On-Surface Cucurbit[n]uril Supramolecular Recognition for an Optical Sensor Design

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Abstract

A novel optical sensor, based on the use of the macrocyclic receptor cucurbit[7]uril as molecular selector and taking part of a sensing PVC-based membrane immobilized onto a quartz slide surface, has been developed and tested to thiabendazole analysis. The method is built upon the increase of the thiabendazole fluorescence as a result of the supramolecular recognition event. Variables involved in the membrane construction and fluorescence measurements have been evaluated and optimized. The sensing membrane is prepared by a spin-coating procedure (1 min at 800 r.p.m.). An increase of more than 2 fold in the fluorescence signal is observed when the supramolecular complex is immobilized into the membrane respect to that observed for the free guest. Under optimized conditions, the dispositive responds in a few seconds to increasing thiabendazole concentrations in solution in the 10^{-7} to 10^{-4} M range. In addition, the characterization of the supramolecular complex, containing lifetime measurements, is included.

Keywords: Cucurbituril, optical sensor, PVC membrane, thiabendazole.

Introduction

During last decades, researches have made a great effort in developing chemical sensors able to be applied in different areas of interest. To this end, either bulk or interface strategies have been proposed [1–6]. Most of those interface devices are designed employing ionophores that change their optical signal in presence of cations such as K^+, Hg^{2+}, Pb^{2+} or H^+ [7–12]. Non covalent interactions, especially host-guest interactions, can contribute to the development of this area of research. Crown ethers or calixarenes are examples of hosts that have been employed as units of these non-covalent recognition processes [13]. During the last years, synthetic macromolecules known as cucurbit[n]urils (CB[n]s; n=5-10) have emerged as solid candidates to compete with those previously mentioned in a wide range of applications including optical sensors development [2, 14]. CB[n]s macrocycles family presents a hydrophobic cavity with different sizes like cyclodextrins that allow the inclusion of guests with suitable size and polarity. In addition to this way of recognition, CB[n]s present negative charge densities, due to the carbonyl groups constituting the CB[n]s portals, that allow them to interact strongly with positively charged guests [15].

A great number of proposals dealing with the fluorescence detection of CB[n] complexes in solution conditions have been reported for the sensing of different analytes. Some of them are based on the direct increase of the fluorescence signal produced as a consequence of the supramolecular encapsulation event or on the optical response increase that the presence of cations such as Cd^{2+} and Zn^{2+} produces in a previously formed CB[7]@fluorescent guest complex [1, 16–19]. In other cases, competitive strategies, as that proposed by Urbach *et al.* for the recognition of the tripeptide Tyr-Leu-Ala by CB[8], have also been reported [20]. However, few proposals for the development of chemical sensors based on the CB[n]s incorporation on a sensing surface for a further electrochemical or optical transduction can be found [21–24]. In this latter case, the variation of the signal corresponding to a fluorescence polymer where the

CB[n] is incorporated in presence of the analyte under investigation, is a strategy usually followed.

It is well known that the fluorescence of benzimidazole fungicides increases as a result of supramolecular interactions with CB[n]s in solution conditions [25–28]. This circumstance results in an excellent support for the research in optical sensors development. The amount of these fungicides in different samples is regulated by the European Union due to the high toxicity of these fungicides in human beings [29]. In this work and to the best of our knowledge, the design of a fluorescence sensor based on the incorporation of CB[7] as recognition molecule into a sensing membrane is presented for the first time. CB[7] was selected for the detection of the fungicide thiabendazole (TBZ) showing the benefits derived from the well documented recognition process as a proof of concept in analytical sensors development area. The achievement of this aim would be a benchmark of the possibility of *in situ* measurements through the CB[n] immobilization on optical fibre surfaces.

Experimental

Reagents

Cucurbit[7]uril and cucurbit[8]uril were obtained from Sigma-Aldrich Chemical Co. The polymer membrane components poly(vinyl chloride) (PVC, high molecular weight) and tributylphosphate as plasticizer (TBP) 99 %, were supplied by Sigma Aldrich (St. Louis, USA). Pure standard of the target compound, thiabendazole (99.8%), L-tryphtophan and quinine sulphate were purchased from Sigma-Aldrich Chemical Co. (St. Louis, USA). Thiabendazole working stock solution was prepared in dimethylformamide at a concentration level of 7.0×10^{-3} M and used for further dilution and spiking of the samples. Standard solutions were daily prepared and conserved at 4 ºC preserved from light.

All reagents used were of analytical reagent grade. Scharlau (Barcelona, Spain) supplied solvents. Ultrapure water was produces by an Ultra Clear^{TM} TWF EDI UV of Siemens AG (Munich, Germany).

Apparatus

Fluorescence measurements were carried out with a HITACHI F-7000 Fluorescence Spectrophotometer supplied by Genesys Instrumentation (Madrid, Spain). An UV-1800 Shimadzu spectrophotometer (Genesys Instrumentation, S.L. Madrid, Spain) was employed for absorbance measurements.

Membrane thicknesses were evaluated with an Ambios Xi-100 Non-Contact Optical Profilometer with nanometric vertical resolution.

Procedures

Sensing membrane preparation

A mixture containing all the sensing membrane components was prepared by adding 35 mg of PVC, 110 μL of TBP, 100 μL of CB[7] 1.00×10^{-4} M and 790 μL of THF in an eppendorf tube. Next, the mixture was subjected to ultrasound-assisted homogenization in a bath. The sensing CB[7] membrane was prepared by spin coating (1 min at 800 r.p.m.) of 100 μL of the as-prepared mixture over a quartz slide of 15 × 40 × 0.5 mm. Finally, the membrane slide was led to dry for *c.a.* 15 min under soft heat (40ºC). For blank measurements, membranes without the recognition element CB[7] were prepared.

Before the spin coating, quartz surfaces were washed with THF (1 mL), H_2SO_4 0.18 M (1 mL) and NaOH 2% w/v (1 mL) and, finally, with abundant ultrapure water before being dried at 110 ºC during 10 minutes [8].

Absorbance and fluorescence membrane measurements

Both, absorbance and fluorescence measurements were carried out using the above described spectrophotometers. After the optimization of the detection angle for the fluorescence measurements, quartz slides were placed into the conventional cuvette holder of the instrument at 35º respect to the excitation beam. In the case of absorbance measurements, quartz slides were placed inside the cuvette holder with the membrane surface perpendicular to the light beam.

Results and discussion

Here we present the development of a PVC-based membrane that includes cucurbit[n]urils (CB[n]s) as recognition elements to analyse thiabendazole (TBZ) improving its fluorescence properties. The macrocycle is incorporated in the membrane expecting an enhancement of the emission properties of the analyte upon hosting so an improvement in the detection capability of the sensor is expected.

Assessment of cucurbit[n]urils encapsulation efficiency of thiabendazole and optical properties.

The first step was to investigate the optical conditions that make the fluorescence process of the possible supramolecular complexes more efficient.

In these optical membrane sensing devices, low complex mass in the final sensitive membrane is expected so, chemical systems with high molar absorptivity coefficient ε are needed ($\varepsilon \cong 10^4$ cm^{-1} M^{-1}). Therefore, the ε values of the CB[n]/TBZ complexes with two of the possible homologues to include TBZ, CB[7] and CB[8], and working in different aqueous media were tested and the results are depicted in Table 1.

Table 1 Molar absorptivity coefficients of TBZ and CB[n]/TBZ (n = 7, 8) complexes

Compound	ε [$cm^{-1}M^{-1}$]*		
	pH = 3	water	pH = 11
TBZ	2.52×10^4	1.68×10^4	2.57×10^4
CB[7]/TBZ	2.67×10^4	2.35×10^4	2.55×10^4
CB[8]/TBZ	2.47×10^4	2.13×10^4	2.58×10^4

*2.00×10^{-5} M concentration level. Path length = 1.00 cm. Measurements performed at 298, 302 and 301 nm (maximum absorbance) for TBZ, CB[7]/TBZ and CB[8]/TBZ, respectively

As shown, both supramolecular systems could result adequate for our purposes as ε values higher than 10^4 were obtained in all cases. Between both complexes, the CB[7]/TBZ results the most favourable specially at acid pH values. On the other hand, a slight decrease in the ε CB[8]/TBZ value respect to that exhibit for CB[7]/TBZ is produced in such a medium. This observation is in good agreement with literature and could be related to the inclusion of two TBZ molecules into the CB[8] cavity [30]. At basic pH values, none relevant signal variation revealing supramolecular interaction is noticed that agrees with expected in potential negatively charged guests as a result of the negative charge density presented in CB[n]s portals. Nevertheless, and from an analytical point of view, the highest increase in the complex ε value (2.35×10^4 cm^{-1} M^{-1}) respect to that exhibit for TBZ (1.68×10^4 cm^{-1} M^{-1}), is obtained when CB[7] is used as host and working in aqueous media.

It is well stablished that analytical procedures based on fluorescence measurements achieve better results in terms of selectivity and sensitivity than UV-Vis spectrophotometry. Depending on the molecule and the conditions, the fluorescence efficiency changes and it is quantified by the quantum yield. It can be calculated by equation 1 that makes use of a fluorescent molecule

with a tabulated quantum yield. With this purpose, tryptophan was employed as standard that has a Φ = 0.13 at an excitation wavelength of 275 nm.

Better selectivity and sensitivity will be reached if fluorescence is employed as detection technique, so, the relative fluorescence quantum yields for each system were also evaluated. With this purpose, and according to below, Tryptophan (Φ tabulated at λ_{exc} 275 nm = 0.13) was employed as standard.

$$\mathbf{\Phi}_x = \mathbf{\Phi}_x \cdot \frac{A_S}{A_x} \cdot \frac{F_x}{F_S} \cdot \left(\frac{n_x}{n_S}\right)^2 \quad (1)$$

Where Φ is fluorescence quantum yield, A is the absorbance, F is the integral of the emission spectrum and n is the solvent refraction index. In equation 1, the subscripts *s* and *x* corresponds to the standard and the analyte, respectively. The measurements were performed in triplicate in aqueous media and in hydrochloric acid, phosphate and borate solutions and the results are depicted in Table 2.

Table 2 Fluorescence quantum yields of TBZ, CB[7]/TBZ and CB[8]/TBZ

Compound	$\Phi_{n=3}$				
	pH 1.25[a]	pH 1.25[b]	Water[a]	pH 6.50[a]	pH 12.00[a]
TBZ	0.63 ±0.12	0.63±0.06	0.08 ±0.01	0.07±0.01	(3.83±0.03)×10^{-2}
CB[7]/TBZ	0.76 ±0.25	0.70±0.09	0.26±0.03	0.14±0.03	(3.5±0.4)×10^{-2}
CB[8]/TBZ	0.51±0.03	0.49±0.08	0.12±0.01	0.09±0.02	(4.18±1.98)×10^{-2}

[a] Tryptophan as standard, λ_{exc} = 275 nm

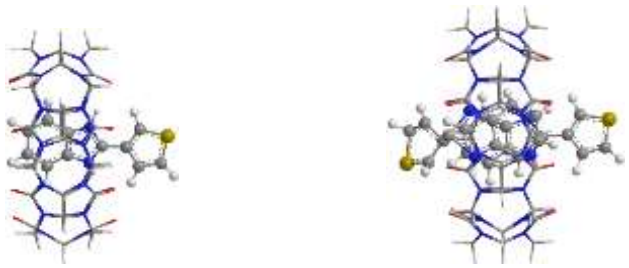
[b] Quinine was the reference, λ_{exc} = 302 nm

As shown, acidic media leads to the highest Φ values in particular for the CB[7]/TBZ system. On the opposite, when using CB[8] as host, the decrease in the Φ value (respect to the analyte)

supports the decrease in the fluorescence signal observed in this media (see Supporting Information, Fig. S1). These results are in agreement with those depicted in Table 1. In this acidic media, in addition to the use of tryptophan, the results were checked using quinine as standard, a well-known fluorescence standard with a Φ tabulated value in acidic pH of 0.577. Good data agreement was obtained from the comparison of both results. Nevertheless, as commented above for the Φ evaluation, it is in aqueous media where the highest increase in the Φ value (up to 3 fold for CB[7]/TBZ complex respect to TBZ) is observed. When CB[8]/TBZ is evaluated, lower difference, close to 1.5 fold CB[8]/TBZ respect to TBZ, is produced. Finally, very low differences in both supramolecular complex fluorescence quantum yields are observed when working in basic media. In addition, the assay was performed in phosphate buffer pH 6.5 in order to evaluate the influence of salts in solution and a comparison with the results obtained in water is made. The lower increase in the complex Φ values produced in phosphate buffer reveals that supramolecular interaction is hindered by the presence of cations in solution that compete for the CB[n] portals. From the results, CB[7]/TBZ complex in aqueous media seems to be the best candidate to follow with the proposed objective in this work.

Literature reports a change in the TBZ pK_a of 2 units when it is included in the CB[7] cavity [27, 28] [27,28]. When we carried out such experiments for both, CB[7]/TBZ and CB[8]/TBZ complexes, the results obtained corroborated just those previously reported for CB[7]. However, a different behaviour was observed in the case of CB[8] (see Fig. S2). In this later case, at pH values higher than 6, the UV absorption increases with respect to lower pH values and also increases respect to that obtained for the free guest. This behaviour could be explained because, at acidic pH values, the CB[8] cavity can hosts two TBZ molecules showing a 1:2 stoichiometry CB[8]/TBZ while a different situation is observed at higher pH values, where a 1:1 CB[8]/TBZ complex exists, so, a change in the complex monitored occurs [30, 31].

Fig. 1 shows the molecular models calculated by MM2 for the TBZ complexes with CB[7] and CB[8]. As seen, CB[7] cavity can host just one TBZ molecule while the higher CB[8] cavity accommodates two TBZ molecules. In both cases, the benzimidazole group remains inside of the cavity leaving outside of the CB[n] the rest of the structure.



CB[7]/TBZ CB[8]/TBZ

Figure 1 Energy-minimized structures (MM2) for the CB[7]/TBZ and CB[8]/TBZ complex

As stated above, from the results obtained from the characterization of both complexes, CB[7] was selected for the design of the membrane platform to detect TBZ in aqueous media, in order to achieve the proposed objective.

To complete the study of this CB[7]/TBZ complex, we addressed the study of the stoichiometry and the binding constant by the Benesi-Hildebrand method [19, 32]. All these experiments as well as further fluorescence measurements were carried out at the fixed wavelength values corresponding to the maximum optical signal (λ_{exc} = 298 nm, λ_{em} = 350 nm). As shown in Fig. S3, a straight line without change in the slope indicates that a 1:1 CB[7]/TBZ complex is formed. From the slope, a binding constant value of 2.0×10^6 M^{-1} is calculated, value that is in good agreement with that previously reported [27].

Other measurement that provides additional information about the interaction of the TBZ compound with the medium is the fluorescence lifetime. Fig. 2 shows the temporal profile measured in aqueous solution and forming the supramolecular complex with CB[7]. In addition, encapsulation inside the cavities of the CB[7] increases luminescence intensity together with a

larger lifetime (0.66 ns *vs* 0.18 ns) which suggest more stabilization of the TBZ molecule [31, 33].

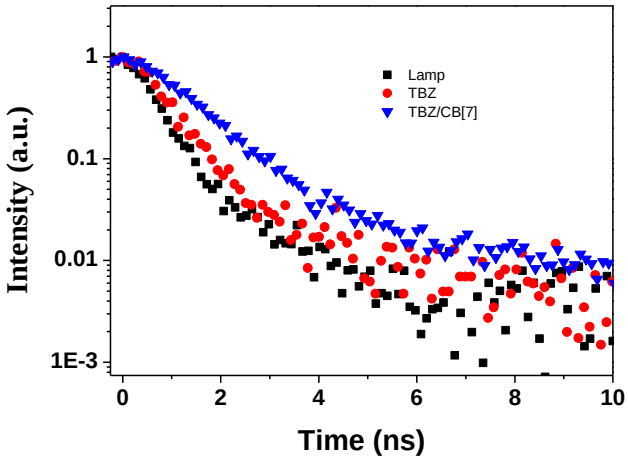


Figure 2 Log-linear plot of fluorescence decay curves of compound TBZ and TBZ supramolecular complex with CB[7] in aqueous media at room temperature. Black squares correspond to the response of the laser diode.

Host-guest recognition on a quartz/solid surface

The herein-presented device was optimized with the aim of obtaining excellent analytical signals so low backgrounds should be recorded. When working with this kind of devices, the background signal is influenced in a great extent by the quartz slide position in the cuvette holder. To this respect, and as stated above in the procedure section, the quartz slides position that was considered as optimum was when the detection was performed at 35º respect to the incident beam. In this latter position, good blank values (the lowest fluorescence values) either from quartz slides (I_f = 81 ± 8), quartz slides modified with membrane without CB[7] (I_f = 111 ± 8) and quartz slides modified with membranes containing CB[7] (I_f = 138 ± 14) were obtained. In addition, the detection limits that can be obtained working with these devices are largely influenced by the thickness of the resulting film as it limits the signal obtained without any analyte-receptor interaction. Regarding to these both, the volume of membrane mixture used

and the rotation rate in the spin-coating process were evaluated. From the results, a slight influence of the volume employed in the background noise response was observed trending to decrease when a volume of 100 µl was used. Moreover, it was observed that the signal of membranes with CB[7] was higher than that prepared without the receptor. These results can be ascribed to thicker films (from c.a. 680 nm to c.a. 1,3 µm respectively evaluated with an optical profilometer). On the other hand, a higher significance was observed from the study of the rotation rate in the spin-coating process. Fig. 3 shows the influence of this parameter in the membrane thickness and how it affects to the fluorescence signal obtained. As it is observed, higher values of rotation rate lead to lower thickness and lower blank response. However, as a home-made spin-coating system was used, the highest rotation rate produced undesirable vibrations, so 800 r.p.m. was selected for further experiments.

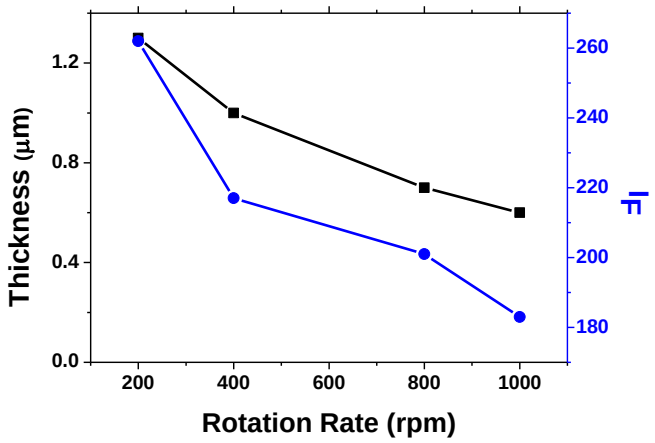


Figure 3 Membrane thickness (black squares) and fluorescence intensity (blue circles) in function of the rotation rate in the spin-coating process

Once the volume of the mixture to be spread on the quartz surface and the rotation rate were optimized to achieve the lowest background signals because they are highly significant in the detection and quantification limits that can be reached, the performance of the sensor was explored. As depicted in Fig. 4, when different membranes containing either TBZ, the complex CB[7]/TBZ or the as-called blank membrane were prepared following the above described spin-

coating procedure (100 µL, 1 min at 800 r.p.m.), a clear increase of more than 2 fold in the fluorescence signal respect to that observed for the "free" guest TBZ was recorded when the supramolecular complex ~~is~~ was immobilized into the membrane. This can be attributed to the noticeably higher capacity of the supramolecular complex CB[7]/TBZ to emit light upon excitement above explained and a possible role of cb7 as an analyte trap if compared with the bare PVC.

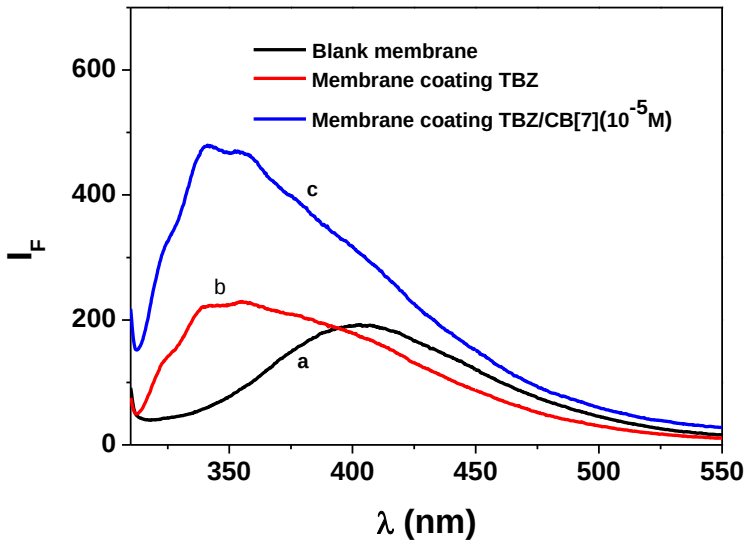


Figure 4 Fluorescence spectra of: a) blank membrane (25% PVC and 74.3 % TBP); b) Membrane containing TBZ (25% PVC, 74.3 % TBP and TBZ (1.0×10^{-5} M)); c) Membrane containing CB[7]/TBZ complex (25% PVC,74.3 % TBP and CB[7]/TBZ (1.0×10^{-5} M)

These results lead us to conclude that the well-known fluorescence behaviour exhibited by these kind of supramolecular complexes in general, and for the bezimidazole fungicides in particular, is maintained in solid state when they are a component of a sensing membrane and support the aim of developing an optical sensor opening great prospects of applications in this area.

Influence of TBZ concentration

Once the volume of the membrane mixture and the rate in the coating process were evaluated, it should be reminded that membranes without the supramolecular recognition element could adsorb/entrap the analyte TBZ exhibiting its native fluorescence. In a set of experiments, different blank membranes (without CB[7]) were submerged in solutions of increasing TBZ concentration for different periods of time and the fluorescence response was recorded. In Fig. 5 it is observed that, irrespective of the concentrations assayed, there were no significant variations in the I_f values and that membranes seem to be saturated for times higher than 1 min.

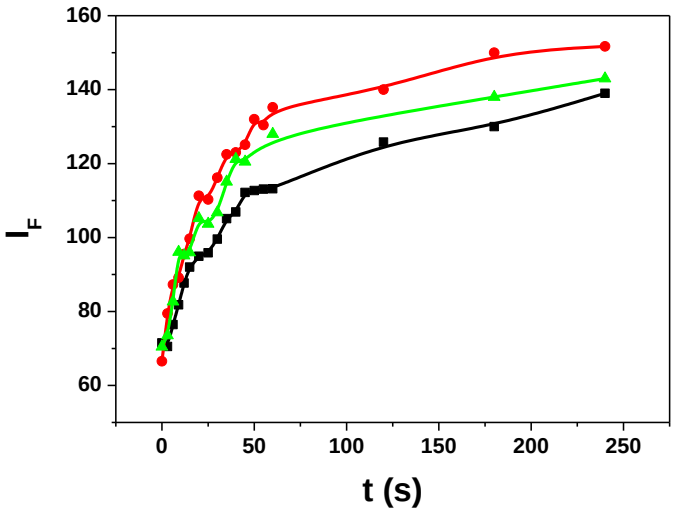


Figure 5 Fluorescence intensity of TBZ adsorbed on blank membranes in function on the time immersed in TBZ solution. Black squares: *[TBZ]* = 1.0×10^{-8} M; Red circles: *[TBZ]* = 5.0×10^{-8} M; Green triangles: *[TBZ]* = 1.0×10^{-7} M

In a set of experiments, the signals recorded from a membrane without CB[7], a membrane with 0.13 mg and another containing 0.49 mg were compared and are shown if Fig. 6. These results show how the corrected fluorescence increases when CB[7] is taking part of the membrane. As it could be expected, the quantity of receptor necessary depends on the initial TBZ level. As

TBZ concentration gets higher, a higher receptor amount is required in the membrane to produce a significant fluorescence increase.

On the other hand, we can observe that the sensor proposed responds quickly to the presence of these low TBZ concentrations. At low times of contact, great increase of fluorescence is produced. Such signal increase at c.a. 10 s., results almost the same as that for higher times.

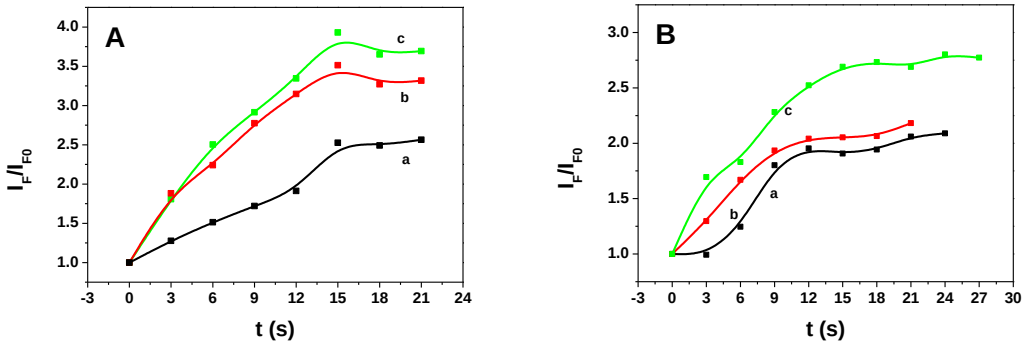


Figure 6 Variation of the fluorescence intensity for TBZ A) *[TBZ]* = 1.0 x 10^{-7} M; B) *[TBZ]* = 1.0 x 10^{-6} M with time. a) Blank membrane, b) 0.13 mg of CB[7] and c) 0.49 mg CB[7]. Data normalized with the corresponding quartz slide signal

If the response of a device containing 0.49 mg of CB[7] is evaluated against different TBZ concentrations in the 1.0 × 10^{-7} M - 1.0 × 10^{-4} M range, it was observed that, after 20 s of immersion, the changes in the fluorescence respect to the free TBZ responded to the increase of the TBZ concentration in solution where the device is submerged. *ΔIF* values ranging from 124 to 7685 units for increasing TBZ concentrations, fitted to $\Delta IF = 312 + 74 \times 10^6 [TBZ]$ (M); r = 0.992. This response of the designed dispositive with the analyte concentration is a really promising results that open new perspectives in the development of optical sensors with improved characteristics respect to selectivity, thanks to the CB[n] recognition properties and suitable to be combined with optical guides in new possible applications. These results are the proof of concept of the new perspective in this receptor family application in the design and development optical sensors.

Conclusions

In this work, the cucurbituril homologue CB[7] has been employed as molecular selector taking part of a sensing PVC membrane to the detection of the fungicide thiabendazole, at 10^{-7} M concentration level, through a recognition even based on the CB[7]/TBZ complex formation. The optical properties of TBZ and its supramolecular complexes were studied in solution. The capability of absorbing electromagnetic radiation and converting all this energy in fluorescence, i.e., the quantum yield, was assayed together with the fluorescent lifetimes. Energy-minimized structures were modelled by MM2 to support our findings. It was explored the composite in terms of good blank signals, layer thickness, position of the support respect to the excitation beam, CB[n] content in the membrane, the time of analyte accumulation and concentration. The supramolecular interaction and the increase in the fluorescence signal exhibited by this inclusion complex, respect to that corresponding to the free guest, is demonstrated to be also maintained in a sensing membrane supported on a quartz surface for the first time. These promising results open new perspectives in these synthetic macromolecules applications in the optode design field.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

Electronic supplementary material: the online version of this article contains supplementary material, which is available to authorized users.

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