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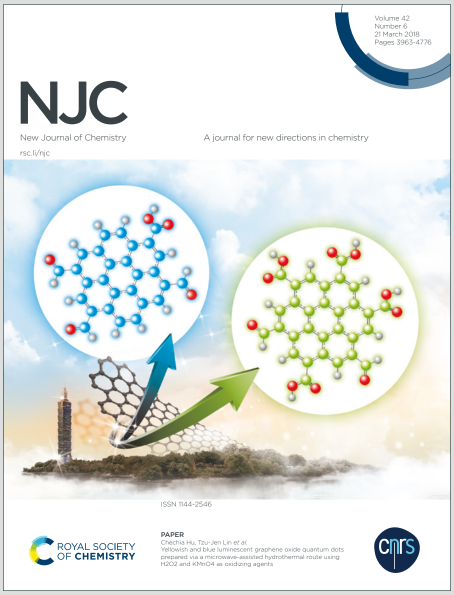

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ARTICLE

Bromination of tetrapyrrolic scaffolds: a sustainable approach

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A sustainable procedure developed for the bromination of organic substrates, such as olefins and small aromatic rings, has been applied to porphyrin derivatives. The synthetic method, based on a V(V) or Mo(VI) catalyzed reaction, occurs in a two-phase medium and uses cheap and environmental friendly reagents such as KBr and H_2O_2 as bromine source and primary oxidant respectively. Compared to the classical protocols for porphyrinoids bromination, this approach is based on milder and safer reaction conditions. The selective formation of mono or polybrominated substrates has been achieved by an accurate tuning of key parameters (H_2O_2 and KBr amount, catalyst). While with Vanadium good results to obtain partially substituted porphyrins have been gained, the fully peripheral functionalization can be obtianed with either Vanadium or Molybdenum catalysis depending on the metal ion coordinated into the inner core.

Introduction

Porphyrins represent the most important example in the family of polypyrrolic macrocycles. The richness of properties of this class of molecules, triggered the interest of scientists to exploit them in different fields of research, ranging from medicine[1] to catalysis[2] to chemical sensors[3] or as dyes in DSSC.[4] The strict structure-property relationship explains the versatility of these tetrapyrroles and their wide diffusion. The introduction of substituents onto the peripheral positions as well as the coordination of metal ions in the inner core makes possible to obtain molecules whose features are tailored for the desired applications. A very interesting modification of porphyrin framework is the bromination reaction. On one hand, brominated derivatives represent the starting point for further modification of molecular framework achieved by cross coupling methodologies, such as Suzuki, Heck, Stille or Sonogashira reactions.[5] This strategy allows the preparation, by a bottom-up approach, of more sophisticated architecture that otherwise would be barely accessible. On the other hand, the properties of brominated macrocycle are affected by the presence of bromine moieties. The electron-withdrawing atoms shift both the oxidation and the reduction potentials to more positive values, a modification that leads to a more difficult electron abstraction and an easier electron addition.[6] This modification is advantageous when porphyrin derivatives are exploited in catalysis. The variation of the cathodic and anodic potentials increases the catalytic efficiency, making the substrate more robust toward the oxidative degradation. In addition, the severe distortion from planarity induced by the bulky substituents contribute to their efficiency as catalysts. Recently the catalytic properties of simple and brominated porphyrin oxidovanadium (IV) complexes have been compared;[7] the electron poor nature as well as the macrocycle distortion allowed to obtain better results by using the bromine containing macrocycle. The request for porphyrinoids scaffold with different number of Br substituents encouraged the pursuit for appropriate procedures to control number and position of halogens. The most common procedures use NBS (*N*-bromosuccinimide) or the corrosive and toxic Br_2 as Br source, and $CHCl_3$, CCl_4, *o*-dichlorobenzene or CH_3OH as solvents.[8-22] Although these methods allowed the preparation of the desired products in good yields, nowadays sustainable and safer procedures are greatly recommended, replacing the classical synthetic methodologies with those as close to “green chemistry” principles as possible.[23] Among the different sustainable procedures developed for the bromination of organic substrates,[24] we applied to tetrapyrrolic macrocycle our bromination protocol, inspired by the mode of action of Vanadium dependent bromoperoxidase enzymes (V-BrPO)[25-29] whose working mechanism is depicted in Fig. 1.

In aqueous acid medium (pH = 1), V(V) or Mo(VI)[30] based catalysts, using H_2O_2 as primary oxidant, convert bromide into a electrophile bromine equivalent intermediate (Br^+, Br_2 or BrO^-), that is transferred into the organic phase, where it reacts with the substrate leading to the brominated products.

The main advantage of this method is the low cost and the harmless nature of the catalyst, the oxidant and the bromine source, that are dissolved in water. Moreover, as previously reported in the functionalization of simple organic molecule,[25,28,30,31] the desired products can be obtained in good to excellent yield.

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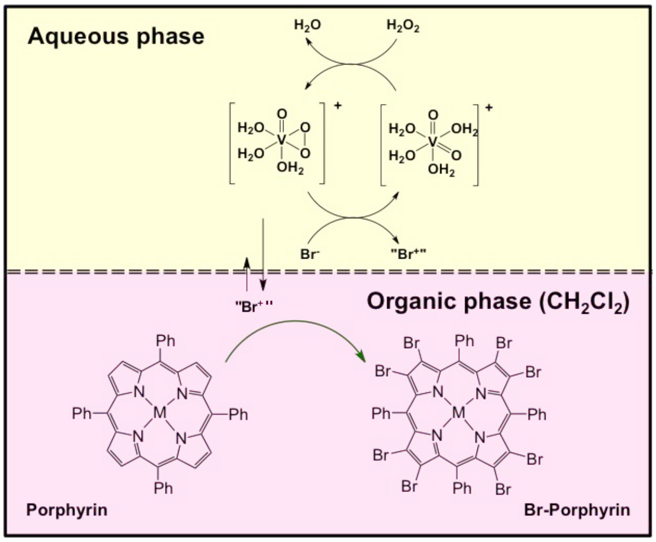


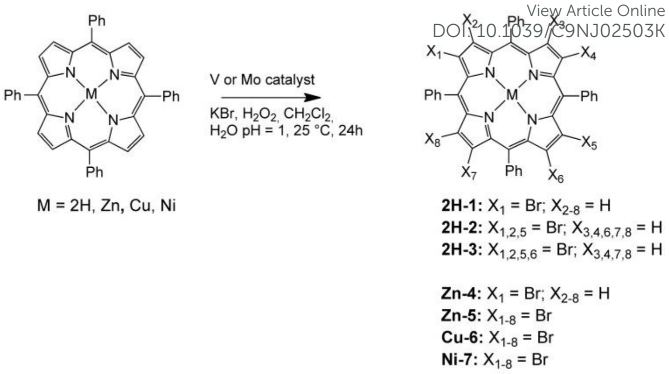
Fig. 1 Vanadium based two-phase system for bromination reactions

The scope of this work is to verify the possibility to prepare halogenated porphyrinoids by the transition metals catalysed system. For this reason, we investigated the insertion of a variable number of Br units on the β-pyrrolic positions of tetraphenylporphyrin free base and its Cu, Ni and Zn complexes (Scheme 1); in detail we were interested to mono, tetra and octa-halogenated derivatives. Br_8- and Br_4-porphyrins are interesting for the possible exploitation as catalyst, taking into account the diffusion of porphyrins as catalytic material,[32,33] while monohalogenated product allows to prepare substrates for the application in the field of energy conversion.[32,34] Good results have been achieved, thus demonstrating that the preparation of β-brominated porphyrin derivatives can be achieved by a modern and sustainable method.

Results and discussion

Monobromination of porphyrin free-base and Zn complex: tetraphenylporphyrin free base (H_2TPP) was chosen as model substrate for the transition metals catalysed halogenation experiments, and the following conditions were generally adopted: 0.02 mmol of substrate dissolved in 3-4.5 mL of CH_2Cl_2, 1 or up to 2.5 mL (volume was increased when more then 10 equivalents of salts were used) of aqueous solution at pH = 1 with 0.5 equivalent of catalyst (Vanadium or Molybdenum salts). The amount of KBr and H_2O_2 was tuned depending by the target brominated molecules.

To note, V(V) catalyst was the initial choice, while the more reactive Mo(VI) was adopted when results with Vanadium were unsatisfactory. The monobrominated porphyrin was our first target molecule; to achieve the preparation of this compound we initially used a 1.25/1/1 KBr/H_2O_2/H_2TPP ratio; however, since the metal catalyst triggers the decomposition of hydrogen peroxide, in some case a second portion of H_2O_2 (usually half equivalents with respect the first one) was added after 6 hours.



Scheme 1 Structure of the bromo-porphyrins derivatives obtained.

Regrettably the attempts to prepare monobrominated H_2TPP (**2H-1**) did not give fair results; indeed, with a slight excess of KBr only a small amount of substrate reacted, while increasing the amount of salt up to two equivalents, two new products were detected on TLC, together with some residual TPP.

The UV-vis spectra of these compounds are consistent with the formation of two isomeric forms of the dibrominated porphyrin, where the second Br unit may lye on adjacent position to the first Br or onto the opposite pyrrole ring. The formation of such a complex mixture (TPP, BrTPP and antipodal dibrominated derivative obtained in a similar 20% yield, while the adjacent dibrominated compound was achieved in a lower 10 % yield) is a common problem when the target molecule is the monohalogenated macrocycle.

As reported in the literature (see for example tables in references 19 and 22) insertion of only one Br unit can be partially driven controlling the amount or the mode of addition of brominating reagent. We then turned our attention to Zn-complex that was reacted with 1.4 equivalent of KBr and 1 equivalent of H_2O_2. After 24 hours, final mixture showed the presence of substrate as major product (isolated 29%) and a low amount of a fraction (isolated: 21%) identified as the monobrominated ZnTPP (**Zn-4**) by the deshielded singlet at 9.07 ppm for the hydrogen atom close the halogen moiety, while the residual β-pyrrolic positions integrate for 7 H. Reaction was repeated several times increasing the amount of KBr up to 1.85 eq. Even if these attempts gave slightly better results in terms of substrate conversion, at the same time the formation of a second fraction was observed on TLC, reasonably ascribable to some dibrominated product. To limit the competition between ZnTPP and ZnBrTPP for reacting with the residual "Br⁺" species, the organic phase/water ratio was raised up from of 3:1 to 12:1, using 1 mL of aqueous solution; KBr amount was increased to two equivalents to compel the substrate consumption. As a matter of fact, a larger conversion was achieved but the formation of some dibrominated derivative could not be avoided. Considering the higher reactivity of Mo complex, this metal was used in the presence of only 1.4 bromide equivalents, obtaining similar results with respect to those reported with Vanadium as catalyst. The formation of ZnBrTPP (**Zn-4**) was estimated to be about 33% (residual TPP: 20%; dibrominated species: 15%).

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Polybromination of porphyrin free-base: due to the tendency of porphyrin to easily form multifunctionalized derivatves, we decided to investigate the preparation of polybrominated macrocycles. This kind of molecules attracted attention in the last decade because they can be further modified (by cross coupling methodologies) and anchored to metal oxide surfaces allowing the exploitation as dye in the DSSC.[34]

It is well known that the maximum level of bromination achievable for porphyrin free base is the tetrafunctionalization, and that only one regioisomer is obtained, where the halogen atoms are located on the antipodalic position (the "iminic" pyrrole).[16] The remarkable selectivity of this process prompted us to apply the Vanadium catalysed method for the preparation of H_2Br_4TPP. The reaction was initially performed on 0.02 mmol of tetraphenylporphyrin dissolved in 3 mL of CH_2Cl_2, 1 mL of aqueous phase at pH = 1 and containing 0.01 mmol of V-based catalyst; finally,—10 times excess of KBr and overall 12 equivalents of oxidant (two partitioned addition, 8 and 4 equivalents), were used to achieve the desired product. The analysis of the final mixture revealed the presence of one main product, which was identified as the 2,3,12,13-Br_4-Tetraphenylporphyrin (H_2Br_4TPP) (**2H-3**) by UV-vis[18,20] (Soret band at 436 nm and three weaker absorbance in the 500-700 region, see Fig. 2), and ^{1}H NMR spectroscopy, where a singlet integrating for 4 H resonates at 8.69 ppm. H_2Br_4TPP was isolated in a 34% yield.

A smaller amount (15%) of a compound with a lesser grade of bromination, as judged by the lower red shift of Soret band, (vs. H_2TPP) was isolated. This fraction was identified as the 2,3,12-Br_3-Tetraphenylporphyrin (H_2Br_3TPP) (**2H-2**) by comparison of its UV-vis spectrum with that reported in literature.[20] The nature of this derivative was also confirmed by ^{1}H NMR analysis, where several signals either for the pyrrolic region (8.69-8.86 ppm) and for the inner NH were detected, as expected due to the product low symmetry.

The presence of H_2Br_3TPP as by-product of the H_2Br_4TPP preparation, suggests that the former could be selectively obtained by decreasing the substrate/reactants ratio, while rising up the reagents/substrate ratio the process selectivity should be shifted toward the formation of H_2Br_4TPP. As assumed, when the reaction was performed with 7.5 equivalents of KBr, H_2Br_3TPP was obtained in a 48% yield, while only a small amount (5%) of H_2Br_4TPP was collected.

As previously discussed, to foster the substrate toward the insertion of four Br moieties, a larger excess of salt (10 eq.) and oxidant (20 eq. in one portion) was used, while no variations were made to the others reaction conditions. The yield for H_2Br_4TPP was raised up to 47%, while H_2Br_3TPP was detected in very small amount (less then 10%).

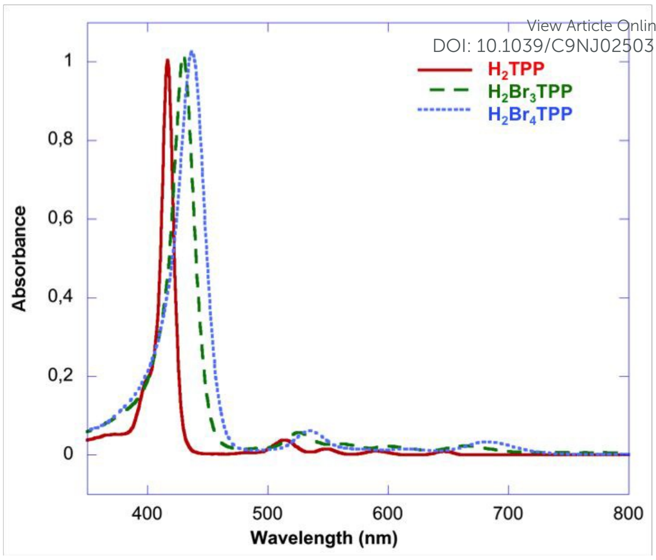

Fig. 2 UV-vis spectra of H_2TPP, tri- and tetrabrominated derivatives.

This result is noteworthy because demonstrates the effectiveness of such sustainable process applied to the tetrapyrrolic macrocycle, leading to a more than satisfying yield for the H_2Br_4TPP formation. In fact, such value is quite close to what obtained with classical method.[18]

Fully bromination of porphyrin Zn and Cu-complexes: while bromination of free base permits the insertion of one to four bromine moieties, to achieve the fully substitution of peripheral positions it is necessary to use a metal-complex as substrate. The higher stability due to the metal coordination, limits the decomposition of the substrate (octabromination usually requires stronger reaction conditions); moreover, the increased symmetry of metal complexes promotes the functionalization of all the β-pyrrolic positions. Indeed, the information about the "fixed double bond" entity that is transmitted via the NH tautomerism, is lost because of the metal ion insertion; thus, the remaining β-pyrrolic positions have almost the same reactivity.[16] For these reasons, the octabromination of easily accessible Zn^{2+}, Cu^{2+} and Ni^{2+} TPP complexes was investigated. Zn^{2+} and Ni^{2+} ions were chosen because the diamagnetic nature of the complexes permits the identification of the products by NMR spectroscopy. In the case of Cu-porphyrin, despite its paramagnetism hampers NMR analysis of the bromination products, we decided to investigate it because of its large stability which should limit the decomposition under the reaction conditions. Then, the metal ion can be removed, thus permitting the characterization of the product also by NMR spectroscopy and the preparation of a wide range of different complexes.

These experimental conditions were chosen: substrate (usually 0.02 mmol) dissolved in 4.5 mL of CH_2Cl_2 (volume of the organic solvent was improved to guarantee the solubilisation of the complexes), 2 or more mL of aqueous phase at pH = 1 with at least 0.5 eq. of catalyst (Exact values are given in the experimental section).

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To ascertain the feasibility of the reaction on porphyrin complexes, the bromination was initially performed on ZnTPP by using the same reaction conditions leading to the H_2Br_4TPP, i.e. 10 times excess of KBr and overall 12 equivalents of oxidant. A main greenish-violet fraction was collected; the red-shift of the Soret band observed at the UV-vis spectrum was consistent with the formation of polybrominated product. Nonetheless, several signals were detected in the 8.5-9.0 ppm region of the ^{1}H NMR spectrum, suggesting the presence of a mixture of differently halogenated derivatives. Even if this result is not useful from a synthetic point of view, it confirmed that the bromination could be performed also with Zn-complex as starting material. Assuming the formation of a mixture of regioisomers of $ZnBr_4$TPP (we adopted the procedure for H_2Br_4TPP preparation), the conversion was ca. 60%. The reaction was then attempted with 16 equivalents of KBr and 12+6 eq. of H_2O_2 and a green fraction was collected. The increased bromination degree was highlighted by the larger red-shift of Soret band located at 447 nm (usually, the higher is the number of Br atoms, the larger is the bathochromic effect[35]), even if this data still indicates the uncompleted functionalization of the macrocycle. This supposition was corroborated by the NMR spectrum, where the presence of several scattered singlets for β-pyrrolic positions still indicates the presence of partially substituted macrocycles.

A further increase of reactants (KBr: 20 eq.; H_2O_2 16+8 eq.), allowed achieving a slightly improvement in the substrate transformation as showed by the spectroscopical analysis: Soret band was located at 466 nm while just traces of not-brominated positions were observed in the ^{1}H NMR spectrum (residual β-pyrrolic protons). The fully brominated Zn-complex (**Zn-5**) was obtained in 22% yield. To the best of our knowledge it represents the first example of direct fully bromination of Zn-tetraphenylporphyrin, usually obtained by removal of Cu ion from $CuBr_8$TPP followed by remetalation with Zn salt.[13] Some example of bromination of Zn-tetraarylporphyrin have been carried out, mainly on macrocycle bearing 2,6-disubstituted meso phenyl rings.[9,10,14,15] Here, the steric hindrance of the substituents may prevent the Zn ion displacement, while the bromination of ZnTPP produces an unexpected two sided ring opening of the substrate.[36]

Albeit encouraging, the results were not really satisfactory. Many attempts to induce the complete bromination were carried out, changing the KBr and H_2O_2 amount, the oxidant mode of addition, volume of acidic solution or catalyst, but the increase of octabrominated product generally occurs together with a large decomposition. Moreover, a partial demetalation because of the low pH was seen. For this reason, the more robust CuTPP was used as substrate; the disadvantage of the paramagnetic nature of this complex can be easily bypassed by acidic Cu removal. Since CuTPP is the substrate chosen for the fully bromination performed with one of the most famous (but not sustainable) classical method,[13] the achievement of $CuBr_8$TPP by the sustainable approach would allow to easily compare these synthetic strategies.

The best conditions for the bromination of Zn-complex were the following: 20 equivalents of KBr and overall 24 of equivalents H_2O_2. Pondering over the results reported for this complex and the different reactivity of Cu-porphyrin (which is more electron poor than Zn-complex, so less reactive toward electrophiles) we increased the reactants amount to 24 and 32 equivalents respectively. The stability of this complex permitted to double the catalyst amount, while with ZnTPP as the substrate 1 eq. of Vanadium led to a marked decomposition. It should be considered that these values correspond to 3 eq. of Br-, 4 eq. of oxidant and 12.5 % by mol of Vanadium versus any β-pyrrolic position.

After the reaction work up, the mixture was analysed by UV-vis spectroscopy that showed a spectroscopical pattern similar to what reported in literature for $CuBr_8$TPP with a strong red shifted and splitted Soret band.[13] Also TLC was promising: a small amount of decomposed material was detected, clearly much less with respect to what reported in the case of the Zn-complex, while the absence of the substrate indicates a complete conversion into the brominated derivatives (**Cu-6**). Mixture was roughly purified to remove the decomposition products, while the fractions containing the brominated species (Br_8 as main product contaminated by the Br_7 porphyrin) were collected all together. Because of the paramagnetic nature of the Cu-porphyrins hampers the NMR characterization of the compounds, we performed the isolation and the characterization of the Br_8-porphyrin after its conversion into the diamagnetic Zn-complex. First of all, the mixture was demetalated treating a $CHCl_3$ solution of the porphyrin with concentrate H_2SO_4.[37] The course of the reaction was monitored by UV-vis spectroscopy where the metal ion removal was highlighted by the appearance of the characteristic band of the porphyrin dication at 735 nm (Figure 3); once completed, the mixture was neutralized and the reaction for the Zn insertion carried out.

Substituted porphyrins are strongly non-planar and the distortion of the macrocycle facilitates the protonation of the inner core which may occurs also during the chromatographic purification. To avoid this problem the central nitrogens were protected by coordination of the diamagnetic Zn^{2+}. The following purification by alumina column yielded two fractions, the first having a residual hydrogen on pyrrolic positions as highlighted by ^{1}H NMR (singlet at 8.51 ppm), while for the second one only the signals for the phenyl rings were observed. The $ZnBr_8$TPP (**Zn-5**) was finally isolated in a 45% yield. Noteworthy, this is the yield calculated after three synthetic steps (bromination-demetalation-remetalation with Zn). Taking into account the values reported in literature for the demetalation of $CuBr_8$TPP to H_2Br_8TPP with H_2SO_4, (68%)[37] and the Zn insertion into the H_2Br_8TPP (90%),[13] we computed a 73% yield for the fully halogenation of the copper complex (**Cu-6**), an almost equal value to that achieved with molecular Br_2 (73 vs 75%).

The above mentioned conditions allow to obtain the best outcome; when the same amount of hydrogen peroxide was added in two portions or when more equivalents of reagents were employed, $ZnBr_8$TPP was obtained in the 25-35% range.

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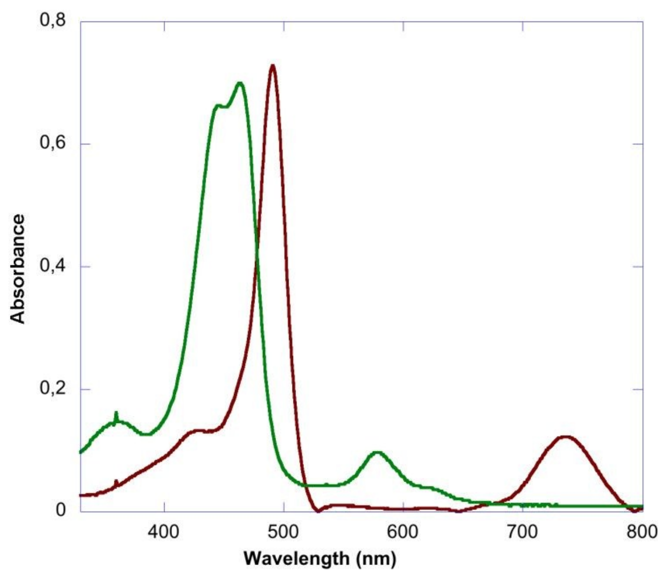

Fig. 3 UV-vis spectra of $CuBr_8TPP$ (green line) and $[H_4Br_8TPP]^{2+}$ indicating the ongoing at demetalation.

Fully bromination of porphyrin Ni-complex: after the achievement of a synthetic protocol for the complete halogenation of Zn and Cu-porphyrins, the reactivity of Ni-complex was investigated. As a first step, we compared the behaviour of Zn, Cu and Ni porphyrins, running on the latter bromination with the same reactants ratios previously used for the preparation of $ZnBr_8TPP$ and $CuBr_8TPP$. Both methods partially failed. Even if no more starting material was detected at the end of the reaction, suggesting the complete substrate conversion, the Soret band of the product was less red-shifted with respect to published spectroscopical data.[13,17] The amount of KBr and H_2O_2 was increased up to 32 eq, with 0.5 eq. of Vanadium-based catalyst. Once more, the NMR spectrum showed several β-pyrrolic signals. The reactivity of the system was increased heating the system at 45 °C (dichloromethane was replaced with 1,2-dichloroethane); regrettably the functionalization of all the peripheral positions was not achieved (final products have the same R_f, thus the purification by chromatographic methods was unmanageable) and a partially demetalation of the complexes has been observed.

A limit of the Vanadium catalyzed reaction is the fast peroxide decomposition operated by the metal.[26] To overcome this drawback, V was replaced with the more reactive Mo catalyst;[30,38] when the reaction was performed at 20 °C, a more complete grade of substitution was achieved. Again, the ^1H NMR spectrum showed the presence of traces of macrocycle with residual protons contaminating the more abundant $NiBr_8TPP$ (**Ni-7**). When the reaction was carried out at higher temperature, a larger decomposition was detected (Conversion: 25% at 20 °C and 8% at 45 °C).

The best results obtained for the preparation of bromo-derivatives are resumed in table 1. The reported values indicate that the transition metal-catalysed system gave comparable yields (H_2Br_3TPP, $CuBr_8TPP$) to those reported with literature method, with advantage of avoiding the exploitation of toxic reagents.

Finally, to consider the sustainability of the process the results obtained with this approach were compared with those of the classical procedures using the corresponding E factor (kg of by-product per kg of product), a parameter that better describes a sustainable processes since it does not consider only the "classical yield".[39,40] The values obtained, indeed, do not generally underline a substantial decrease of E (with the noticeable exception of $CuBr_8TPP$), nonetheless an "environment friendly process" not only minimizes the formation of undesired products but also optimizes the utilization of resources, decreases the energy consumption and overall uses substances as less hazardous as possible thus following some of the "Green Chemistry" principles.[23] By the pure E-factor values (see table S1 in the Supplementary), it seems that the methods described in this paper is not advantageous with respect to the common systems to brominate tetrapyrrolic macrocycle; nevertheless, the transition metals catalyzed bromination is far better considering hazardousness of the reagents employed and the lower energetic cost.

Table 1. Yields for the sustainable bromination of porphyrin derivatives.

Product	KBr eq.	H_2O_2 eq.	Catalyst, eqs.	Yield this work	Yield literature (ref.)
H_2Br_3TPP	7.5	6+3[a]	V, 0.5	48%	40% (19)
H_2Br_4TPP	10	20	V, 0.5	47%	65% (17)
ZnBrTPP	1.4	1+1[a]	Mo, 0.5	33%	51%[b] (20)
$ZnBr_8TPP$	20	16+8[a]	V, 0.5	22%[b]	54%[c] (12)
$CuBr_8TPP$	24	32	V, 1.0	73%	75% (12)
$NiBr_8TPP$	32	32	Mo, 0.5	25%	85% (16)

[a] Second portion of H_2O_2 added after 6 hours; [b] 3,5-di-tert-butylphenyl groups on meso positions [c] Multi-steps procedure

DFT calculations: As already mentioned above, the increasing bromination level of the macrocycle implies a bathochromic shift in the UV-vis spectra. Such effect is due to different reasons: the electron-withdrawing effect of the bromine substituents, as well as to the lost of planarity of the macrocycle once brominated for steric hinderance

Hence, DFT calculations have been carried out in the *vacuum,* to confirm such saddling effect. Geometry optimization of the polybrominated metal and metal-free TPPs has been performed using B3LYP hybrid functional and 6-31G(d) basis set. According to UV-vis data, the planar TPP results significantly tilted when four or eight Br atoms are introduced onto peripheral positions. A more severe distortion is observed in highly substituted derivatives (Fig. 4).

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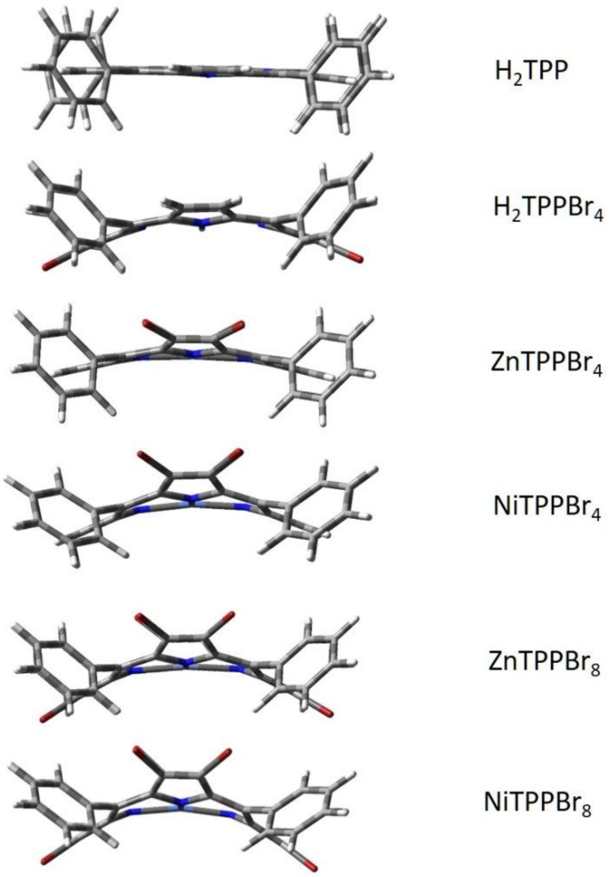
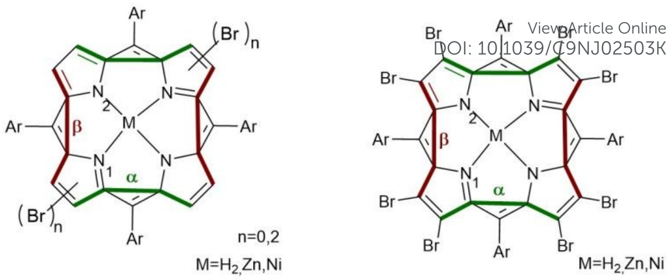


Fig. 4 DFT optimized geometry for H_2TPP and brominated porphyrins, side view. Bromine atom is represented in red; nitrogen in blue; carbon atoms are in grey and hydrogen in white.

Dihedral values have been calculated for all compounds (Fig. 5).[41,42] Here, the saddling of the macrocycle is highlighted by the significant widening of dihedrals. Moreover, M-N distances have been calculated and results show that the bromine substitution at the peripheral position slightly affect also the metal coordination. As a matter of fact, fully substituted porphyrins show a M-N distance of 2.03 Å for $ZnBr_8TPP$ and 1.91 Å for $NiBr_8TPP$. Conversely, the tetrasubstituted derivatives present the same values for the M-N1 bond, while shorter values have been calculated for M-N2, where N2 represents the nitrogen belonging to the non-brominated pyrroles.



	M-N_1 distance	M-N_2 distance	α	β
H_2TPP	-	-	15,1°	-9,1°
H_2Br_4TPP	-	-	32,3°	-32,3°
$ZnBr_4TPP$	2,03 Å	1,99 Å	22,8°	-22,8°
$NiBr_4TPP$	1,94 Å	1,91 Å	25,1°	-25,1°
$ZnBr_8TPP$	2.03 Å	2,03 Å	41,8°	-41,9°
$NiBr_8TPP$	1,91 Å	1,91 Å	38,0	-37,6°

Fig. 5 Calculated dihedral values and M-N.

Conclusions

Vanadium or Molybdenum catalyzed bromination represents an innovative and sustainable strategy for the functionalization of tetrapyrrolic macrocycles. Some noteworthy results have been achieved: substitution of NBS or the toxic and corrosive Br_2 with the much safer KBr as bromine source; use of a cheap oxidant as H_2O_2, also characterized by the highest active oxygen content after O_2 itself; and last but not the least the use of CH_2Cl_2 in place of the more dangerous $CHCl_3$ or CCl_4 as organic solvents. This kind of process has been made possible by the ability of the transition metal to convert a safe but unreactive form of Br (Br^-) in a reactive, electrophile species by using a common oxidant such as H_2O_2.

By the amount of catalyst used, the method seems to be quite far from a catalytic process. Anyway, two important points should be considered: first of all, up to eight peripheral positions may undergo the functionalization, lowering the real catalyst/substrate ratio (12.5% by mol. for the fully brominated species). Then, the active catalytic system requires low pH and H_2O_2. Since the decomposition of hydrogen peroxide is triggered also by the low pH, a large amount of transition metals is needed to allow the reaction to quickly take place before the unavoidable reactant decomposition. Finally, to force the reaction toward the formation of the desired product, the amount of KBr and H_2O_2 has been modified to overcome the low reactivity of porphyrin β-positions. Of course, too large reactants excess is inadvisable because it would make the process not sustainable. Obviously, a higher yield is a desirable outcome to avoid or simplify the purification step, enhancing the sustainability of the process. In some cases our procedure allowed to achieve the target molecules with a comparable (H_2Br_3TPP) or superior ($CuBr_8TPP$) yields with respect to those obtained by the literature methods, demonstrating that the "sustainable way" for the halogenation of tetrapyrrole

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macrocycles periphery is a practical and effective approach. Moreover, by an accurate optimization of the reaction conditions, considerable improvements of the yields may be anticipated, in order to reach satisfactory results for a wide series of porphyrin derivatives, as already described for simple arenes or alkenes.[25,28,30-31]. A plausible explanation for the difficulties observed in the case of $ZnBr_8TPP$ and $NiBr_8TPP$ formation, is the partial demetalation/protonation of the inner core which deactivate the peripheral positions (Zn-complex easily undergoes Zn removal under acidic condition) or of a marked decomposition due to the presence of oxidant, catalytic metals and long reaction time. However, the formation of H_2Br_3TPP, H_2Br_4TPP and $CuBr_8TPP$ in more than acceptable amount, suggests that only some substrates may suffer of such a drawback. Much more, it should be highlighted the versatility of the procedure, which allows the insertion of a variable number of Br moieties on tetrapyrrolic macrocycles, free base or metal complexes.

Finally, a further “environment friendly” aspect is connected with the lower energy consumption, since the reaction proceeds at room temperature, at odd with many literature protocols.

In conclusion, these preliminary results clearly demonstrate that there is an open new way to obtain differently brominated porphyrinoids with modern and sustainable protocol, indeed further studies to optimize the reactions are warranted.

Experimental

Instrumentation: UV-vis spectra were recorded in CH_2Cl_2 with a Shimadzu UV/Vis spectrophotometer UV-2401 PC. ^1H NMR spectra were recorded at 300 K with a Bruker Avance III 400 BBFO spectrometer operating at 400 MHz. Chemical shifts are given in ppm to residual solvent ($CHCl_3$ = 7.26 ppm).

Purity of compounds was checked by HPLC with a Shimadzu LC10AT Liquid Chromatography equipped with a SPD10AV UV-vis detector and a Chiralcel OD column (250x4.6 mm,10 μm particles size, Daicel Chemical Industries) with toluene as eluent; detector was set at λ_{abs} = 550 nm. It was measured a purity > 99% for H_2Br_3TPP, H_2Br_4TPP, ZnBrTPP and > 98% for $ZnBr_8TPP$ and $NiBr_8TPP$.

Materials: Silica gel 60 (70–230 mesh, Sigma–Aldrich) was used for column chromatography. Reagents and solvents (Aldrich, Fluka, Carlo Erba) were of the highest grade available and were used without further purification.

5,10,15,20-Tetraphenylporphyrin (H_2TPP),[43] [5,10,15,20-Tetraphenylporphyrinato]Ni(II) (NiTPP)[44], [5,10,15,20-Tetraphenylporphyrinato]Cu (II) (CuTPP)[44], and [5,10,15,20-Tetraphenylporphyrinato]Zn(II) (ZnTPP)[44] were prepared according to literature methods.

DFT Calculation: DFT geometry optimizations have been performed with Gaussian 16 rev. A.03[45], using the B3LYP functional and a 6-31G (d) basis set.

Synthesis of 2,3,12-Tribromo-5,10,15,20-tetraphenylporphyrin (H_2Br_3TPP) (2H-2).

H_2TPP (12.2 mg, 0.02 mmol) was dissolved in 3 mL of CH_2Cl_2, then 1 mL of aqueous solution at pH = 1 ($HClO_4$) containing NH_4VO_3 (1.1 mg, 0.01 mmol) and KBr (17.8 mg, 0.15 mmol) was added, followed by H_2O_2 (46 μL 2.6 M, 0.12 mmol). Mixture was vigorously stirred at 20 °C for 6 hours; a second aliquot of H_2O_2 (23 μL 2.6 M, 0.06 mmol) was added and mixture stirred for further 18 hours, then organic phase was washed with satured $NaHCO_3$, water and finally dried over Na_2SO_4. Residue was purified by silica gel column eluted with CH_2Cl_2/petroleum ether 2:1; fractions containing the H_2Br_3TPP were collected, solvent removed under vacuum and residue crystallized from CH_2Cl_2/MeOH. Yield: 8.2 mg, 48%.

UV-vis (CH_2Cl_2) λ_{max} (nm) [log ε, M^{-1}, cm^{-1}]: 428 (5.42), 525 (4.25), 562 (sh), 602 (3.54), 663 (3.73).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.86-8.77 (m, 3H, β-pyrrole), 8.73-8.69 (m, 2H, β-pyrrole), 8.19-8.03 (m, 8H, meso *o*-phenyl), 7.81-7.71 (m, 12H, meso *m*-phenyl + meso *p*-phenyl), -2.87 (s, 1H, inner NH), -2.99 (s, 1H, inner NH).

Elemental Analysis: calcd. for $C_{44}H_{27}Br_3N_4$ C, 62.07; H, 3.20; N, 6.58: found C, 61.82; H, 3.09; N, 6.62

Synthesis of 2,3,12,13-Tetrabromo-5,10,15,20-tetraphenylporphyrin (H_2Br_4TPP) (2H-3).

H_2TPP (12.2 mg, 0.02 mmol) was dissolved in 3 mL of CH_2Cl_2, then 1 mL of aqueous solution at pH = 1 ($HClO_4$) containing NH_4VO_3 (1.1 mg, 0.01 mmol) and KBr (23.8 mg, 0.20 mmol) was added, followed by H_2O_2 (38 μL 10.4 M, 0.40 mmol). Mixture was vigorously stirred at 20 °C for 24 hours, then organic phase was washed with satured $NaHCO_3$, water and finally dried over Na_2SO_4. Residue was purified by silica gel column eluted with CH_2Cl_2/petroleum ether 2:1; a small amount of H_2Br_3TPP eluted first, followed, by a red-brownish band fractions containing the H_2Br_4TPP; solvent was removed under vacuum and residue crystallized from CH_2Cl_2/MeOH. Yield: 8.7 mg, 47%.

UV-vis (CH_2Cl_2) λ_{max} (nm) [log ε, M^{-1}, cm^{-1}]: 436 (5.50), 534 (4.31), 612 (3.56), 682 (4.03).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.69 (s, 4H, β-pyrrole), 8.17-8.16 (m, 8H, meso *o*-phenyl), 7.81-7.74 (m, 12H, meso *m*-phenyl + meso *p*-phenyl), -2.81 (s, 2H, inner NH).

Elemental Analysis: calcd. for $C_{44}H_{26}Br_4N_4$ C, 56.81; H, 2.82; N, 6.02: found C, 56.34; H, 2.91; N, 6.22

Synthesis of [2,3,7,8,12,13,17,18-Octabromo-5,10,15,20-tetraphenylporphyrinato]Zinc ($ZnBr_8TPP$) (Zn-5).

ZnTPP (13.5 mg, 0.02 mmol) was dissolved in 4.5 mL of CH_2Cl_2, then 2.5 mL of aqueous solution at pH = 1 ($HClO_4$) containing NH_4VO_3 (1.1 mg, 0.01 mmol) and KBr (47.6 mg, 0.40 mmol) was added, followed by H_2O_2 (31 μL 10.4 M, 0.32 mmol). Mixture was vigorously stirred at 20 °C for 6 hours; a second aliquot of H_2O_2 (16 μL 10.4 M, 0.16 mmol) was added and mixture stirred for further 18 hours, then organic phase was washed with satured $NaHCO_3$, water and finally dried over Na_2SO_4. (Note: some demetalation may occur, as evidenced by a large band around 710 nm; the metal complex can be restored heating the reaction mixture with a satured solution of $Zn(AcO)_2$ in methanol for a few minutes). Residue was purified by silica gel column eluted with CH_2Cl_2/petroleum ether 1:1, followed by PLC (silica gel, CH_2Cl_2/petroleum ether 1:1). Fractions containing the $ZnBr_8TPP$ were collected, solvent removed under reduced pressure and residue crystallized from CH_2Cl_2/MeOH. Yield: 5.7 mg, 22%.

UV-vis (CH_2Cl_2) λ_{max} (nm) [log ε, M^{-1}, cm^{-1}]: 349 (4.65) 466 (5.39), 589 (4.12), 656 (4.08).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, 8H, J = 6.93 Hz, meso *o*-phenyl), 7.82-7.72 (m, 12H, meso *m*-phenyl + meso *p*-phenyl)

Elemental Analysis: calcd. for $C_{44}H_{20}Br_8N_4Zn$ C, 40.36; H, 1.54; N, 4.28; found C, 40.41, H, 1.42; N, 4.31

Synthesis of [2,3,7,8,12,13,17,18-Octabromo-5,10,15,20-tetraphenylporphyrinato]Copper ($CuBr_8TPP$) (Cu-6).

CuTPP (27 mg, 0.04 mmol) was dissolved in 9 mL of CH_2Cl_2, then 5 mL of aqueous solution at pH = 1 ($HClO_4$) containing NH_4VO_3 (4.7 mg, 0.04 mmol) and KBr (114 mg, 0.96 mmol) was added, followed by H_2O_2 (123 μL 10.4 M, 1.28 mmol). Mixture was vigorously stirred at 20 °C for 24 hours, then organic phase was washed with satured $NaHCO_3$, water and finally dried over Na_2SO_4. Residue was purified by neutral Al_2O_3 (Grade III) eluted with $CHCl_3$. Fractions containing the $CuBr_8TPP$ were collected, solvent removed under reduced pressure and residue crystallized from CH_2Cl_2/MeOH. Since mixture containing $CuBr_8TPP$ was contamined by some $CuBr_7TPP$ yield was not calculated and product was identified by comparison of the UV-vis spectra with literature data.[12] Product was directly used for the demetalation and the Zn insertion steps.

Synthesis of 2,3,7,8,12,13,17,18-Octabromo-5,10,15,20-tetraphenylporphyrine H_2Br_8TPP and of [2,3,7,8,12,13,17,18-Octabromo-5,10,15,20-tetraphenylporphyrinato]Zinc ($ZnBr_8TPP$) (Zn-5).

Mixture containing the $CuBr_8TPP$ (47 mg) was dissolved in 20 mL of $CHCl_3$, then 0.8 mL of concentrated sulphuric acid was added and mixture vigorously stirred for 5 minutes. Demetalation process was monitored by UV-vis spectroscopy as indicated by the dication porphyrin band at 735 nm. Reaction was then poured into 30 mL of water, organic phase extracted with $CHCl_3$, neutralized with satured $NaHCO_3$, washed with water, then dried over Na_2SO_4. Residue was purified by basic Al_2O_3 (Grade III) eluted with $CHCl_3$. Fractions containing the porphyrins free base were collected, solvent reduced to 20 mL and a satured solution of $Zn(OAc)_2{\cdot}2H_2O$ in methanol was added. Reaction was heated to reflux for 10 minutes and complex formation monitored by UV-vis spectroscopy. Solvent was removed and residue purified by neutral Al_2O_3 (Grade III) eluted with $CHCl_3$/hexane 3:2 to collected the first band identified as the $ZnBr_7TPP$ by the residual singlet (8.56 ppm) observed at ^1H NMR spectroscopy, then $CHCl_3$/hexane 4:1 to collect the desired $ZnBr_8TPP$, crystallized from CH_2Cl_2/MeOH. Yield: 23.5 mg, 45% (Note: yield has been calculated after three steps, with respect CuTPP as the starting material).

UV-vis (CH_2Cl_2) λ_{max} (nm) [log ε, M^{-1}, cm^{-1}]: 349 (4.65) 466 (5.39), 589 (4.12), 656 (4.08).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, 8H, J = 6.93 Hz, meso *o*-phenyl), 7.82-7.72 (m, 12H, meso *m*-phenyl + meso *p*-phenyl)

Synthesis of [2,3,7,8,12,13,17,18-Octabromo-5,10,15,20-tetraphenylporphyrinato]Nickel ($NiBr_8TPP$) (Ni-7).

NiTPP (13.4 mg, 0.02 mmol) was dissolved in 4.5 mL of CH_2Cl_2, then 2 mL of aqueous solution at pH = 1 ($HClO_4$) containing $(NH_4)_2MoO_4$ (1.8 mg, 0.01 mmol) and KBr (76.1 mg, 0.64 mmol) was added, followed by H_2O_2 (61 μL 10.4 M, 0.64 mmol). Mixture was vigorously stirred at 20°C for 6 hours; a second aliquot of H_2O_2 (61 μL 10.4 M, 0.64 mmol) was added and mixture stirred for further 18 hours, then organic phase was washed with satured $NaHCO_3$, water and finally dried over Na_2SO_4. Residue was purified by silica gel column eluted with CH_2Cl_2/petroleum ether 1:1; fractions containing the $NiBr_8TPP$ were collected, solvent removed under reduced pressure and residue crystallized from CH_2Cl_2/MeOH. Yield: 6.5 mg, 25%.

UV-vis (CH_2Cl_2) λ_{max} (nm) [log ε, M^{-1}, cm^{-1}]: 342 (4.43), 449 (5.45), 560 (4.16), 596 (sh).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.92-7.90 (m, 8H, meso *o*-phenyl), 7.75-7.65 (m, 12H, meso *m*-phenyl + meso *p*-phenyl).

Elemental Analysis: calcd. for $C_{44}H_{20}Br_8N_4Ni$ C, 40.57; H, 1.55; N, 4.30; found C, 41.02; H, 1.62; N, 4.19

Synthesis of [2-Bromo-5,10,15,20-tetraphenylporphyrinato]Zinc (ZnBrTPP) (Zn-4).

ZnTPP (13.5 mg, 0.02 mmol) was dissolved in 12 mL of CH_2Cl_2, then 1 mL of aqueous solution at pH = 1 ($HClO_4$) containing $(NH_4)_2MoO_4$ (1.8 mg, 0.01 mmol) and KBr (3.3 mg, 0.028 mmol) was added, followed by H_2O_2 (20 μL 1.0 M, 0.02 mmol). Mixture was vigorously stirred at 20°C for 6 hours; a second aliquot of H_2O_2 (20 μL 1.0 M, 0.02 mmol) was added and mixture stirred for further 18 hours, then organic phase was washed with satured $NaHCO_3$, water and finally dried over Na_2SO_4. Residue was purified by PLC (silica gel column eluted with CH_2Cl_2/petroleum ether 3:4; fractions containing the ZnBrTPP were collected, solvent removed under reduced pressure and residue crystallized from CH_2Cl_2/MeOH. Yield: 4.9 mg, 33%.

UV-vis (CH_2Cl_2) λ_{max} (nm) [log ε, M^{-1}, cm^{-1}]: 420 (5.56), 549 (4.27), 584 (3.93).

^1H NMR (400 MHz, $CDCl_3$): δ = 9.07 (s, 1H, β-pyrrole), 8.94 (d, 1H, *J* = 4.75 Hz, β-pyrrole), 8.91 (m, 3H, β-pyrrole), 8.88 (d, 1H, *J* = 4.74 Hz, β-pyrrole), 8.83 (d, 1H, *J* = 4.74 Hz, β-pyrrole), 8.21-8.17 (m, 6H, meso *o*-phenyl), 8.07-8.05 (m, 2H, meso *o*-phenyl), 7.79-7.68 (m, 12H, meso *m*-phenyl + meso *p*-phenyl).

Elemental Analysis: calcd. for $C_{44}H_{27}BrN_4Zn{*}H_2O$ C, 68.19; H, 3.77; N, 7.23; found C, 68.52; H, 3.92; N, 7.15

Conflicts of interest

There are no conflicts to declare.

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