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## Highly selective optical chemosensor for cyanide in aqueous medium

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### Abstract

New cyanide selective chromogenic chemosensors based on metal-phthalocyanines containing four tosylamino groups were developed. These new receptors have high sensitivity for several anions ( $\text{AcO}^-$ ,  $\text{F}^-$ ,  $\text{CN}^-$ ,  $\text{NO}_2^-$ ,  $\text{H}_2\text{PO}_4^-$  and  $\text{OH}^-$ ) over other anions, such as:  $\text{Br}^-$ ,  $\text{Cl}^-$ ,  $\text{NO}_3^-$  and  $\text{HSO}_4^-$ . The experiments were conducted by UV-Vis spectroscopy in DMSO and THF solutions. The selectivities were also checked in DMSO:water mixtures. In solutions containing water the highest selectivity was obtained for  $\text{CN}^-$  anion. The host:guest complexes formed during the sensing event can be undo by acid treatment with a solution of trifluoroacetic acid without loss of the sensing ability of the chemosensors allowing their reuse.

### 1. Introduction

Anions are one of the most important species in the natural world and are involved in many vital processes, being ever-present in the environment [1-4]. Anions are also critical to the preservation of life as we know it. Indeed, the transport, recognition or transformation of anions are involved, at some level, in almost every possible biochemical processes [5-8]. Anionic species are larger in size, having varied shapes in comparison to the metal ions, consequently a higher degree of design and complementarity is required to make receptors that are selective for a particular anionic guest [1, 9]. The design and preparation of materials able to recognize and host selectively anionic species have assumed great importance in several areas in the past few years and are still a challenge for organic and materials chemists [10-13]. The design and synthesis of chemosensors able to detect anions by colorimetric, fluorescent or electrochemical means is still an important aspect but the main challenge is to the design chemosensors with high selectivity and sensitivity [14, 15]. Among the different types of chemosensors, chromogenic chemosensors have many advantages due to their simplicity, low-cost, and rapid tracking of analytes. Therefore, this type of chemosensors are getting popular due to their capability to detect analytes by naked eye, that is, without resort to any instrument [16, 17].

One of the most interesting anions to monitor is the cyanide ion ( $\text{CN}^-$ ) due to its environmental, biological and industrial importance. Cyanide is one of the most toxic and harmful anions to human health and environment, since it can suppress the transport of oxygen. Because its wide application in various fields, such as mining, metallurgy, photographic processing, synthesis of

nylon and other synthetic fibers and resins, the development of simple methods that are selective and sensitive towards  $\text{CN}^-$  detection, especially in aqueous and physiological conditions, continues to be an important topic of research [18-29]. In general, the anion chemosensors incorporate N–H containing groups, such as: amide, urea/thiourea, pyrrole, among others [30-32].

In biological and environment systems, the host:guest interactions with anions occur typically in aqueous solution. Therefore much attention has been paid to develop anion chemosensors that could work in aqueous phase. However, chemosensors that are able to recognize anions in water are scarce [11, 21-23, 33-36]. The problem is that hydration of the anion makes difficult (or prevents) the chemosensor to recognize it.

Recently, we have shown that a free-base phthalocyanine bearing two tosylamino groups in each isoindole ring of the macrocycle is an efficient chromogenic anion chemosensor [15]. That octatosylaminophthalocyanine displays different colours in the presence of various test anions and, since it is possible to undo the host:guest complexes, it can be reused without loss of sensing ability [15]. A major drawback of the octatosylaminophthalocyanine is the difficult and low yielding process of preparing the required 4,5-ditosylaminophthalonitrile precursor [37]. In order to surpass this shortcoming, we decided to develop a new family of phthalocyanines bearing only four tosylamino groups and to evaluate their sensing abilities for anions. Our main goal was to increase the overall yield of the phthalocyanines, starting from commercially available precursors, and to confirm if the presence of two vicinal tosylamino groups is, or not, mandatory for the anion sensing ability.

The results show that robust and selective anion chemosensors (a free-base phthalocyanine and the corresponding Mg(II) and Zn(II) complexes) can be prepared in high yields starting from 4-aminophthalonitrile and *p*-toluenesulfonyl chloride. The structures of the new phthalocyanines were confirmed by NMR, UV-vis and mass spectra.

## 2. Experimental Section

### 2.1. Reagents

All reagents and solvents were used as received from commercial sources without further purification. Tetrabutylammonium salts of acetate, bromide, chloride, cyanide, nitrate, nitrite, dihydrogen phosphate, hydrogen sulfate and hydroxide were used as the anion sources. These salts were purchased from Sigma–Aldrich.

### 2.2. Apparatus

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance-300 spectrometer at 300.13 and 75.47 MHz, respectively. Tetramethylsilane was used as the internal reference. HRMS spectra were recorded on LTQ Orbitrap XL mass spectrometer using 3-nitrobenzyl alcohol (NBA) as matrix. Absorption spectra were recorded using a Shimadzu UV-2501-PC.

### 2.3. Synthesis

#### **4-tosylaminophthalonitrile (1)**

Pyridine (1 mL) was added to a solution of 4-aminophthalonitrile (100 mg, 0.69 mmol) and *p*-toluenesulfonyl chloride (152 mg, 0.76 mol) in toluene (1 mL). The reaction was stirred at 70 °C, under nitrogen atmosphere for 3 hours. After this time, the toluene and pyridine was evaporated under reduced pressure. The reaction mixture was neutralized with a solution of saturated sodium carbonate, washed with water, extracted with dichloromethane and the organic phase was dried with anhydrous sodium sulfate. Compound **1** was crystallized from dichloromethane/hexane (230 mg, 89% yield). **mp** = 147.8 °C. **<sup>1</sup>H NMR** (300.13 MHz, DMSO-*d*<sub>6</sub>): δ 2.36 (s, 3H, CH<sub>3</sub>), 6.72 (s, 1H, NH), 7.42 (d, *J* = 8.2 Hz, 2H, *o*-Ts H), 7.52 (dd, *J* = 8.7, 2.3 Hz, 1H, H-5), 7.61 (d, *J* = 2.3 Hz, 1H, H-3), 7.79 (d, *J* = 8.2 Hz, 2H, *m*-Ts H), 7.98 (d, *J* = 8.7 Hz, 1H, H-6). **<sup>13</sup>C NMR** (75.47 MHz, DMSO-*d*<sub>6</sub>): δ 21.1 (CH<sub>3</sub>), 108.1, 115.6, 115.95, 116.04, 121.8, 121.9, 126.9, 130.2, 135.6, 135.8, 142.9, 144.5. **HRMS** (ESI) *m/z*: calculated for C<sub>15</sub>H<sub>12</sub>N<sub>3</sub>O<sub>2</sub>S (M+H)<sup>+</sup>: 298.0650; found: 298.0636.

### ***2(3),9(10),16(17),23(24)-Tetratosylaminophthalocyaninato magnesium(II) (Pc 1)***

Magnesium filings (24.5 mg, 1.01 mmol) and pentan-1-ol (1.5 mL) were added in a sealed tube and heated at 150 °C until a slurry was formed (2 h). Octan-1-ol (1.5 mL) was added, followed by compound **1** (600 mg, 2.02 mmol). The reaction mixture was then heated at 180 °C for 12 h. After this time, the reaction mixture was cooled to room temperature and poured into a 1:10 water/methanol mixture (100 mL). The precipitate was filtered and dissolved in a mixture of dichloromethane/methanol. The organic solution was washed with H<sub>2</sub>O and then evaporated under reduced pressure. The residue was dissolved in dichloromethane/methanol and then it was precipitated with hexane leading to a green solid identified as phthalocyanine **Pc 1** (208 mg, 71% yield). **<sup>1</sup>H NMR** (300.13 MHz, DMSO-*d*<sub>6</sub>): δ 2.26 (s, 12H, CH<sub>3</sub>), 7.41 (d, *J* = 8.1 Hz, 8H, *o*-Ts H), 7.87-8.08 (m, 12H, *m*-Ts H + β-H), 9.11 (dd, 4H, *J* = 14.5, 1.6 Hz, α<sub>2</sub>-H), 9.21 (dd, 4H, *J* = 8.1, 1.6 Hz, α<sub>1</sub>-H), 11.17 (s, 4H, NH). **<sup>13</sup>C NMR** (75.47 MHz, DMSO-*d*<sub>6</sub>): δ 20.9 (CH<sub>3</sub>), 112.6, 113.0, 121.4, 123.7, 127.0, 130.0, 133.7, 136.8, 139.4, 139.8, 143.6, 152.2, 153.6. **UV-Vis** (DMSO) λ<sub>max</sub> (log ε): 360 (4.6), 690 (5.2) nm. **HRMS** (ESI) *m/z*: calculated for C<sub>60</sub>H<sub>45</sub>MgN<sub>12</sub>O<sub>8</sub>S<sub>4</sub> (M+H)<sup>+</sup>: 1213.2217; found: 1213.2165.

### ***2(3),9(10),16(17),23(24)-Tetratosylaminophthalocyanine (Pc 2)***

Phthalocyanine **Pc 1** (100 mg) was dissolved in dry THF (10 mL) in a 50 mL flask equipped with a water condenser. Trifluoroacetic acid (1 mL) was added and the mixture was heated at 50 °C for 3 hours. The removal of the coordinated metal ion was monitored during this time by UV-Vis spectroscopy and by TLC. The reaction mixture was cooled, neutralized with a KHCO<sub>3</sub> solution, washed with H<sub>2</sub>O and the organic phase extracted with dichloromethane/methanol (95:5) and then concentrated. **Pc 2** was crystallized from dichloromethane/hexane and was obtained as a green solid (110 mg, 98% yield). **UV-Vis** (DMSO) λ<sub>max</sub> (log ε): 350 (4.1), 680 (4.4), 710 (5.1) nm. **HRMS** (ESI) *m/z*: calculated for C<sub>60</sub>H<sub>47</sub>N<sub>12</sub>O<sub>8</sub>S<sub>4</sub> (M+H)<sup>+</sup>: 1191.2523; found 1191.0396.

### ***2(3),9(10),16(17),23(24)-Tetratosylaminophthalocyaninato zinc(II) (Pc 3)***

In a sealed tube, phthalocyanine **Pc 2** (100 mg, 0.084 mmol) was dissolved in DMF (3 mL) and then the zinc acetate (36.7 mg, 0.210 mmol) was added. The reaction mixture was heated at 150 °C for 3 hours (until the metalation was complete). During this period the formation of the complex was monitored by UV-Vis spectroscopy and TLC. The reaction mixture was cooled, washed with H<sub>2</sub>O and the organic phase extracted with dichloromethane/methanol (95:5) and concentrated. The product was then precipitated from dichloromethane/hexane. A green product was obtained, which was identified as phthalocyanine **Pc 3** (112 mg, 98% yield). **UV-Vis** (DMSO)  $\lambda_{\max}$  (log  $\epsilon$ ): 355 (4.5), 688 (5.2) nm. **HRMS** (ESI)  $m/z$ : calculated for C<sub>60</sub>H<sub>45</sub>N<sub>12</sub>O<sub>8</sub>S<sub>4</sub>Zn (M+H)<sup>+</sup>: 1253.1658; found: 1253.1607.

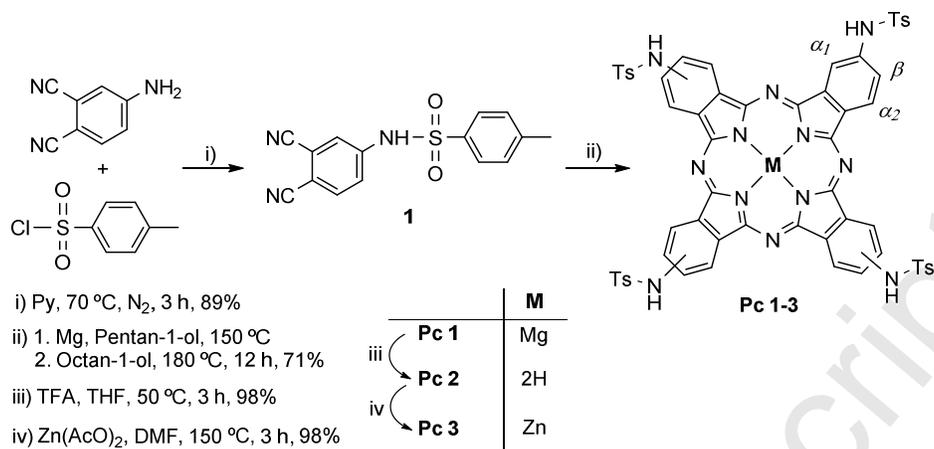
## 2.4. Anion binding studies

Anion binding studies were carried out by means of UV-vis spectroscopic titrations in two different solvents: DMSO and THF. The titrations were performed using stock solutions of **Pc 1-3** (order 10<sup>-6</sup> M) upon the addition of aliquots of an anion solution (order 10<sup>-3</sup> M). The variation on the absorbance caused by the addition of the anion, at a selected wavelength, was used to obtain binding isotherms. The binding isotherms were analyzed assuming a 1:2 binding stoichiometry via a non-linear regression analysis in accordance with the following equation [38]:  $(\Delta A/I) = ([C] \times (K_{11} \cdot \Delta \epsilon_{11} \cdot [\text{anion}] + K_{11} \cdot K_{12} \cdot \Delta \epsilon_{12} \cdot [\text{anion}]^2) / (1 + K_{11} \cdot [\text{anion}] + K_{11} \cdot K_{12} \cdot [\text{anion}]^2))$ . As noted above, binding isotherms were obtained for experiments conducted in THF and DMSO at 22 °C. Measurements were repeated 2–3 times and found to be reproducible within a 15–20% error range. The consistency between the calculated and experimentally observed binding profiles was taken as evidence of the proposed 1:2 binding stoichiometry. Support for this conclusion came from the so-called Job plot analyses.

## 3. Results and Discussion

### 3.1. Synthesis and characterization

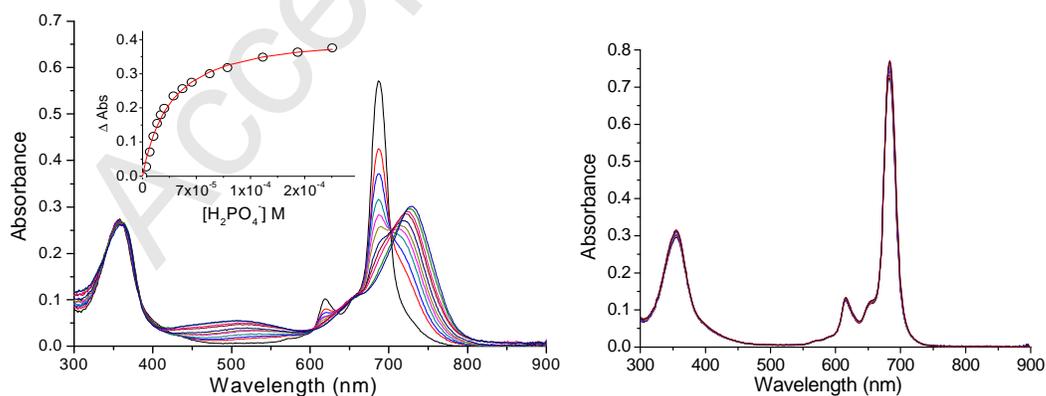
**Pc 1** was prepared in 71% yield by cyclotetramerization of 4-(tosylamino)phthalonitrile (**1**) (**Scheme 1**). Removal of the inner metal ion afforded **Pc 2** and subsequent metalation with zinc acetate afforded **Pc 3**; both compounds were obtained in almost quantitative yields. The UV-Vis spectra of **Pc 1** and **Pc 3** show a Soret band at 360 nm and a Q band at 680 nm but the UV-vis spectrum of **Pc 2** shows a split Q band with maximum absorption values at 680 and 710 nm, typical of free-base phthalocyanines.



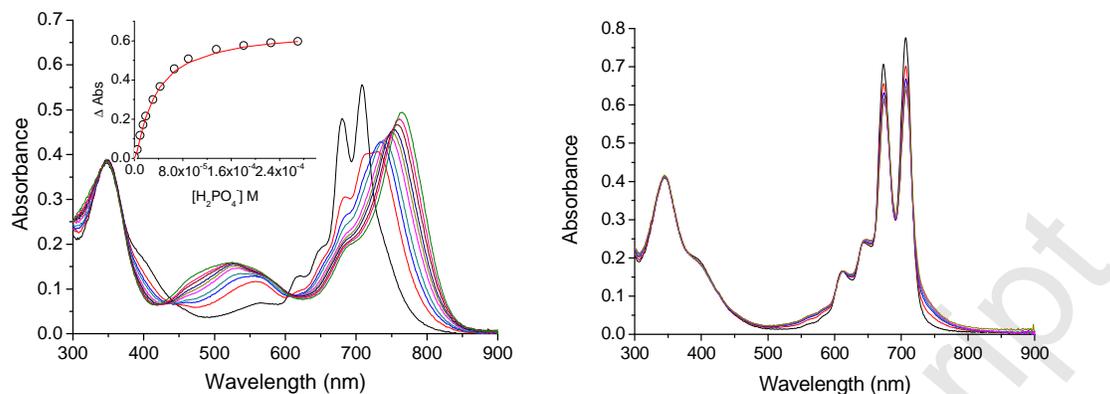
**Scheme 1** – Synthesis of the receptors **Pc 1-3**

### 3.2. Absorption studies of receptors **Pc 1-3** towards various anions

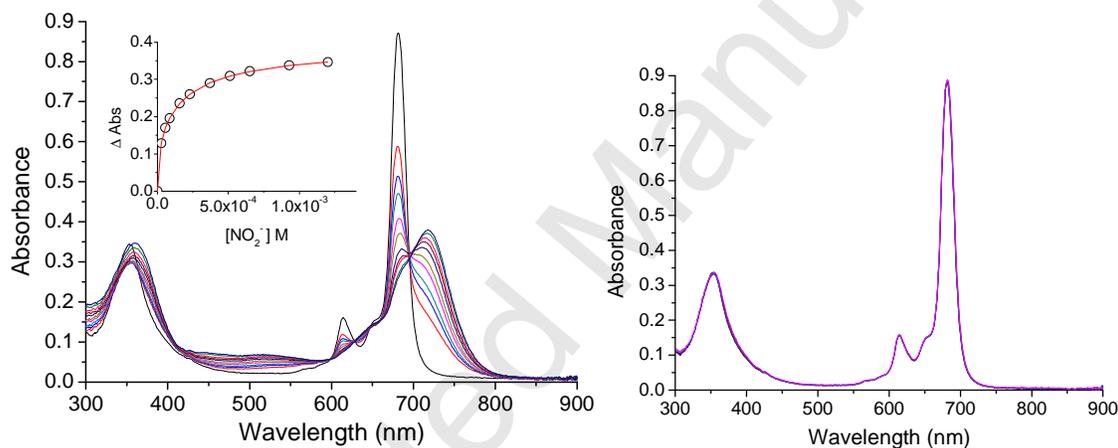
The anion binding abilities of the different receptors were investigated by UV-vis spectroscopic titration in THF and DMSO at 22 °C. Addition of F<sup>-</sup>, CN<sup>-</sup>, AcO<sup>-</sup>, NO<sub>2</sub><sup>-</sup>, H<sub>2</sub>PO<sub>4</sub><sup>-</sup> and OH<sup>-</sup> (as TBA salts) to **solutions** of the receptors **Pc 1-3** resulted in prominent changes in their UV-vis spectra. However, addition of Br<sup>-</sup>, Cl<sup>-</sup>, NO<sub>3</sub><sup>-</sup> and H<sub>2</sub>SO<sub>4</sub><sup>-</sup> (as TBA salts) didn't induce any change in their UV-vis spectra, as shown in **Figures 1-3**. For **Pc 1** and **Pc 3**, the absorption band at 688 nm disappeared and a new absorption band appeared at 740 nm. For **Pc 2** the Q split band (at 680 and 710 nm) disappeared and a new band appeared at 770 nm. The NMR titration studies (see below) show that these changes presumably occur via deprotonation of the NH-tosyl groups followed by the interaction with the anions. Meanwhile, the solutions of receptors **Pc 1-3** showed a dramatic color change from green to violet (AcO<sup>-</sup>, F<sup>-</sup>, NO<sub>2</sub><sup>-</sup> and H<sub>2</sub>PO<sub>4</sub><sup>-</sup>) or yellowish for **Pc 1** and **Pc 3** (CN<sup>-</sup>), easily detected by naked-eye (**Figure 4**).



**Figure 1** – Absorption spectra of **Pc 1** in THF upon addition of increasing concentration of H<sub>2</sub>PO<sub>4</sub><sup>-</sup> (left) and Br<sup>-</sup> (right). The insets show the binding profiles and the generated fits (left).



**Figure 2** – Absorption spectra of **Pc 2** in THF upon addition of increasing concentration of  $\text{H}_2\text{PO}_4^-$  (left) and  $\text{Cl}^-$  (right). The insets show the binding profiles and the generated fits (left).



**Figure 3** – Absorption spectra of **Pc 3** in THF upon addition of increasing concentration of  $\text{NO}_2^-$  (left) and  $\text{NO}_3^-$  (right). The insets show the binding profiles and the generated fits (left).

The absorption variation, at a specific wavelength, in function of the anion concentration allowed the quantification of the anion affinity constants between chemosensors **Pc 1-3** and the corresponding anions. To do this, the observed data points were fitted to a 1:2 binding profile using a non-linear regression analysis as detailed in Section 2. Fitting the variation of the absorbance at the Q band as a function of the concentration of the added anion (**Figure 1-3** left) allowed calculating the corresponding affinity constants ( $K$ ), which are indicated in **Table 1**. Comparing the affinity constants shown in Table 1, it can be concluded that:

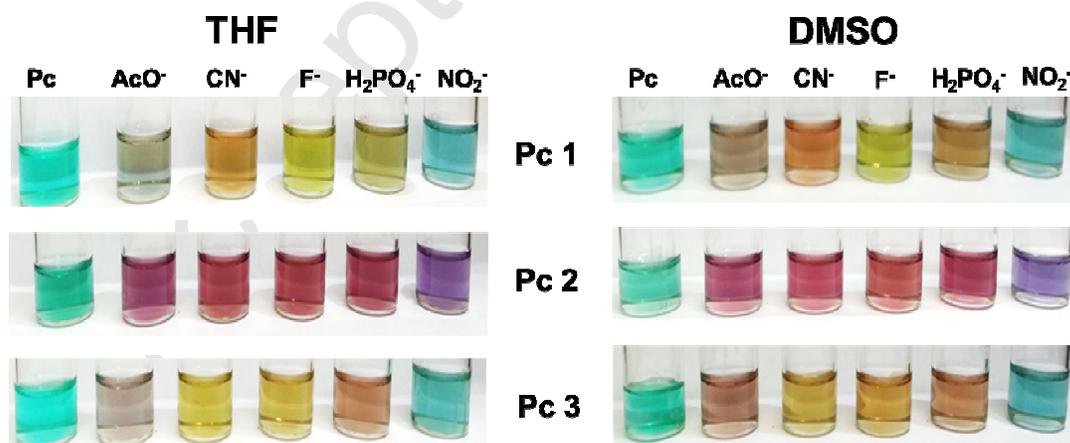
- i) for all phthalocyanines, the affinity constants are higher in THF than in DMSO. This solvent effect is concordant with the results described in our previous work [15];
- ii) despite **Pc 2** presents only four aminotosyl groups, half of our previous multi-amintotsyl phthalocyanine [15], the obtained affinity constants were similar for both;
- iii) in both solvents, the affinity constants for the metalated phthalocyanines (**Pc 1** and **Pc 3**) are higher than those for the free-base **Pc 2**, most probably due to some type of co-axial

coordination between the anions (electron rich species) and the metal atoms [39, 40]. Titration of ZnPc with  $\text{AcO}^-$  and  $\text{CN}^-$  showed a small change of the Soret band, confirming a small contribution of these interaction forces to the final affinity constant values (see SI).

**Table 1** - Affinity constants ( $\text{M}^{-2}$ ) at 22 °C corresponding to the interaction between **Pc 1-3** with the different anions in two different solvents.

Anion	Pc 1		Pc 2		Pc 3	
	THF	DMSO	THF	DMSO	THF	DMSO
$\text{AcO}^-$	$6.43 \times 10^{10}$	$2.81 \times 10^9$	$3.86 \times 10^9$	$4.64 \times 10^8$	$1.69 \times 10^{10}$	$2.96 \times 10^8$
$\text{CN}^-$	$7.77 \times 10^9$	$2.35 \times 10^9$	$2.65 \times 10^9$	$9.29 \times 10^8$	$1.67 \times 10^9$	$9.36 \times 10^8$
$\text{F}^-$	$7.40 \times 10^9$	$4.72 \times 10^9$	$3.79 \times 10^9$	$3.43 \times 10^8$	$7.65 \times 10^9$	$3.39 \times 10^8$
$\text{H}_2\text{PO}_4^-$	$2.55 \times 10^9$	$1.89 \times 10^9$	$6.65 \times 10^8$	$2.16 \times 10^8$	$4.59 \times 10^9$	$3.39 \times 10^8$
$\text{NO}_2^-$	$2.27 \times 10^8$	$3.34 \times 10^7$	$6.46 \times 10^8$	$2.81 \times 10^6$	$2.52 \times 10^8$	$6.96 \times 10^6$
$\text{OH}^-$	$5.95 \times 10^8$	$4.38 \times 10^7$	$3.16 \times 10^8$	$4.59 \times 10^8$	$1.28 \times 10^8$	$1.55 \times 10^9$

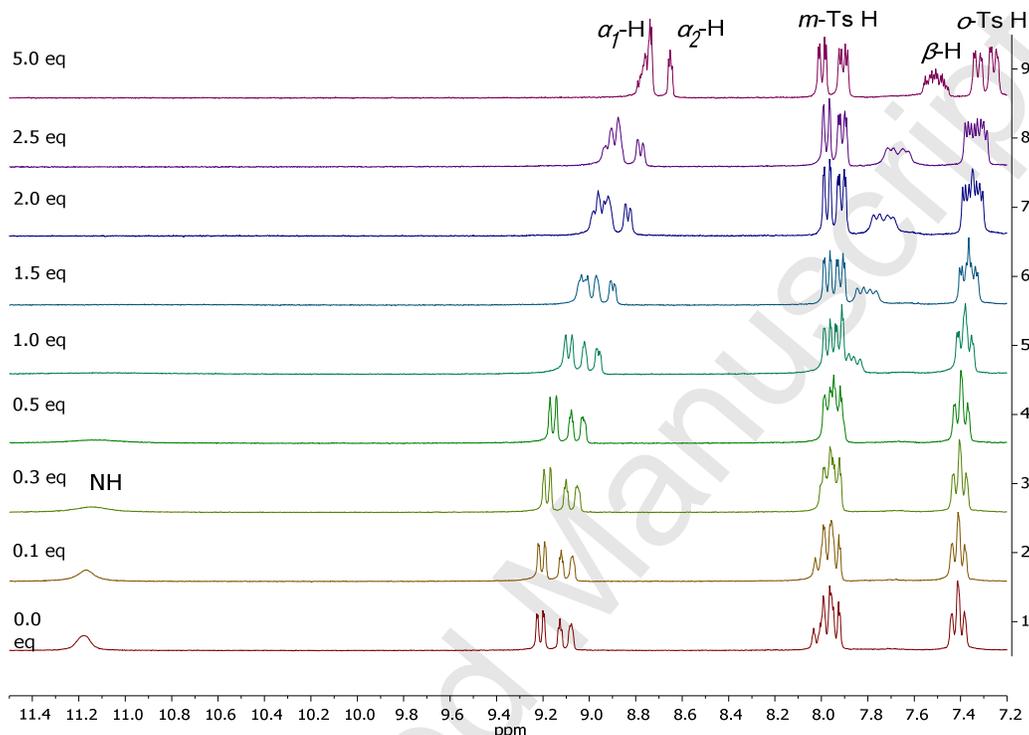
The macroscopic changes of the chemosensors in solution were recorded in both solvents, and they are in concordance with the values found for the affinity constants since the most dramatic changes were observed for fluoride and cyanide anions. The introduction of metal in the **Pc 2** macrocycle lead to more expressive changes on the solution color making possible the discrimination of different anions such as fluoride and cyanide. In the other hand, nitrite anion can be detected by naked eye with **Pc 2**, since all the solutions of **Pc 2** when interact with the different anions pass into a red tone, while with nitrite anion changes to a violet tone (**Figure 4**).



**Figure 4** – Changes in the color of THF (left) and DMSO (right) solutions of **Pc 1-3** observed upon the addition of different anions (as TBA salts).

### 3.3. NMR titration

To understand the main interactions that can occur between the chemosensors and the anions,  $^1\text{H}$  NMR experiments of **Pc 1** with  $\text{F}^-$  and  $\text{CN}^-$ , were carried out in  $\text{DMSO-}d_6$ . The spectral differences with  $\text{CN}^-$  are shown in **Figure 5**.



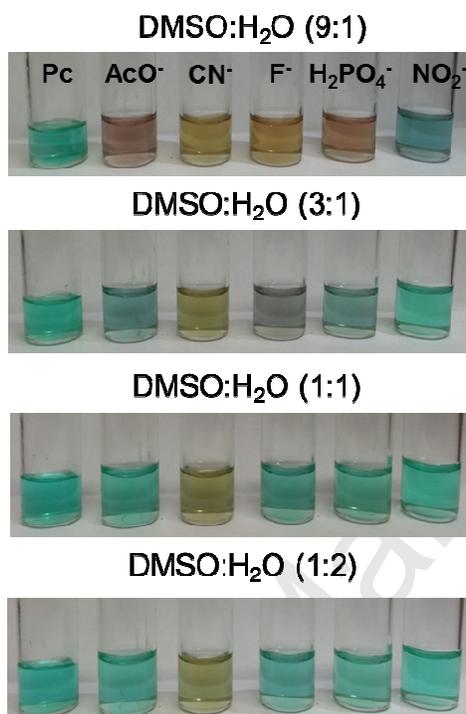
**Figure 5** - Partial  $^1\text{H}$  NMR titration plots of **Pc 1** with  $\text{CN}^-$  in  $\text{DMSO-}d_6$ .

From **Figure 5**, it is evident that the addition of  $\text{CN}^-$  leads to the disappearance of the signal corresponding to the NH-tosyl groups (at ca. 11.2 ppm) while the signals corresponding to the  $\beta$ - (around 7.9 ppm) and  $\alpha$ -protons (9.1 and 9.2 ppm) start to shift as the  $\text{CN}^-$  concentration increases, presumably due to Van der Waals interactions and/or co-axial coordination to the magnesium ion, leading to complexes with different conformation.

### 3.4. Chromogenic response in aqueous solutions

The water effect on the binding selectivity of receptors **Pc 1–3** was also evaluated for  $\text{AcO}^-$ ,  $\text{CN}^-$ ,  $\text{F}^-$ ,  $\text{H}_2\text{PO}_4^-$  and  $\text{NO}_2^-$  anions. Upon the addition of those anions to chemosensor **Pc 3** in mixtures of  $\text{DMSO:H}_2\text{O}$  starting with 10% up to 66% of water ( $\text{DMSO:H}_2\text{O}$ , 90:10 to  $\text{DMSO:H}_2\text{O}$ , 1:2 v/v), the color due to the complexation phenomena changed from the previous observed ones to the original light green color (**Figure 6**). With the increasing amount of water only the cyanide anion is able to induce a color change to **Pc 3** solution. The color modification with cyanide addition is observed even in water rich mixtures ( $\text{DMSO:H}_2\text{O}$  1:2). The yellowish coloration caused by the

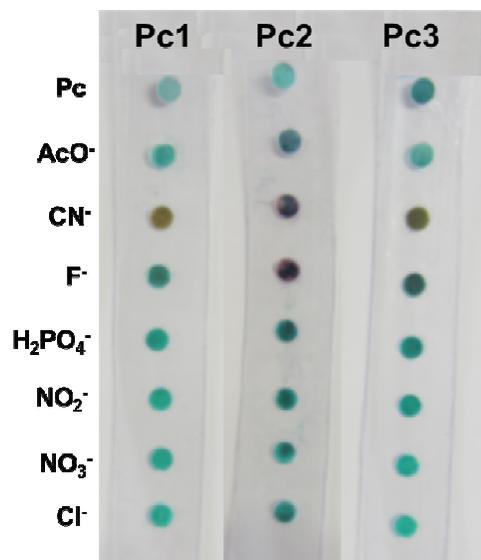
cyanide addition allows a positive discrimination of this anion. Due to the low solubility of the three receptors in water, the evaluation of their chromogenic response in water only was not possible.



**Figure 6** – Color of **Pc** 3-anion complexes in various DMSO:H<sub>2</sub>O mixtures (DMSO:H<sub>2</sub>O ratio: 9:1, 3:1, 1:1, and 1:2).

### 3.5. Substrate-induced color changes

In order to prepare a practical sensor for anion detection, small pieces of regular filter paper were immersed in solutions of the **Pc 1-3** in THF and then left to dry overnight. As a result, three greenish papers were obtained. These colored papers were cut in small pieces and then they were put in a polystyrene sheet. A drop of each anion solution was added to these small pieces and the color changes were recorded (**Figure 7**). The resulting color changes are in concordance with the results discussed above; the anions that induce a stronger color change are the ones that present higher affinities in solution. As expected, the cyanide anion induces a change from green to yellow, showing that these new chemosensors are able to discriminate cyanide in solution and also when adsorbed in paper.

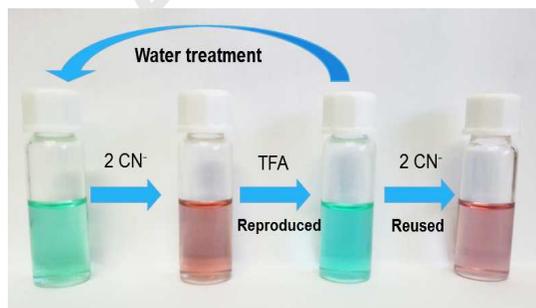


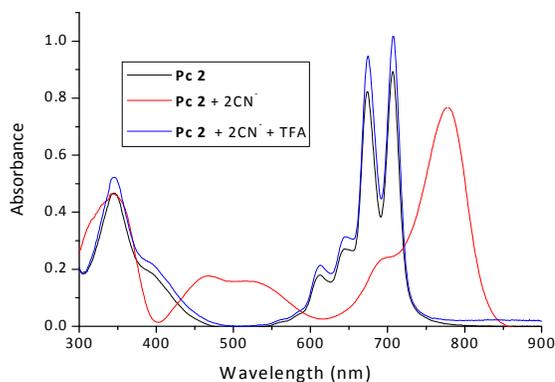
**Figure 7** – Filter paper with adsorbed **Pc 1–3** after the addition of different anion

### 3.6. Reversibility and reusability studies

To better determine the applicability of our chemosensors their reversibility and reusability were determined. The regeneration of the chemosensors **Pc 1–3** was studied by the complexation of the **Pc 1–3** with cyanide anion ( $4 \times 10^{-3}$  M) in THF. As shown in **Figure 8a**, there is a colorimetric change in the solution of **Pc 2** from green to pink when treated with 2 equivalents of cyanide in THF. This change can also be followed by UV-visible spectral changes (**Figure 8b**). Upon full complexation, the solution was treated with aliquots of 10  $\mu$ L of a previously prepared TFA solution ( $4 \times 10^{-3}$  M in THF), until complete regeneration of our chemosensor. This acid treatment of **Pc 2**·2CN<sup>-</sup> adduct immediately restored **Pc 2**, leading to a complete regeneration of the chemosensor, with the consequent colorimetric change from pink to the initial green colour. To confirm the reusability of the resulting mixture it was washed with water and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Then, the recovered **Pc 2** was again treated with 2 equivalents of CN<sup>-</sup> ions, which showed similar spectral features as that of the starting solution of **Pc 2** with cyanide anion. Similar results were observed for **Pc 1** and **Pc 3** (Figure S39-42 in the SI).

a)





b)

**Figure 8** – a) colorimetric response of **Pc 2** for reversibility and reusability tests with  $\text{CN}^-$  ions; b) UV-Visible spectral changes of the complex **Pc 2**· $2\text{CN}^-$  treated with a THF solution of TFA.

#### 4. Conclusions

Selective chromogenic anion chemosensors for cyanide anion based on phthalocyanine macrocycles in aqueous media and also when adsorbed in filter paper are described. These new phthalocyanines were prepared with excellent yields and the effect of the metal in the macrocycle core was studied. Metals in the phthalocyanine core allow dramatic changes in the solution color. It was also possible to prepare an anion simple detection kit based on filter paper and polystyrene sheet. Thus, these macrocycles have potential application monitoring cyanide anion in contaminated environments.

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**Keywords:** Anions, anion binding, chemosensor, chromogenic, cyanide, naked-eye, phthalocyanines

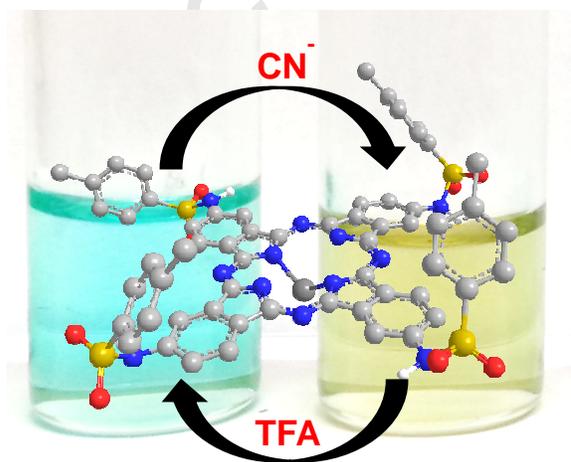
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### Highly selective optical chemosensor for cyanide in aqueous medium



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