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Light-Induced Regiospecific Bromination of *meso*-Tetra(3,5-di-*tert*-butylphenyl)Porphyrin on 2,12 β-Pyrrolic Positions

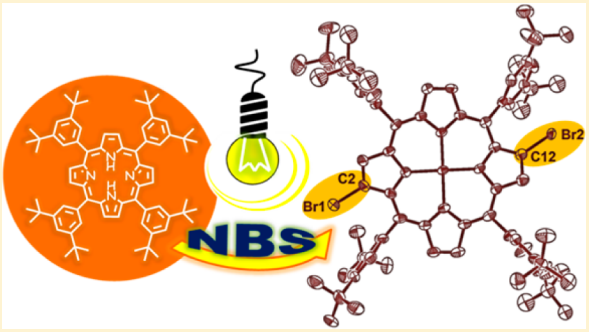
Gabriele Di Carlo,*[,†] Alessio Orbelli Biroli,[‡] Francesca Tessore,[†] Silvia Rizzato,[†] Alessandra Forni,[†,‡] Giulia Magnano,[†] and Maddalena Pizzotti[†]

[†]Department of Chemistry, University of Milan, Via C. Golgi 19, 20133 Milano, Italy

[‡]Institute of Molecular Sciences and Technologies of CNR (ISTM-CNR), Via Golgi 19, 20133 Milano, Italy

Supporting Information

ABSTRACT: The antipodal introduction of two bromine atoms on the 2,12 β-pyrrolic position of 5,10,15,20-tetra(3,5-di-*tert*-butylphenyl)porphyrin was successfully achieved by a light-induced reaction of the substrate with excess NBS. Complexation with Ni^{II} of the major regioisomer led to good quality crystals, suitable for X-ray structure determination with unprecedented probability levels. The regiospecific character of the synthetic procedure and the exactness of the bromine atom position assignment were thus confirmed, suggesting an unexpected electrophilic aromatic substitution pathway rather than a free-radical halogenation process. A QTAIM topological analysis on the DFT-optimized wave function of the monosubstituted free-base porphyrin intermediate carrying a bromine atom in C2 β-pyrrolic position confirmed the largest negative charge for the C12 carbon atom in antipodal position, in agreement with the proposed electrophilic aromatic substitution mechanism.



INTRODUCTION

Porphyrins are one of the most widely investigated classes of molecules in chemistry[1] because they feature high chemical stability, interesting optical and photophysical properties, and catalytic activities, all of which are being used in a wide range of research fields such as medicine,[2] biology,[3] catalysis,[4] optoelectronics,[5−7] and green energy engineering.[8−10] Porphyrins can also be subjected to a modulation of their chemical structure resulting in rational control of their electronic properties. In particular, chemical functionalization of the porphyrinic core via a bromination strategy[11] followed by cross-coupling reactions[12] or nucleophilic aromatic substitutions[13,14] appears to be beneficial in tuning the properties of macrocyclic systems in accordance with the structural requirements necessary for a specific application. In fact, it was recently reported by some of us that the properties of β-functionalized Zn^{II}-porphyrinates are strongly influenced by introducing π-delocalized systems to the macrocyclic core.[5,15] These substituents directly linked on pyrrolic positions exert strong steric and electronic effects on the porphyrinic rings[16] resulting in a dramatic alteration of their optical, electrochemical, and spectroelectrochemical properties.[17] For these reasons, brominated porphyrinic intermediates are considered extremely important building blocks to synthesize more complex and extended structures, and thus numerous synthetic approaches have been proposed in order to selectively functionalize the macrocyclic ring on its different positions.[11]

Owing to the large number of delocalized π-electrons, the porphyrinic core is highly sensitive to electrophilic aromatic substitution reactions that can occur on two different receptive positions. The carbon atoms at the *meso*-positions, consisting of four methenyl bridges on the porphyrinic core, exhibit excellent reactivity to the substitution of a hydrogen with a bromine atom, so that their functionalization occurs with high yields under relatively mild conditions.[18,19] On the contrary, β-positions comprising the eight carbon atoms of the four pyrrolic rings are less responsive to the bromination reaction requiring stricter settings.[20,21] These severe reaction conditions strongly influence the substitution degree of the porphyrinic core, which is difficult to control. Hence, a mixture of polybrominated derivatives and several regioisomers are typically obtained by various β-bromination procedures.[11] Furthermore, hard purification steps of the reaction mixture are required, inducing, in turn, a decrease of the overall yield of a single specifically brominated species.

Since the 1970s, several bromination procedures have been investigated in order to obtain various β-functionalized tetraarylporphyrinic structures, in particular via synthetic pathways involving *N*-bromosuccinimide (NBS). Among all of the reported approaches, the method first proposed by Callot,[20,21] which requires refluxing a solution of tetraphenylporphyrin (TPP) in $CHCl_3$ with appropriate equivalents of NBS, is still the most commonly used. Thanks to this approach, it has been possible to functionalize the porphyrinic core with a range of bromine atoms from one to eight. Numerous authors

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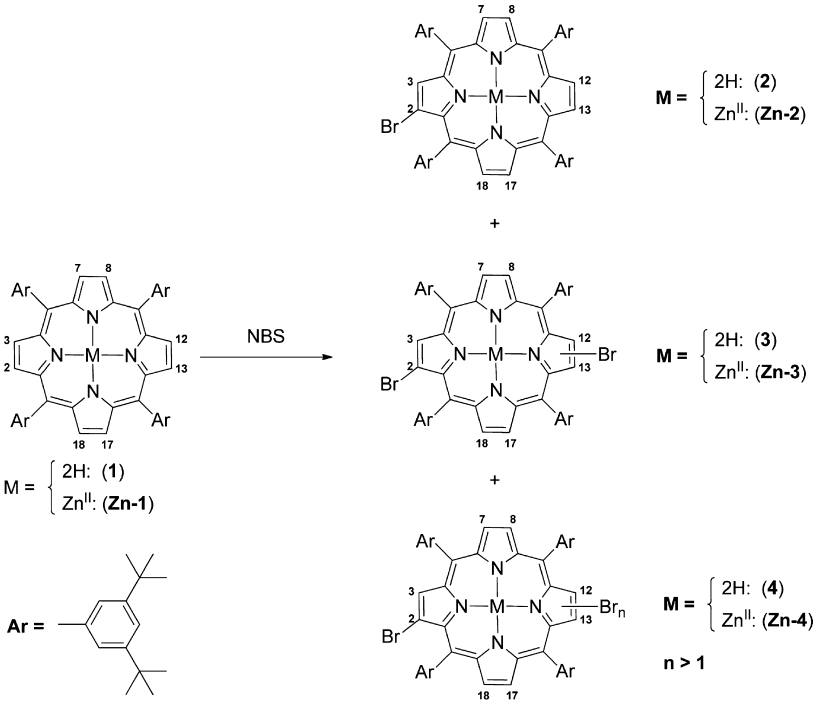
Scheme 1. Schematic NBS-Mediated Bromination of the Free-Base Porphyrin (1) and the Zn^{II}-porphyrinate (Zn-1) on β-Pyrrolic Positions[a]



[a]The positions of substituents in dibrominated (**3** and **Zn-3**) and in polybrominated (**4** and **Zn-4**) porphyrinic structures depend on bromination conditions.

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 (equiv)	reaction conditions	unreacted porphyrin (**1** or **Zn-1**)	monobromo deriv (**2** or **Zn-2**)	dibromo deriv[a] (**3** or **Zn-3**)	polybromo deriv[a] (**4** or **Zn-4**)
a[20,21]	●		1.7	$CHCl_3$; 1 h reflux	XX	X	X	XX
b[31]	●		1.1	Py; $CHCl_3$, 1 h, rt	XX	XX	X	X
c[32]	●		1.1	CH_2Cl_2/CH_3OH; 10 min reflux	XX	X	X	XX
d[33]	●		1.7	$CHCl_3$; 18 h reflux	X	X	X	XXX
e[12]		●	1.1	CH_3OH; 1 h reflux	XXX			
f[10,17]		●	1.8	CCl_4; 2 h reflux		XXX	XXX	
g	●		2.1	CCl_4; 2 h reflux	X	XXX	XX	
h	●		2.1	CCl_4; 200 W lamp, 4 h	X	XX	XX	X
i	●		2.2	CH_2Cl_2; 200 W lamp, 4 h	X	XX	XXX	
j		●	2.2	CH_2Cl_2; 200 W lamp, 4 h		XXX	XX	X
k	●		2.2	CH_2Cl_2; 4 h, reflux	X	X	XX	XX

[a]mixtures of regioisomers.

have employed this procedure to brominate either TPP or other different tetraarylporphyrins.[22−24] Subsequently, other NBS-mediated bromination procedures[12,25] were proposed to attain polyfunctionalized porphyrins;[26−28] however, only in a few cases was the reaction mechanism investigated in detail. Consequently, factors and reaction conditions which drive the regiochemistry of these substitutions,[13] especially when various bromine atoms should be introduced in specific positions of the porphyrinic ring, are still quite unknown.

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

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 in nonlinear optics (NLO)[5,6] and in dye-sensitized solar cell (DSSC)[10] applications. The regiospecific functionalization of opposite pyrrolic units is thus considered the focal step to obtain the key building blocks

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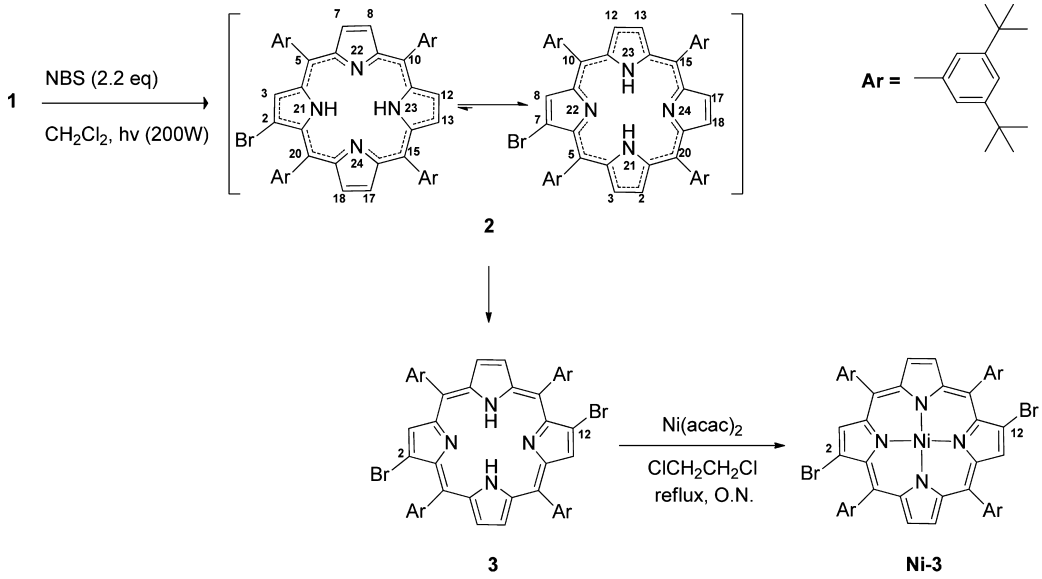
Scheme 2. Schematic Representation of the Tautomeric Equilibrium of the 18-π-Annulene System in the Monobromo Intermediate 2 and the Assignment Variation of the Bromine Substituent According to the Different Ways of Fixing the Inner Hydrogens. Regiospecific Synthesis of the Free Base 2,12-Dibromo-Substituted Porphyrin (3) and Its Ni^{II}-porphyrinate (Ni-3)



for the synthesis of attractive push−pull porphyrinic systems. Therefore, it has become of great interest to develop a facile and effective synthetic procedure to successfully introduce two bromine atoms on specific antipodal positions, thus reducing the formation of regioisomers and increasing the overall synthetic yield of such specific porphyrinic systems.

As the electronic distribution of the π-delocalized porphyrinic core is strongly influenced by the four *meso*-aryl substituents, which then affect the pyrrolic substitution degree and consequently the functionalization yields, it is unrealistic to design a general bromination procedure suitable for all tetraarylporphyrinic systems. For these reasons, in this work we have focused our attention on a specific substrate consisting of the free base 5,10,15,20-tetra(3,5-di-*tert*-butylphenyl)-porphyrinic core **1** and on its Zn^{II} -complex **Zn-1** (Scheme 1).

With the aim of comparing 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).

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

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 (Å) and angles (deg) for compound **Ni-3** (Table S2) are reported in the Supporting Information.

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

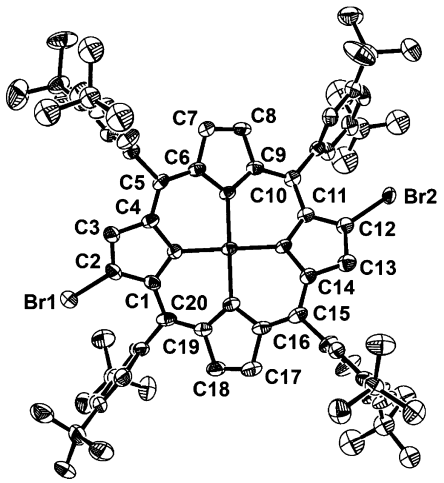


Figure 1. View of the molecular structure of **Ni-3** with the atom-numbering scheme. Thermal ellipsoids are represented at the 50% probability level. Hydrogen atoms and disorder are omitted for clarity. Only one set of rotationally disordered bromine substituents is shown.

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.

RESULTS AND DISCUSSION

In the last decades, several efforts were devoted to optimize the conditions to regiospecifically brominate the pyrrolic rings of the porphyrinic core.[11−13,34] Until now, the reported synthetic procedures led mainly to complex mixtures of variously

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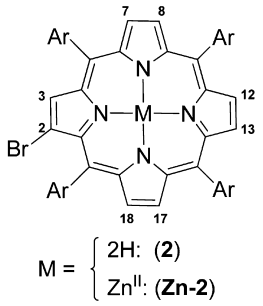
Table 2. M06/6-311G(d)-Integrated Net Charges q (e) of the Atomic Basins of Monobrominated Free Base 2 in Vacuo and in CH_2Cl_2 and Its Zn Complex (Zn-2) in Vacuo and in CCl_4, Computed by QTAIM Partitioning



Atom	Free-Base (**2**)		Zn^{II}-Complex (**Zn-2**)	
	vacuum	CH_2Cl_2	*vacuum*	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

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 regiospecific introduction of four 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 an 18-π-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 attach resulted on the antipodal pyrrolic position compared to the 18-π-annulene system with a more prominent aromatic character. Subsequently, Crossley et al.[13] have also shown that the reaction of free-base porphyrins with 4.3 equiv of NBS in boiling ethanol-free chloroform afforded the 7,8,17,18-tetrabromo-substituted porphyrin rather than the misassigned 2,7,12,17-tetrabromo isomer as previously proposed by Callot.[20,21] Moreover, Smith et al.[36] have described a further attractive synthetic approach to drive a dibromination of porphyrins regiospecifically on C2 and C3 pyrrolic positions. A suitable electron-withdrawing moiety, such as a nitro group, previously introduced in a β-pyrrolic site, was able to impose the electrophilic attack at both carbons of the antipodal pyrrolic ring.

Here, we focused our attention on the specific porphyrinic core **1** consisting of four 3,5-di-*tert*-butylphenyl units directly linked on 5,10,15,20 *meso*-positions (Scheme 1). This substrate was previously selected, by some of us, as a suitable precursor to synthesize various β-substituted porphyrinic Zn^{II} complexes as promising sensitizers to assemble highly performing DSSCs.[10,15,37] The bulky aryl substituents were evidenced to confer a great sterical hindrance to the dye structures, thus suppressing the undesired aggregation among porphyrinic systems and simultaneously inducing excellent passivation of the TiO_2 photoanode[37] thanks to its intrinsic shielding character.

With the aim of optimizing the selective β-pyrrolic functionalization of the porphyrinic core on specific antipodal sites, we have performed several NBS-mediated bromination procedures both on free-base porphyrin **1** and on its Zn^{II} complex **Zn-1**. An overview of the tested methods is schematically reported in Table 1. The reaction conditions of entries a–f[10,12,17,20,21,31−33] were previously optimized and reported for TPP or other similar porphyrinic molecules. On the contrary, the reaction conditions of entries g–k have been specifically designed for our substrates, **1** and **Zn-1**, in order to improve both regioselectivity and reaction yield. It was observed that a–e bromination procedures yielded a complex mixture of products consisting of the unreacted porphyrin (**1** or **Zn-1**), the monobromo derivative (**2** or **Zn-2**), dibrominated regioisomers (**3** or **Zn-3**), and the polyfunctionalized derivatives (**4** or **Zn-4**), resulting in a hard purification of the crude. The monofunctionalization of the core was observed to occur successfully in good yield by optimizing the procedure proposed by D'Souza.[17] In particular, a solution of the Zn^{II}-porphyrinate **Zn-1** in CCl_4 was refluxed in the presence of a slight excess of NBS (1.1 equiv), as previously reported by some of us,[10] while 1.8 equiv was necessary to give the dibrominated Zn^{II}-porphyrinate **Zn-3**. This latter was obtained with good yield (60%) as a major component of the reaction mixture following the procedure f, but we failed in the first attempts to discriminate which of the dibrominated regioisomers are mainly formed as previously suggested.[10] Only the slow evaporation at low temperature of a THF solution of **Zn-3** has allowed us to obtain crystals good enough for an X-ray crystallographic structure determination (see Figure S1, Supporting Information). The crystallographic investigation has revealed the presence of the 2,13-dibromo derivative as the major component in a crystal containing at least three disubstituted regioisomers. In fact, the **Zn-3** X-ray structure has shown a disorder similar to those previously reported;[29,30] thus, it was necessary to refine the crystal structure by using a site-occupancy disorder model. The bromine substituents were located in the Fourier difference map and were refined with free occupancy variables and fixed B-factors. The similarity in the resulting occupancies has allowed the identification of the three regioisomers, although problems related to poor quality of the crystal and the low intensity of the diffraction pattern have not led to satisfactory R values. Despite these limitations, the occupancy of the 2,13-disubstituted isomer has been found to be 50%, whereas the occupancies of the 2,7 and 2,3 isomers have been 33% and 17%, respectively. These findings have suggested a reduced selectivity

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of the bromination of a metallo-porphyrinate that could be rationalized by the loss of localized double-bond character in the macrocyclic π system after metalation of the porphyrinic core.[13] Nevertheless, it is noteworthy that no unreacted product has been recovered by bromination of **Zn-1** using the f and j procedures, suggesting an increased reaction yield when the reaction takes place on the Zn^{II}-porphyrinate, with the exception of procedure e, which was ineffective because of the low solubility of the porphyrinate in methanol. The observations reported in Table 1 have also suggested that at least 1.8 equiv of NBS (entries f−k) are necessary to obtain an appreciable amount of β-dibrominated porphyrins. Moreover, in order to reduce the formation of polybrominated products and to improve the regiospecific functionalization of the pyrrolic rings of the porphyrinic core, mild reaction conditions are mandatory (entries h−j). Finally, the synthetic procedure i has been appointed as an effective route to unquestionably provide a specific antipodal dibromo regioisomer. In this procedure the light-induced bromination approach has specifically provided the pure 2,12-dibromo isomer **3** with 42% yield starting from the free base 5,10,15,20-tetra(3,5-di-*tert*-butylphenyl)porphyrin (**1**) as summarized in Scheme 2. This regiospecific functionalization process takes place in the presence of 2.2 equiv of NBS by irradiating the reaction mixture with a 200 W lamp, which maintains a slight reflux in dichloromethane. Hence, with the aim of validating the positive effect of the light irradiation on regioselectivity, we have also performed the bromination step of the free-base porphyrin **1** by refluxing the reaction vessel in dark conditions (entry k, Table 1). This latter method has provided a complex mixture of regioisomers that is hard to purify, similar to that achieved by the Callot procedure,[20,21] thus confirming our assumptions.

The β-disubstituted porphyrinic regioisomer **3**, obtained as a major component by the light-induced procedure i, after chromatographic purification successfully reacted overnight in a 1,2-dichloroethane refluxing solution, with Nickel(II) acetylacetonate ($Ni(acac)_2$) giving quantitatively the pure Ni^{II}-porphyrinate **Ni-3**, as shown in Scheme 2. This latter step has given crystals of very good quality thus allowing an X-ray structure determination with unprecedented probability levels. The **Ni-3** molecular structure, reported in Figure 1, presents a bromine distribution and a rotational disorder very similar to those reported for the molecular structure of 2,12-dibromo-5,10,15,20-tetraphenylphorphyrin,[30] wherein half of the molecule, and therefore only one bromine, was present in the asymmetric unit. The second antipodal substituent was generated by symmetry leading to one specific regioisomer. Actually, in that structure, the bromine atoms were disordered over three different positions, refined with different occupancies, generating a clear and well-defined rotational disorder. On the contrary, in the **Ni-3** crystal structure there is only one crystallographically independent molecule which shows four disordered bromine atoms in the 2,3 and 12,13 positions. However, the rotational disorder is well resolved because it is limited to the two specific positions, and the high quality of the data has allowed us to couple the bromine atoms in 2,12 antipodal positions. Thus, the nature and the purity of **Ni-3** regioisomer, and consequently of its free-base precursor **3**, have been confirmed.

It is noteworthy that a dibromo derivative, very similar to the porphyrin **3**, was previously identified by Crossley et al.[13,35] as a 7,17- rather than a 2,12-disubstituted regioisomer. This particular attribution was ascribed to the introduction of bromine atoms on β pyrrolic carbons with the inner hydrogens at the porphyrinic ring fixed in N-21 and N-23 positions (Scheme 2), thus imposing the character of double bonds in $\Delta^{7,8}$ and $\Delta^{17,18}$. On the other hand, metal complexation reverts the attribution to the 2,12-dibromo regioisomer since no tautomeric forms are allowed due to the lack of inner hydrogens. Such effect on the assignment of the substituents position could make the comparison of the free-base porphyrinic derivatives with their metal complex forms rather unclear. Hence, for a better comprehension of our results, we have arbitrarily assigned the substituents position starting from C2 even for the free-base porphyrin **3**. Consequently, the free-base porphyrin **3** will be referred as to the 2,12-dibrominated regioisomer (Table 2) rather than to its 7,17 tautomeric form.

With the aim of gaining deeper insight about geometrical characteristics of the 2,12-dibrominated Ni^{II}-porphyrinate, the distances among atoms within the porphyrinic core and the resulting distortion of structure were further investigated. The Ni^{II} metal center adopts a quasi-ideal square-planar coordination geometry with the N−Ni−N angles near 90° (89.33−90.74°) and a maximum deviation of 0.003 Å from the NiN4 mean plane. The average Ni−N distance of 1.909 Å is quite similar to that found in other analogous complexes,[38] though the bond lengths in the case of the two nitrogens of the brominated pyrrolic rings result slightly longer distances (1.898−1.896 Å; 1.911−1.932 Å). This is due essentially to the distortion of the porphyrinic core that results in a different transannular distance for the two N· ·N couples. Thus, the macrocyclic hole is *stretched* in the direction of the two substituted rings as frequently observed in the distortion pattern of metal-complexed porphyrins.[30,36,39] The significant distortion of the porphyrin core can be described as a mixing of saddle and ruffle distortion modes with a maximum displacement from the 24-atom core mean plane of 0.64 and 0.40 Å for the *meso*-carbons (ruffle-shaped distortion) and β-pyrrolic positions (saddle-shaped distortion), respectively. The noteworthy contribution of the ruffling distortion to the macrocycle deformation is stressed by the value of the dihedral angles between the planes of the opposite pyrrolic rings (38.9° and 37.6°). Instead, the dihedral angles between the phenyl rings and the mean plane formed by the 24-atom core lie in the range 73.5−89.1°, which suggests only weak steric interactions between the phenyl rings and the adjacent antipodal bromine substituents.

With the aim of rationalizing the impressive regiospecificity obtained by the light-induced NBS-mediated bromination of **1**, we were interested in figuring out the mechanism which drives the introduction of the two bromine atoms on 2,12 pyrrolic positions of the porphyrinic core. As previously reported[40] and now confirmed by our results, the free-base porphyrinic ring **1** is less reactive to the bromine aromatic substitutions than the Zn^{II}-porphyrinate **Zn-1**; thus, the light irradiation has been initially employed to improve the reaction rates. At first, this approach was reasonably expected to promote a radical pathway involving a homolytic bond cleavage of NBS. With the light irradiation, instead, the NBS-mediated bromination has specifically provided the 2,12-dibromo regioisomer **3** as the major product, the monobromo derivative **2** as the minor component, and only small traces of other dibromo regioisomers and polybrominated derivatives (**4**). Even if it is known that NBS can react both by radical mechanisms in the case of nondelocalized double bonds[41] or by electrophilic aromatic substitution in polar[42] and nonpolar solvents,[43] the

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observed remarkable regiospecificity by a light-induced bromination was unexpected. However, similar findings were previously reported by Gruter et al.,[44] who evidenced that the nuclear bromination of anisole took place via an electrophilic aromatic substitution mechanism under irradiation conditions.

Consequently, an in-depth theoretical investigation has been performed to support and rationalize the electrophilic aromatic substitution process. The results of a QTAIM topological analysis on the charge density distribution of the free-base monobrominated porphyrin **2**, as determined by M06/6-311G(d) DFT calculations both in vacuo and in the same solvent used for the synthesis (CH_2Cl_2), are summarized in Table 2. In this table, we report the net atomic charges obtained by integration over the volume of atomic basins as defined within QTAIM. It can be noticed that the carbon atoms C12 and C13, in antipodal position with respect to the pyrrolic unit bearing the bromine atom, show the largest negative charges, while the carbon atom C3, adjacent to the bromine substituted carbon, is the less negative one. By comparing the net charges on C12 and C13 very small differences can be observed, with the former showing slightly more negative charge than the latter. This trend is confirmed to be the same both in vacuo and in CH_2Cl_2 solvent and also by varying the computational methodology (see Table S3, Supporting Information), thus suggesting a slight preference of an electrophilic aromatic substitution on C12 position rather than on C13, as experimentally observed.

In order to better understand the influence of the metal complexation on the electrophilicity of the porphyrinic core, the atomic net charges on the pyrrolic carbons of the porphyrinic intermediate **Zn-2** have been also determined in vacuo and in CCl_4, the solvent used for the synthesis (see Table 2). A slightly more negative charge was obtained for the C12 carbon atom on the opposite side of pyrrolic ring bearing the bromine substituent. Nevertheless, in this case, the charge values are much more homogeneous within the different carbon atoms, except for the C3 position which shows a significantly less negative net charge. Therefore, the computational investigation has evidenced that (i) the electrophilic aromatic substitution is prevented on the C3 position, as experimentally observed, almost certainly due to the inductive effect of the bromine atom linked to the C2 carbon; (ii) the selective introduction of a second bromine atom on a specific carbon atom of the opposite pyrrolic ring appears to be much more pronounced on the mono functionalized free-base porphyrin **2** rather than on its Zn^{II} complex counterpart **Zn-2**, confirming the loss of regioselectivity in the bromination reaction after metal complexation step of the porphyrinic core; and (iii) our QTAIM findings are consistent with an electrophilic aromatic substitution mechanism, which drives the introduction of the second bromine atom specifically on the pyrrolic sites having the most electronegative character. On the other hand, calculations on all the possible cationic intermediates approximating the transition state from the mono- to the dibrominated free-base derivatives provided essentially, in the more stable configuration, the same energies for the species leading to the 2,12 and the 2,13 regioisomers. The former emerged to be more stable than the latter for less than 0.1 kcal/mol, and slightly higher energies (up to 1.9 kcal/mol) were obtained for the other possible intermediates (see the Supporting Information for details). Although a free-radical halogenation mechanism therefore cannot be ruled out entirely, all the experimental evidence suggested an electrophilic aromatic substitution process.

CONCLUSIONS

In this work, we have tested and compared some of the most used NBS-mediated bromination procedures on both the free-base 5,10,15,20-tetra(3,5-ditertbutylphenyl)porphyrin (**1**) and on its Zn^{II} complex **Zn-1**. Furthermore, some alternative synthetic procedures have been also reported for the same substrates. We have found that the light-induced bromination of **1**, under rather controlled conditions, occurs regiospecifically on the 2,12 antipodal positions giving the 2,12-dibrominated porphyrin **3** as the major component with remarkable reaction yields. The subsequent complexation step of **3** with $Ni(acac)_2$ has provided suitable crystals for the Ni^{II}-porphyrinate **Ni-3** for an in-depth crystallographic investigation. The 2,12-dibromo regioisomer, thus obtained, has been identified with an unprecedented confidence degree due to the impressive probability levels of the X-ray analysis, confirming the high regiospecificity of the light-induced bromination of the porphyrinic core by NBS. Interestingly, some differences have been observed in the behavior of the **Zn-1** complex. In this latter case, the NBS-mediated bromination occurs rapidly and with high yields but with a limited regioselectivity, although the 2,13-disubstituted regioisomer was evidenced as the major component.[45]

Finally, a computational investigation has been performed to gain mechanistic information about NBS-mediated bromination of porphyrinic substrates and to support the findings concerning the regiospecificity of such reaction. In particular, after introducing a first bromine atom in C2 position, significant differences between the free-base porphyrin **2** and its Zn^{II} complex **Zn-2** have been evidenced as far as the relative values of negative net charges on the pyrrolic carbons were concerned. Such charges have been found to be quite different in the free-base porphyrin **2** and rather homogeneous in Zn^{II}-porphyrinate **Zn-2**, except for the C3 position adjacent to bromine substituted carbon atom. In the case of **2**, the higher negative charges have been located respectively on carbons in antipodal position, in agreement with the observed significant reactivity of these positions to electrophilic substitution reaction. Conversely, in the case of **Zn-2**, the reduced differences in the net charges of the β-pyrrolic carbons fully support the limited regioselectivity observed for the complexed porhpyrin. This different behavior is rationally explained by the loss of localized double-bond character of the antipodal pyrrolic ring, as previously suggested by Crossley at al.[13] for metal-complexed porphyrins.

In conclusion, the reported results have shed some more light on the dibromination reaction of the porphyrinic ring. They have also shown that the regiospecific introduction of two bromine atoms on the opposite pyrrolic rings is in good agreement with an electrophilic aromatic substitution mechanism, although further mechanistic studies would be needed to confirm this hypothesis.

EXPERIMENTAL SECTION

Materials. All reagents and solvents used in the synthesis were purchased by Sigma-Aldrich and used as received, except *N*-bromosuccinimide (freshly crystallized in boiling water). The **Zn-2** and **Zn-3** porphyrins were synthesized as reported elsewhere,[10] and a schematic synthetic pathway is illustrated in Scheme 1. Silica gel for gravimetric chromatography (Geduran Si 60, 63−200 μm) and for

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flash chromatography (Geduran Si 60, 40−63 μm) was purchased by Merck. Glassware was flame-dried under vacuum before use when necessary. A 200 W commercial tungsten light bulb was adopted for the light source.

^{1}H NMR spectra were recorded at 25 °C in $CDCl_3$ as solvent with addition, when necessary, of a drop of pyridine-d_5 or in THF-d_8 (Cambridge Isotope Laboratories, Inc.). Mass spectra were obtained by a magnetic mass spectrometer with an LSIMS ionic source.

*Synthesis of 2,12-Dibromo-5,10,15,20-tetrakis(3,5-di-tert-butylphenyl)porphyrin (**3**).* In a 250 mL, two-neck, round-bottom flask were introduced a solution of porphyrin **1** (200 mg, 0.19 mmol) in CH_2Cl_2 (75 mL) and NBS (73 mg, 0.41 mmol). Afterward, a light source consisting of a 200 W lamp was placed at about 10 cm distance from the reaction vessel so that a slight reflux was maintained. The mixture was allowed to react, and after 4 h, the complete disappearance of the starting porphyrin was evidenced by TLC (CH_2Cl_2/*n*-hexane = 2/8). The reaction was quenched by addition of acetone, and after removal of the solvent in vacuo, the crude was purified by flash chromatography (SiO_2; column diameter = 3.5 cm; column height = 30 cm; CH_2Cl_2/*n*-hexane = 12/88). The major product, consisting of dibromo porphyrin **3**, was collected in the first eluted fraction as a deep pink powder (96 mg, 42% yield), while the minor product **2** obtained by incomplete bromination of the porphyrinic core was contained in the second eluted fraction.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 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 $C_{76}H_{92}Br_2N_4$: 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-tetrakis(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 while the solution was stirring, $Ni(acac)_2$ (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 H_2O Milli-Q: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 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 $C_{76}H_{90}Br_2N_4Ni$: C, 71.42; H, 7.10; N, 4.38. Found: C, 71.68; H, 7.07; N, 4.40.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures for X-ray crystal structure determination and computational details. 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 modeled compounds (Table S6). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00367.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gabriele.dicarlo@unimi.it.

Notes

The authors declare no competing financial interest.

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