the 2,12 regioisomer, while this work suggests to be the 2,13 isomer. In accordance
16 also to the push-pull dyes produced by subsequent reactions of the b dibromo Zn^{II}-porphyrinate, the
17 2,13 isomeric structure should be assigned.
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