

Antioxidant properties of water-soluble phthalocyanines containing quinoline 5-sulfonic acid groups

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Received: 09.04.2019

Accepted/Published Online: 24.06.2019

Final Version: 06.08.2019

Abstract: In the present study, the antioxidant properties of peripherally and nonperipherally water-soluble tetra (quinoline 5-sulfonic acid) substituted metal-free (**1**, **2**), Zn(II) (**3**, **4**), Co(II) (**5**, **6**), and Mn(III)Cl (**7**, **8**) phthalocyanine (Pc) derivatives were reported. In order to determine the antioxidant properties of the Pc compounds, three different commonly known antioxidant methods were used: DPPH (α, α -diphenyl- β -picrylhydrazyl) radical scavenging, ferrous ion chelating, and reducing power assays. Compound **6** showed the best DPPH activity among the other tested compounds except for the standards. The ferrous ion chelating IC₅₀ value of compound **7** was nearly as good as that of the EDTA standard. The reducing power activity results indicated that the tested Pc compounds were as sensitive as standard reducing agents such as butylated hydroxytoluene and ascorbic acid. Overall, all tested compounds showed good antioxidant properties and it may be suggested that they could be used as new positive controls for reducing power assays in the future works.

Key words: Water-soluble, quinoline, phthalocyanine compounds, antioxidant activity

1. Introduction

Antioxidants are compounds that can retard or inhibit free radicals resulting from oxidation reactions that occur under the influence of atmospheric oxygen or reactive oxygen species during various metabolic reactions in living organisms. Thus, they play a very important role in the defense mechanisms of all living organisms [1]. Antioxidants can be natural or synthetic. The most common natural antioxidants are vitamin C and E, carotenoids, phenolic compounds (stilbenes, phenolic acids such as benzoic and hydroxybenzoic acids), and cinnamic and hydroxycinnamic acids. Synthetic antioxidants such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and sodium metabisulfite (SMB) have been extensively used in food, cosmetics, and pharmaceutical processes [2]. Also, photodynamic therapy (PDT) is one of the applications of antioxidants. Some antioxidant molecules are reported to increase the photodamaging effect of photosensitizers used in PDT with many kinds of sensitizers [3].

Synthetic antioxidants are especially widely used because they are effective and cheaper than natural antioxidants. Despite the widespread use of synthetic antioxidants in the pharmaceutical and food industries, these adjuvants have numerous hazardous effects for human health and the environment [4]. Therefore, there is always a need to develop new antioxidants that are less harmful and closer to natural ingredients.

Synthetic antioxidant metal-based compounds, such as phthalocyanines (Pcs), have received much atten-

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tion in biological applications due to their many health benefits [5]. Both ligands and metals are responsible for the activity of synthetic antioxidants. Their activity may vary according to the metal used. Compared to other main group elements, transition metals are very important for this aim because of having various coordination numbers, oxidation states, and geometries [6–8].

Due to their 18- π electron structure and high thermal and chemical stability, Pcs have recently been used in a great number of important applications [9] in many fields, such as antibacterial agents [6], chemical sensors [10], photosensitizers for photodynamic therapy [11], antioxidant agents [7,12], and therapeutic medicine [13].

The use of Pc compounds in these areas depends on their solubility in common organic solvents and water. The aggregation properties (by attractive π - π stacking interactions) of Pcs may affect their solubility. In particular, unsubstituted Pcs have this kind of solubility problem. The solubility in common organic solvents and water can be enhanced by the introduction of bulky or long chain groups, e.g., alkyl, sulfonate, carboxy, or alkoxy on the peripheral positions and nonperipheral positions of the Pc macrocycle, and this causes the formation of additional solvation centers. Water-soluble Pcs are of great scientific and technological importance, such as in PDT and medical applications [14–18].

In this study, we present the antioxidant activity of water-soluble phthalocyanines (**1–8**) bearing quinoline 5-sulfonic acid substituents in the peripheral or nonperipheral positions using different antioxidant methods.

2. Experimental

2.1. Materials and methods

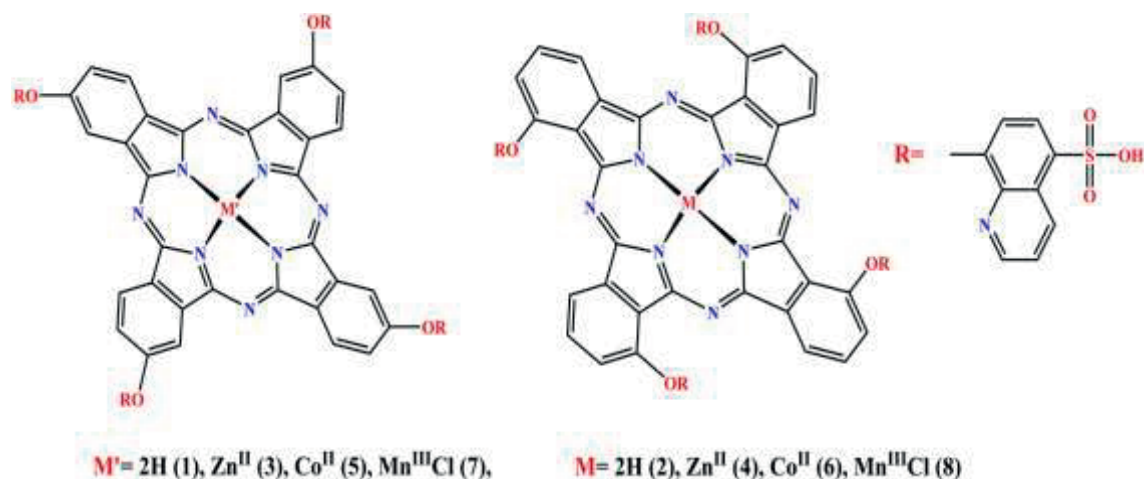
2(3),9(10),16(17),23(24)-Tetrakis(8-(3,4-dicyanophenoxy) quinoline-5-sulfonic acid) phthalocyaninato metal-free (**1**), 1(4),8(11),15(18),22(25)-tetrakis(8-(2,3-dicyanophenoxy) quinoline-5-sulfonic acid) phthalocyaninato metal-free (**2**), 2(3),9(10), 16(17),23(24)-tetrakis(8-(3,4-dicyanophenoxy) quinoline-5-sulfonic acid)-zinc(II) phthalocyanine (**3**), 1(4),8(11),15(18),22(25)-tetrakis(8-(2,3-dicyanophenoxy) quinoline-5-sulfonic acid)-zinc(II) phthalocyanine (**4**), 2(3),9(10),16(17),23(24)-tetrakis(8-(3,4-dicyanophenoxy) quinoline-5-sulfonic acid)-cobalt(II) phthalocyanine (**5**), 1(4),8(11),15(18),22(25)-tetrakis(8-(2,3-dicyanophenoxy) quinoline-5-sulfonic acid)-cobalt(II) phthalocyanine (**6**), 2(3),9(10),16(17),23(24)-tetrakis(8-(3,4-dicyanophenoxy) quinoline-5-sulfonic acid)-manganese(III) chloride phthalocyanine (**7**), and 1(4),8(11),15(18),22(25)-tetrakis (8-(2,3-dicyanophenoxy) quinoline-5-sulfonic acid)-manganese(III) chloride phthalocyanine (**8**) were prepared according to the procedure in the literature (Scheme) [14].

2.2. Antioxidant activity determination

The following assays were used to estimate the antioxidant properties of the test compounds.

2.2.1. DPPH radical scavenging assay

The DPPH assay was chosen for use for the determination of antioxidant free radical scavenging activity. This assay was based on the measurement of the scavenging capacity of α, α -diphenyl- β -picrylhydrazyl (DPPH) free radical as developed by Bios [19]. In this method, a 0.004% methanolic solution of DPPH was mixed with different concentrations ranging from 100 to 500 $\mu\text{g/mL}$ of Pc compounds. The stock solutions of Pc compounds were prepared in DMSO. The mixture was mixed and incubated in the dark for 30 min at 25 °C. The color change of the mixture after 30 min of incubation was measured at 517 nm wavelength with a UV-Vis



Scheme. The structures of water-soluble phthalocyanines (1–8) bearing quinoline 5-sulfonic acid substituents on the peripheral or nonperipheral positions.

spectrophotometer. The control reaction was carried out in the same manner as for the above mixture without any Pc complexes.

DPPH radical scavenging capacity was calculated with the following equation:

$$\text{DPPH scavenging activity (\%)} = (1 - A_{\text{sample517}}/A_{\text{control517}}) \times 100$$

In the above equation, $A_{\text{control517}}$ is the control absorbance and $A_{\text{sample517}}$ is the absorbance of the Pc compound or standard. As standards, Trolox and butylated hydroxytoluene (BHT) were used, and the scavenging capacities were discussed with the calculated Pc results.

The 50% inhibitory concentrations (IC_{50}) of metal-free and metallophthalocyanine compounds and standards (BHT and Trolox) were determined. The value of IC_{50} means that the concentration of the sample will scavenge 50% of DPPH free radicals. The concentrations versus inhibition percentages of the Pc compounds were plotted. The values of IC_{50} were calculated from these plots for each of the compounds.

2.2.2. Ferrous ion chelating (FIC) assay

The FIC assay was used in determining the ferrous ion chelating abilities of the Pc compounds competing with ferrozine as in the method described by Dinis et al. [20]. The stock solutions of Pc compounds were prepared in DMSO. Various concentrations ranging from 100 to 500 $\mu\text{g/mL}$ of the Pc compound solutions were mixed with 2 mM FeCl_2 in deionized water. The solution was kept at room temperature for 30 min. The mixture reaction was initiated by addition of 5 mM ferrozine. The mixture was incubated at room temperature for 10 min. The reaction absorbance was monitored at 562 nm. FeCl_2 and a ferrozine mixture were used as the control. The inhibition percentage of the ferrozine- Fe^{2+} complex was calculated by the following equation:

$$\text{FIC effect (\%)} = (1 - A_{\text{sample562}}/A_{\text{control562}}) \times 100$$

$A_{\text{control562}}$ is the control absorbance and $A_{\text{sample562}}$ is the absorbance of the Pc compounds or standards. Ethylenediaminetetraacetic acid (EDTA) was used as a known standard. The results of the Pc compounds were discussed with the results of the standard.

The IC_{50} values of metal-free and metal Pc compounds and EDTA (as standard) were determined. The IC_{50} value of a compound represents that the concentration of a sample is supposed to inhibit 50% of the ferrous ion-ferrozine complex formation (FIC ability). The concentrations versus inhibition percentages of the Pc compounds were plotted. Thus, the IC_{50} values of each compound were calculated from the calibration curves to show the amount of antioxidant necessary to inhibit ferrous ion-ferrozine complex formation by 50%.

2.2.3. Reducing power assay

The reducing power assay was used to determine the antioxidant capacity of Pc compounds as in the method of Oyaizu [21]. Different concentrations from 5 to 100 $\mu\text{g/mL}$ of the Pc compounds were incubated with 0.2 M phosphate buffer (pH 6.6) and 1% (w/v) potassium ferricyanide at 50 °C for 20 min. Then the reaction was ended by adding trichloroacetic acid (10%) and the mixture was centrifuged. The supernatant was stirred with FeCl_3 (0.1%) and distilled water. The absorbance of the formed Perl's Prussian blue potassium ferrocyanide-ferrous complex was measured at 700 nm. Among the known standards, ascorbic acid and BHT were chosen as standards. The enhancement of reaction absorbance signifies good reducing power.

3. Results and discussion

3.1. Determination of DPPH free radical scavenging activity

The DPPH free radical scavenging technique is a technique extensively used for evaluating the antioxidant properties of compounds such as synthetic ones and plant extracts. The DPPH molecule is a highly stable free radical molecule capable of capturing an electron or hydrogen radical to become stable [22]. The radical scavenging capability induced by antioxidant molecules can be interpreted by monitoring the decrease in UV absorption at 517 nm. This causes the radicals to be cleared by hydrogen provided by antioxidant molecules. This results in a visually noticeable switch in color to yellow [23].

In this work, we used the DPPH free radical scavenging method to evaluate the antioxidant potential of the synthesized Pc compounds. The DPPH activities of metal-free and metallophthalocyanine compounds and BHT-Trolox as known standards are presented in Figure 1. According to our results, the highest antioxidant capacity among all compounds was exhibited by compound **6** with 28.3% inhibition of radical formation at 500 $\mu\text{g mL}^{-1}$. The descending order of radical scavenging activity of the tested Pc compounds was **6** > **4** > **1** > **2** > **5** > **7** > **3** > **8**. The Pc compounds showed lower DPPH activity in comparison to the known Trolox and BHT standards (Figure 1). The DPPH scavenging activities of metal-free Pc compounds were also measured. Their radical scavenging activities were higher than those of the nonperipheral Pc compounds but lower than those of the peripheral Pc compounds except compound **8**. The DPPH scavenging activities of the Pc compounds tested were enhanced by increasing concentrations of the compounds. According to the obtained results, it was observed that the position of the substituted groups was not significant in terms of DPPH scavenging activity when Pc compounds contained the metal atom Co. These results were found to be compatible with the literature values [24]. In contrast, Keleş et al. reported that nonperipherally substituted Pc compounds showed higher DPPH radical scavenging activity [25].

Additionally, IC_{50} values of metal-free and metallophthalocyanine compounds and known standards (Trolox and BHT) were also calculated and are shown in the Table. The DPPH scavenging IC_{50} values of metallophthalocyanine compounds were found to be much higher than the IC_{50} values of the standards. A high IC_{50} value indicates low antioxidant capacity.

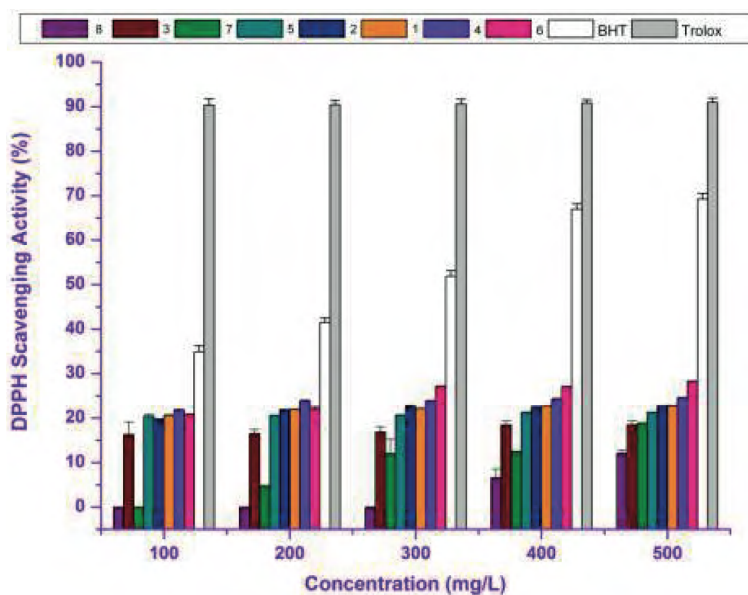


Figure 1. Radical scavenging activity on DPPH radicals (%) of the compounds.

Table. IC₅₀ values of Pc compounds (with and without metal) for DPPH scavenging assay and ferrous ion chelating assay. *ND means 'not detected', i.e. did not show any activity. BHT and Trolox were used as standards for DPPH assay; EDTA was used as standard for FIC assay.

Pc compounds/standards	IC ₅₀ (mg/mL)	
	DPPH radical scavenging	Ferrous ion chelating
1	6.0 ± 0.05	ND*
2	4.6 ± 0.01	ND*
3	4.8 ± 0.42	0.2 ± 0.014
4	4.7 ± 0.42	3.5 ± 0.566
5	8.4 ± 1.06	0.8 ± 0.480
6	1.5 ± 0.01	0.7 ± 0.028
7	1.3 ± 0.04	0.09 ± 0.003
8	2.1 ± 0.21	ND*
BHT	0.27 ± 0.001	-
Trolox	0.02 ± 0.003	-
EDTA	-	0.06 ± 0.004

3.2. Determination of ferrous ion chelating activity

Currently, there are several studies emphasizing the role of metal-induced toxicity and carcinogenesis in the formation of nitrogen and reactive oxygen species (ROS) in living systems. The formation of free radicals by the action of metals can increase lipid peroxidation, as well as various modifications in DNA bases. In addition to ROS formation, metal exposure can also result in the formation of reactive nitrogen species. It is known in the literature that various metals are dangerous because they are toxic and lead to serious diseases. An excessive amount of iron in the body in particular poses a risk for a variety of diseases including vascular diseases,

some neurological conditions, and cancer. Antioxidants can easily form chelates with metal ions responsible for ROS formation. For this reason, the FIC activity of an antioxidant compound becomes important because of inhibiting the oxidative stress caused by ROS [26].

The metal-free and metallophthalocyanine compounds were analyzed in terms of their ability to compete with ferrozine to form a structure with iron(II) ions in free solution. The results are presented in Figure 2. All the tested metallophthalocyanine compounds except **4** displayed an ability to form a structure with iron(II) ions in a concentration-dependent way. The chelating ability of the compounds increased with increased concentrations. However, metal-free Pc compounds did not show any FIC activity under the experimental conditions. Compounds **5**, **6**, and **8** chelated ferrous ions by $31 \pm 0.05\%$, $34 \pm 0.1\%$, and $8 \pm 0.07\%$, respectively, at $500 \mu\text{g mL}^{-1}$, whereas **3** and **7** showed excellent chelating ability of $89 \pm 0.09\%$ and $91 \pm 0.64\%$, respectively, at the same concentration. EDTA, one of the best chelating compounds, was chosen as a standard in this study. It was determined that the chelating activities of all the compounds tested were lower than the chelating activity (100%, at $500 \mu\text{g mL}^{-1}$) of the EDTA standard. The FIC abilities of the compounds were in the following order: $7 > 3 > 6 > 5 > 8$. According to this order, it can be seen that the Pc compound gained FIC ability due to containing a metal atom in the inner core. In addition, the peripheral position of the substituted groups positively affected this activity [24]. According to the study of Kantar et al., the FIC activity results of Pcs containing resorcinol azo dyes were found to be similar to our results. In our study, compound **3** showed much higher FIC activity than the other compounds tested in both studies [27].

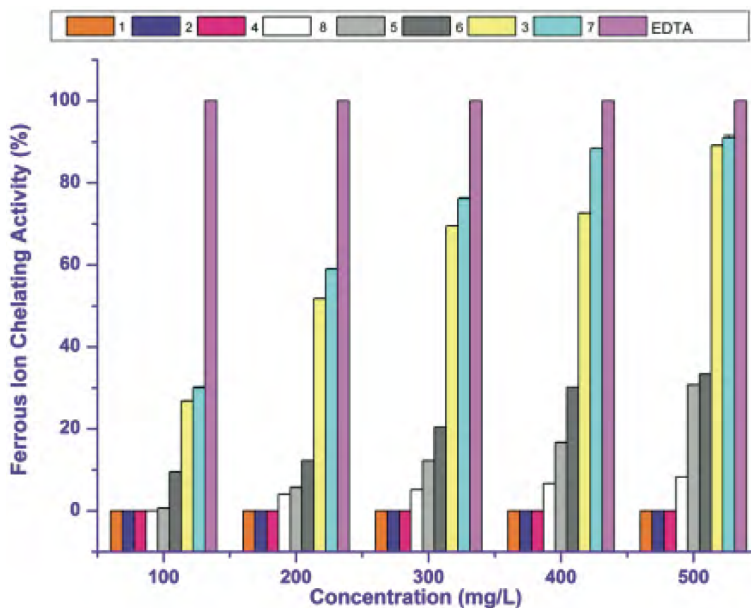


Figure 2. Chelating activity of the compounds on ferrous ion.

When the IC_{50} values of the FIC activities of Pc compounds were examined, **7** had a chelating ability almost as good as the positive control (standard), EDTA. In addition, FIC IC_{50} values of all compounds tested were not lower than those of EDTA. The IC_{50} values of the other compounds on ferrous ion-ferrozine complex formation are presented in the Table. Generally, lower values indicate high antioxidant properties. Thus, the results of IC_{50} values shown in the Table support the FIC results of the compounds tested at various concentrations.

3.3. Determination of reducing power capacity

The reducing power assay is the most common method for determining the antioxidant capacity of compounds. It is based on the reduction of Fe^{3+} of the ferric cyanide complex $[\text{FeCl}_3/\text{K}_3\text{Fe}(\text{CN})_6]$ to the ferrous (Fe^{2+}) form by the reducer compound (antioxidant). When the reduction occurs, the color of the reaction solution may turn from green to blue depending on the reduction power capacity of the antioxidant compounds. Hence, the reduced iron (Fe^{2+}) ion can be monitored by detecting the development of the Perl's Prussian blue complex at a wavelength of 700 nm [21]. Antioxidants react with the free radicals formed during various metabolic reactions in living organisms and cause them to turn into more stable structures. Thus, they can terminate the radical chain reactions that can be dangerous to living beings [28].

In this study, the metal-free and metallophthalocyanine compounds and additionally two different standards, BHT and ascorbic acid, were investigated for their reducing power capacity and the results are presented in Figure 3. It has been determined that the reducing power activities of all compounds tested depend on the concentration. Considering the results obtained, all Pc compounds tested had very high reducing power activities. On the other hand, all of the tested compounds displayed somewhat lower reducing power compared to the tested well-known antioxidant standards (ascorbic acid and BHT) at all concentrations. Reducing power capacities of all Pc compounds tested increased with increasing concentrations (Figure 3).

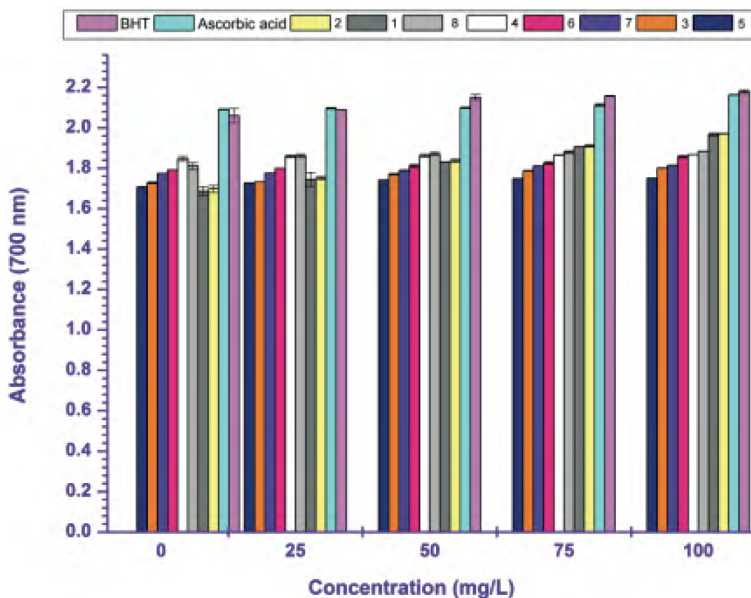


Figure 3. Reducing power of the compounds.

When the results are evaluated, there is no significant difference between all the compounds tested at all concentrations. However, metal-free Pc compounds showed higher reducing power activity than the others and it was observed that the nonperipheral position was more effective when we compared Pc compounds containing the same metal atom.

The descending order is as follows at $100 \mu\text{g mL}^{-1}$ concentration: BHT (2.18 ± 0.01) > ascorbic acid (2.16 ± 0.008) > **2** (1.97 ± 0.2) > **1** (1.96 ± 0.7) > **8** (1.88 ± 0.2) > **4** (1.87 ± 0.1) > **6** (1.86 ± 0.6) > **7** (1.81 ± 0.1) > **3** (1.8 ± 0.1) > **5** (1.75 ± 0.1).

The results show that the compounds of Pc tested are as sensitive as known reducing agents and can

ultimately be used as new positive controls for reducing power determination studies. In another study, Farajzadeh et al. determined the antioxidant activity of novel octasubstituted Pcs bearing (trifluoromethoxy) phenoxy groups in the peripheral positions. When the results were compared, all tested water-soluble Pcs containing quinoline 5-sulfonic acid groups exhibited much better reducing power activity at much lower concentration levels [29].

3.4. Conclusions

Antioxidant properties of previously synthesized free and metallophthalocyanine compounds were evaluated using three different antioxidant methods. It was established that all the tested compounds had good antioxidant properties and even showed activities as good as those of the known antioxidant standard agents in FIC and reducing power methods. This may mean that the water-soluble Pc compounds tested can be used for future studies as new antioxidant standard agents.

Acknowledgment

This work was supported by the Research Fund of Sakarya University (Project Number: HIZDEP-2019-5-19-56).

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