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A click mediated route to a novel fluorescent pyridino-extended calix[4]pyrrole sensor: synthesis and binding studies

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A novel fluorescent aryl-extended phenoxycalix[4]pyrrole ditopic sensor, with enhanced cations recognition properties was efficiently synthesized via click chemistry and characterized through both molecular fluorescence and nuclear magnetic resonance spectroscopies. Results demonstrate the selectivity of this fluorescent sensor for fluoride when taking into account its interaction with anions, while its cation binding properties showed selectivity for iron, and sensing properties for several cations in dimethylsulfoxide. This work introduces a new ditopic receptor able to complex major environmentally relevant species and depicts the importance of the click chemistry in the introduction of new tetra-chromophoric calix[4]pyrrole binding platforms with specific photophysical properties.

Introduction

The recognition of anionic and cationic substrates has been one of the main focus of research in the field of supramolecular chemistry for the past few decades. [1] This was due to its pervasive role in the development of fluorescent sensors, [2] ion selective electrodes and biocompatible anions transporters. [3] For this purpose, continuous efforts were devoted to give a large variety of supramolecular architectures the ability to handle selective and efficient recognition for metals and non-metals in organic and aqueous solvents.

Calix[4]pyrroles are tetrapyrrolic supramolecules that were discovered first by Baeyer in 1886 as an octamethylcalix[4]pyrrole molecule (OMCP). [4] The fact that it bears an anion binding site on the level of its NH arrays was unknown until 1996, when it was discovered through a study carried by Sessler et al. [5] Since then, these molecules became notorious for their anion binding capacity [6] and especially for their preference towards the anionic fluorine among halide salts. [7] Taking into account such considerations conjointly to the relative ease of calix[4]pyrroles synthesis, these molecules were given advantage in terms of practical and

commercial manipulations. [8] As a result, they were more and more studied and engaged in different biomedical, [9] chemical and environmental fields. Over the years, several improvements were made to this molecule in order to upgrade its selectivity and affinity to both anions and cations. Accordingly, new anionic [10] and ditopic ion pair sensors [11] were introduced. This was possible through the addition of new straps to the molecule via its β -position and/or its meso-carbons.

In 1999, a study carried by Bonomo et al. introduced a new meso-rim OMCP derivative, called phenoxycalix[4]pyrrole or meso-tetramethyltetraKis(hydroxyphenyl)calix[4]pyrrole. [12] Its general synthesis relies on the condensation of pyrrole with p- or m-hydroxyacetophenone and leads to various conformers with multiple sites acting as ready to functionalize or hosting sites. The major conformer was the so-called $\alpha\alpha\alpha$ -phenoxycalix[4]pyrrole isomer (**CP1**), that was characterized by a pre-organized structure where all the phenol groups are set in the same direction in such a way that it formed an electron- π rich cavity. [13] **CP1** host medium was converted into other different molecules through addition or substitution made to its active hands (the carbon-rim or the phenol radical) producing new structures with enhanced molecular recognition properties. [7]

The term of click chemistry was introduced by Sharpless in 2001. [14] Among click reactions, the popular Huisgen cycloaddition consist of a reaction between azides and terminal alkynes, occurring in the presence of a copper catalyst and resulting in the formation of a 1,2,3-triazole entity. Click chemistry is favoured because of its reliability, specificity, synthetic simplicity and the addition of a triazole fluorescent strap that plays a twofold role of cation or anion chelation site as well as being a platform that allows the addition of new functionalities to the receptor. [15]

Ahmad Rifai and Nancy AlHaddad have contributed equally to this work.

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Nevertheless, the molecular fluorescence properties of triazole remain underexploited.

While previous studies [6] [10] [11] were found to introduce click-functionalized calix[4]pyrroles, few [16] employed click chemistry to develop $\alpha\alpha\alpha$ -phenoxy-calix[4]pyrroles and none investigated its binding properties for triazole molecular fluorescence.

In 2017, a study of Sessler et al. introduced two new functionalized phenoxy-calix[4]pyrroles using click chemistry. Both acted as ion pair receptors binding simultaneously Fe^{2+} and F^- , however no investigations were performed with cations other than Fe^{2+} . This study opened the door for a new type of functionalization to aryl-extended phenoxy-calix[4]pyrroles. [16] The addition of long-chained and aromatic-electron rich straps gave the molecule extraction properties towards FeF_2 and specific interfacial molecular interactions.

In that sense, this paper addresses a study of the synthesis of a new fluorescent pyridine-extended $\alpha\alpha\alpha$ -phenoxy-calix[4]pyrrole sensor, **CP3**, via click chemistry (Figure 1) and its ionic recognition properties in dimethylsulfoxide (DMSO). The functionalization of this molecule was based on the expansion of its aromatic arms via the addition of two new entities: a triazole strap and a pyridine moiety. This latter represents to the best of our knowledge the first

calix[4]pyrrole molecule studied for its molecular fluorescence properties towards ionic species. The fluorescent identity of this ligand, allowed a first step for the use of fluorescent phenoxy-calix[4]pyrroles for metals detection due to the superiority of the molecular fluorescence spectroscopy over other common methods. In fact, this method possesses high sensitivity allowing the use of fluorescent entities, as often as possible in sub-micromolar concentrations, a non-destructive analysis, a rapid response, a relative ease of manipulation and a low cost compared to other tools. [17] Thus, characterizations and investigations were achieved using molecular fluorescence, time-resolved fluorescence and nuclear magnetic resonance spectroscopies. Results depicted that **CP3** acts as a ditopic receptor capable of selectively complexing fluoride on the level of its pyrrolic ring. Moreover, two major environmentally relevant species Fe^{2+} , Fe^{3+} on the level of its nitrogen-crowded extended aromatic arms as well as recognition and sensing properties for other cations, and more specifically for Hg^{2+} , were detected.

In addition to these latter methods, a brief and one of the rare type of investigations applied on supramolecules was carried through Time-of-Flight Secondary Ion Mass Spectrometry (TOF-SIMS) in order to build a more detailed study of **CP3**'s molecular recognition towards metals and anionic species.

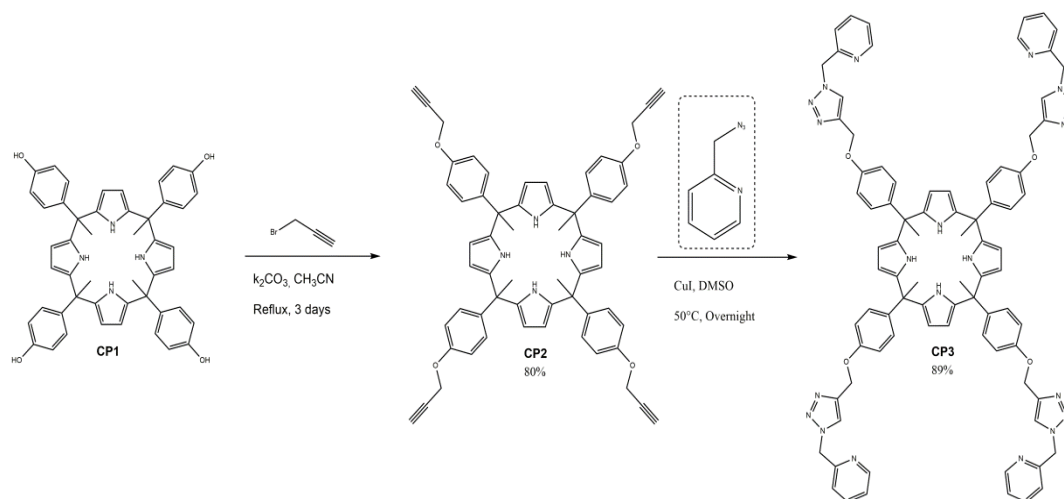


Figure 1: Synthesis of the fluorescent compound **CP3**

Results and discussion

Synthesis of **CP3** receptor

The overall synthesis of **CP3** receptor was depicted in Figure 1. **CP2** was first synthesized via a reaction of **CP1** with propargyl bromide in acetonitrile. Although this compound was already described in the study of Sessler et al. in 2017 [16] with a yield of 65%, the proposed protocol reports an improved yield of 80%. **CP2**, including a ready-to-click alkyne platform, was used next to anchor a 2-pyridino moiety through an azide-alkyne condensation with 2-(azidomethyl)pyridine synthesized by microwave irradiation. [18] Based on previous studies in which several conditions were tested in the aim of optimizing the click reaction conditions, [15] the reaction was carried in DMSO in the presence of copper iodide and triethylamine to grant **CP3** with 89% yield. The synthesized

molecule was fully characterized by ^1H , ^{13}C NMR spectroscopy (see supplementary data Figure 1 to 8) and TOF-SIMS.

Optical properties of **CP3**

Owing to the presence of four 1,2,3-triazole chromophores [19] in **CP3**, absorbance, fluorescence spectroscopy, time-resolved fluorescence and quantum yield investigations were undertaken in order to understand the photophysical properties of **CP3** and study its complexing and recognition capacities towards several ionic guests in DMSO.

Molecular fluorescence emission and excitation spectra were recorded in DMSO and it showed that **CP3** exhibited a maximal emission at 446 nm upon excitation at 300 nm (see supplementary data Figure 9). Quantum yield experiments for **CP3** were carried in comparison with an anthracene reference standard [20] and was found to be 0.02 which is fully coherent with other values reported

in the literature for similar pyridin-2-yl-1,2,3-triazole supramolecular platforms (β -cyclodextrins and calix[4]arenes). [21]

Time-resolved fluorescence of **CP3** was investigated. Fluorescence decays of **CP3** in DMSO were recorded upon excitation using a NanoLED light source (330 nm) (see supplementary data Figure 10). A sum of four exponentials was required in order to obtain an adequate fit of the fluorescence decay for a channel width of 82 ns and thus an average decay time of approximately 7 ns and a satisfactory chi-squared value of 1.19. It is difficult to explain physically the presence of several decays as it could be attributed to the presence of residual protonated forms of **CP3** or to the heterogeneity of the microenvironments of the fluorophores.

Anions recognition study

Upon addition of anions, ^1H NMR and molecular fluorescence titrations clearly indicate that **CP3** was able to discriminate between tetrabutylammonium salts of anions to recognize and bind selectively the fluoride over chloride, bromide, iodide and hydrogensulfate (see supplementary data Figure 11 and 12). The design of **CP3** resulted in a deep aromatic "fluoride only" recognition cavity. ^1H NMR titrations of **CP3** with TBAF (Figure 2) records the chemical shift and shows the progressive disappearance of the free ligand signals in favor of the new fluorine-complexed ligand. While new resonances appeared upon addition of 3 TBAF equivalents, total complexation was achieved upon addition of 11 equivalents and was evidenced by the disappearance of the NH singlet resonance at 9.4 ppm in favor of a new doublet resonance at 12.6 ppm (H-F J=46 Hz). These changes demonstrate the hydrogen bond formation between the fluorine and the pyrrolic ring, leading to the reorganization of the macrocycle that gets locked into a cone conformation when all the four NH pyrrolic functions get involved in the complexation. [3] [13] [22]

In fact, the whole complexation process was governed by several phenomena. Upfield chemical shifts were recorded mainly for the phenolic entity ($\Delta\delta = 0.25$ and 0.14 ppm): during the complexation process, fluorine took advantage of the π -aromatic systems shielding the pyrrolic cavity to tighten their bonding by additional non-covalent anion- π interactions. This result indicates that fluorine, once complexed by **CP3** will occupy the upper rim of the pyrrolic cavity surrounded by its extended aromatic arms. [23]

In order to determine the stoichiometry of the predominant complex, a Job plot was carried in d6-DMSO in a total concentration of 5 mM (see supplementary data Figure 13). This latter showed a maximum at **CP3**'s molar fraction close to 0.5, demonstrating that the predominant complex has a binding stoichiometry of 1:1.

While most calix[4]pyrroles are well known to complex fluorine, as expected, **CP3** was able to bind selectively fluoride considered toxic to the environment and the human health. In fact, this latter occurs naturally in the environment, but was also produced by different anthropic activities. Different sources, like diet, water and mainly tooth brushing could lead to ingesting relatively high amounts of fluorine. Despite its preventive role of protecting teeth from dental cavities, potentially serious health risks may result upon its ingestion, in the form of dental fluorosis and osteoporosis. [8] [24]

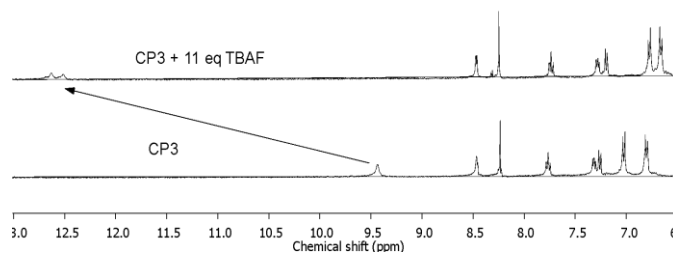


Figure 2: Partial ^1H NMR spectra of **CP3** with Tetra-butylammonium fluoride (TBAF) in d6-DMSO.

Following ^1H NMR titrations, anions selectivity of **CP3** was investigated as well by molecular fluorescence spectroscopy. As expected, fluoride anion induced a drastic decrease of fluorescence intensity of 36 % while other anions presented minor variations. The small decrease of fluorescence upon addition of iodide could be attributed to the heavy atoms effect [25] usually encountered with this anion.

Cations recognition study

Initially, this ligand was designed in order to bring new active electron- π rich sites close to the phenolic parent moieties, in order to access better molecular recognition. For this purpose, two potential nitrogen-crowded straps (i.e. triazole units) were added to **CP1**. Through this modification, new cations recognition and signaling capacities were created.

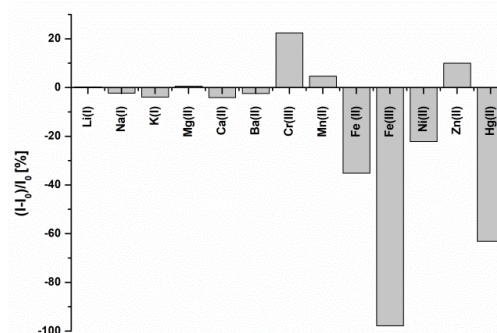


Figure 3: Change in fluorescence emission of **CP3** ($5 \times 10^{-5}\text{M}$, $\lambda_{\text{ex}} = 300$ nm, DMSO) upon addition of 10 equivalents of various metal cations as perchlorate salts.

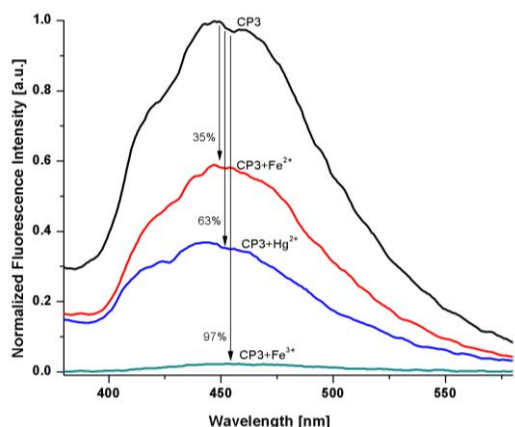


Figure 4: Fluorescence quenching of **CP3** (5×10^{-5} M, $\lambda_{\text{ex}} = 300$ nm, DMSO) upon addition of 10 equivalents of various metal cations as perchlorate salts.

Investigations of **CP3** fluorescent photophysical properties upon metal recognition

Fluorescence variations were investigated by fluorimetric titrations at constant **CP3** concentration (50 μ M) by following the molecular fluorescence emission intensity at 446 nm. Figure 3 shows the variation of fluorescence emission after addition of 10 equivalents of thirteen different metal cations to a solution of **CP3**. Interestingly enough, only three metals Fe^{2+} , Fe^{3+} and Hg^{2+} induced a significant quenching (over 25%) of the fluorescence intensity: 97% for Fe^{3+} , 35% for Fe^{2+} and 63% for Hg^{2+} (Figure 4). Plus, the addition of Ni^{2+} led to a smaller quenching of 22%. While both Cr^{3+} and Zn^{2+} produced a moderate enhancement of respectively 22% and 10%, other metals gave no or negligible responses of **CP3**.

In order to better understand the underlying mechanisms leading to the fluorescence quenching upon addition of metallic species of **CP3** in solution, the Stern-Volmer method combined with measurements of fluorescence lifetimes was undertaken. It allowed to distinguish between dynamic, static and both static and dynamic quenching for the four metallic quenchers. As a result, an increasing slope of τ_0/τ plot as a function of increasing Hg^{2+} and Ni^{2+} concentrations indicates the pure dynamic nature of the decrease in fluorescence. For those cations, quenching occurs when excited fluorophores experience contacts with these species and therefore non-radiative transitions to the ground state were facilitated. Conversely, experiments with Fe^{2+} indicated a purely static quenching i.e a linear relation was observed for F_0/F plot against increasing concentration of Fe^{2+} without evolution of fluorescence lifetime. A photo-induced electron transfer probably occurs upon chelation of Fe^{2+} with electrons rich moieties of **CP3**. Concerning the 97% decrease of fluorescence intensity of **CP3** by addition of 10 equivalents of Fe^{3+} , unchanged τ_0/τ ratio and quadratic dependency of F_0/F with an upward curvature shape were observed, indicating the presence of both dynamic and static quenching. This duality could contribute to explain the results obtained in the previous fitting experiments. As for the two moderate fluorescence emission enhancements caused by the addition of Cr^{3+} and Zn^{2+} it may be due

to chelation-enhanced-fluorescence as previously reported on similar structure including pyridyl groups and triazole units [26].

A Good correlation between experimental and calculated data [27] was obtained for Fe^{2+} assuming the 1:1 host/guest complex stoichiometry usually observed for this kind of compounds. Remarkably the 1:1 model could not explain the quenching of **CP3** fluorescence emission by Fe^{3+} while a coexistence of 1:1 and 1:2 complexes perfectly fit the observed quenching. Association constants were found to be 2.400 ± 700 and 34.000 ± 5.000 for Fe^{2+} and Fe^{3+} respectively (see supplementary data Figure 14 and 15).

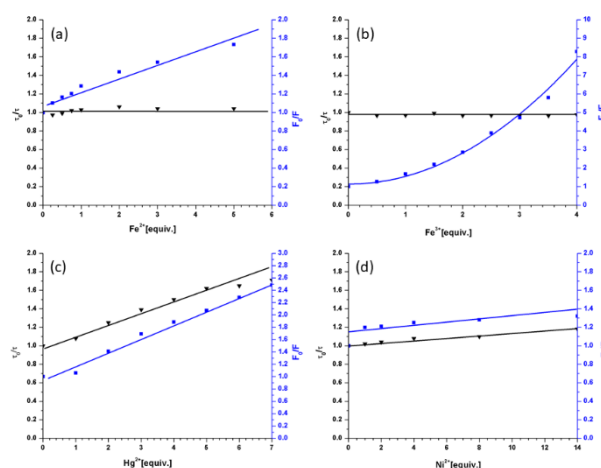


Figure 5: Fluorescence quenching of **CP3** upon addition of (a) Fe^{2+} , (b) Fe^{3+} , (c) Hg^{2+} and (d) Ni^{2+} (F/F_0 , blue square; τ_0/τ black triangle)

Time-of flight secondary ion mass spectrometry (TOF-SIMS) study

CP3 was detected in both positive and negative ionization emission modes with a molecular formula proposed as $\text{C}_{84}\text{H}_{77}\text{N}_{20}\text{O}_4^+$ for $[\text{M}+\text{H}]^+$ (m/z 1429.6461) and $\text{C}_{84}\text{H}_{75}\text{N}_{20}\text{O}_4^-$ for $[\text{M}-\text{H}]^-$ (m/z 1427.6292). Figure 6, Figure 7 and Figure 8 represent the comparison of **CP3**'s spectrum with three other different spectra, each representing **CP3** upon its interaction respectively with F^- (TBAF), Fe^{3+} and Hg^{2+} (as perchlorates). Results show the complexation of **CP3** with fluorine with a ratio of 1:3 (Figure 6) and a $[\text{M}+2\text{Fe}]^+$ was detected for its interaction with Fe^{3+} (Figure 7).

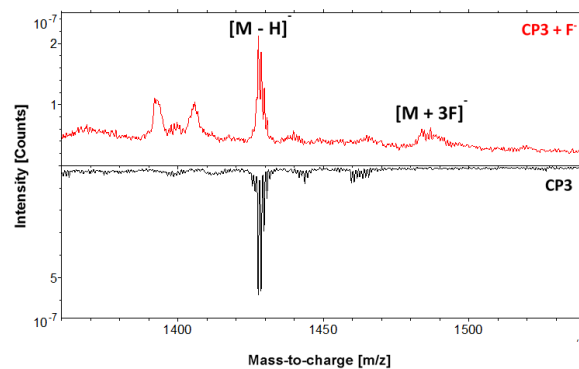


Figure 6: Part of negative ion mass spectra of "**CP3**" (in black) and "**CP3**+ fluorine" (in red) samples between m/z 1460 and m/z 1540. The spectra are normalized to the total primary ion dose.

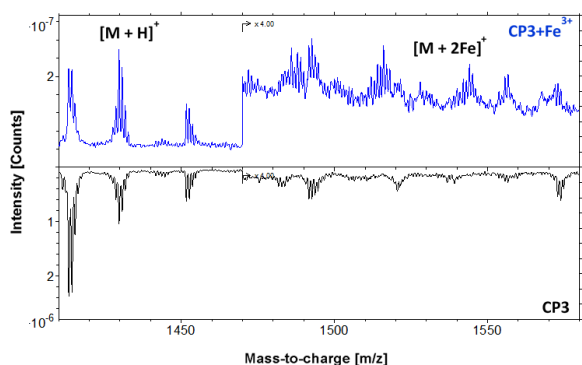


Figure 7: Part of positive ion mass spectra of “CP3 (in black) and “CP3+ iron” (in blue) samples between m/z 1410 and m/z 1580. The spectra are normalized to the total primary ion dose.

As for Figure 8, when comparing between the mass spectra of pure CP3 and CP3 with mercury, an emission of Hg^{2+} (m/z 201.97 for main isotope) in the positive ionisation mode was observed. Nevertheless no emission of pure CP3 neither as $[M+H]^+$, nor as $[M+Hg]^+$ or $[M+nHg]^+$ was detected; yet significant changes in the peaks of the mass spectra were observed after addition of the mercury salt to the CP3. This result is in agreement with molecular fluorescence results that indicates the absence of static interactions between CP3 and Hg^{2+} .

In order to understand whether these ratios define intra and/or intermolecular interactions, the polymeric distribution as well as the absence of different reputable m/z peaks in the mass spectra of CP3 with these ions, additional analyses and optimized experimental conditions are required. However detecting the calix[4]pyrrole molecule on TOF-SIMS, to the best of our knowledge was not reported in the literature and was rarely mentioned in the field of supramolecular chemistry. More detailed studies will be carried through TOF-SIMS in order to further our knowledge on the behaviour of CP3 towards ionic species in different experimental conditions.

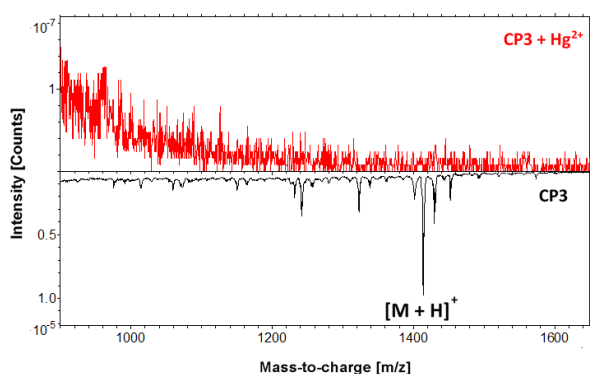


Figure 8: Part of positive ion mass spectra of “CP3” (in black) and “CP3 + mercury” (in red) samples between m/z 250 and m/z 1645. The spectra are normalized to the total primary ion dose.

Conclusions

A novel aryl-extended phenoxy-calix[4]pyrrole derivative CP3 was efficiently synthesized owing to click chemistry in a two-step protocol from native phenoxy-calix[4]pyrrole. This receptor presents one anion chelation site on the level of its pyrrolic ring and a cation binding site on the level of its aromatic arms. The 1,2,3 triazole “click-added” linker confers on this receptor new physico-chemical fluorescent properties which allowed its study by molecular fluorescence spectroscopy. CP3 proved to be a turn-off fluorescent sensor upon detection of fluoride, iron and mercury. Therefore, fluorescence quenching mechanisms were evaluated using Stern-Volmer formalism coupled with time-resolved fluorescence and it indicated that CP3 is able to form stable complexes with iron cations while purely collisional effects were observed for mercury and nickel. Moreover, this study introduces the first evaluation of supramolecules complexation behaviour using time-of flight secondary ion mass spectrometry. All of these findings make this fluorescent ditopic sensor a potential material that could serve for cations recognition, but also as an ion-selective sensor for fluorine. Our future effort will be devoted to improving selectivity of phenoxy-calix[4]pyrrole sensors.

Experimental Section

Procedures and characterization

Synthesis of 2-(azidomethyl)pyridine

2-(Chloromethyl)pyridine hydrochloride (1.0 g, 6.10 mmol) was suspended in dichloromethane (30 mL) and neutralized by a saturated solution of sodium hydrogen carbonate (3*15mL). The organic phase was later evaporated and the desired product was obtained as an orange oil. After addition of 20 mL of water and sodium azide (0.66 g, 10.15 mmol) to the aforementioned oil, the resulting mixture was placed in a sealed microwave vessel and irradiated (biotage initiator) for one hour at 120°C. Then it was extracted with diethyl ether (3*25mL) and evaporated to dryness. The azido compound was finally obtained as a consistent oil in a 61% yield. 1H NMR (400 MHz, $CDCl_3$): δ : 8.62 – 8.53 (m, 1H), 7.74 – 7.65 (m, 1H), 7.32 (t, J = 6.1 Hz, 1H), 7.25 – 7.20 (m, 1H), 4.47 (s, CH_2-N_3 , 2H).

Caution! Although no problem has been encountered, it is noted that azide derivatives are potentially explosive. They should be handled with care.

Synthesis of CP2 (CP-alkyne)

CP1 (330 mg, 0.45 mmol) and K_2CO_3 (750 mg, 5.43 mmol) were suspended in acetonitrile (30mL) and stirred for 30 minutes in order to activate the calix[4]pyrroles. A mixture of Propargyl bromide 80% in toluene (270.7 μ L) was added slowly and the mixture was refluxed for 3 days. After cooling the solution, the solvent was removed in vacuo. The resulting product was dissolved in 30mL of dichloromethane and washed with water, a solution of HCl (1M) and a saturated solution of $NaHCO_3$ (2*15 mL each time). The organic phase was evaporated affording a brown powder in an 80% yield. 1H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.04 (d, J = 8.8 Hz,

2H), 6.84 (d, $J = 8.9$ Hz, 2H), 5.74 (d, $J = 2.0$ Hz, 2H), 4.66 (d, $J = 2.3$ Hz, 2H), 2.54 (t, $J = 2.3$ Hz, 1H), 1.94 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 156.2, 141.3, 136.8, 128.7, 114.0, 106.3, 78.8, 75.7, 56.0, 44.2, 28.4.

Synthesis of CP3 (CP-Click 2-pyridine)

A solution of the alkyne calix[4]pyrrole **CP2** (300 mg, 0.34 mmol) in dimethylsulfoxide (25 mL) was stirred and 2-(azidomethyl)pyridine (365 mg, 2.72 mmol), copper iodide (325 mg, 1.71 mmol) and triethylamine (310 μL , 2.24 mmol) were added. The mixture was left overnight at 50°C. After cooling, the mixture was quenched slowly in water (40 mL). Therefore, a greenish aqueous phase was obtained, and filtered, giving a dark green solid. This latter was mixed with 30 mL of dichloromethane, to be washed later by ammonia 10% until the disappearance of the blue coloration of the aqueous phase. After that, HCl 1N was added to the organic phase and **CP3** precipitates as a light green solid which was then washed with NaHCO_3 (2*30 mL) and H_2O (2*30 mL). The **CP3** was obtained as a green powder in a 89% yield after being purified over silica column chromatography in a mixture of dichloromethane and methanol (10:1). ^1H NMR (500 MHz, DMSO): $\delta = 9.43$ (s, NH, 1H), 8.47–8.45 (m, pyridine, 1H), 8.24 (d, $J = 6.5$ Hz, triazole, 1H), 7.76 (td, $J = 7.7$, pyridine, 1.8 Hz, 1H), 7.33–7.25 (m, pyridine, 2H), 7.04–7.02 (d, $J = 8.9$ Hz, phenolic H, 2H), 6.81–6.79 (d, $J = 8.7$ Hz, phenolic H, 2H), 5.94 (s, CH_2 -pyridine, 2H), 5.67 (s, pyrrolic H, 2H), 5.07 (s, O- CH_2 , 2H), 1.75 (s, CH_3 , 3H). ^{13}C NMR (125 MHz, DMSO) δ 156.9, 154.9, 149.5, 149.4, 142.8, 142.5, 137.4, 127.9, 125.5, 125.4, 123.3, 122.3, 122.3, 114.5, 104.6, 61.2, 54.4, 43.5, 31.31. HRMS (TOF-SIMS) calc for $\text{C}_{84}\text{H}_{77}\text{N}_{20}\text{O}_4^+$ m/z 1429,6431 found m/z 1429.6461.

General procedures for ^1H NMR and fluorescence titrations

^1H and ^{13}C NMR measurements were recorded at 298 K. **CP3** solutions of well-determined concentrations (10^{-3}M) were prepared in deuterated dimethylsulfoxide. Investigations concerning **CP3** and its interactions with anions (fluoride, chloride, bromide, iodide and hydrogen sulfate as tetra-n-butylammonium salts) were carried by several titrations where the anions were prepared in the same solvent dissolving **CP3** in the same concentration conditions (10^{-3}M). Upon addition of the anion salts, chemical shifts of the free and the complexed ligand were recorded.

As for the cations binding capacity (Li^+ , Na^+ , K^+ , Mg^{2+} , Ca^{2+} , Ba^{2+} , Cr^{3+} , Mn^{2+} , Fe^{2+} , Fe^{3+} , Zn^{2+} , Ni^{2+} , Hg^{2+} as perchlorate salts), **CP3** was studied by molecular fluorescence spectroscopy in DMSO ($5 \times 10^{-5}\text{M}$).

Time-of flight secondary ion mass spectrometry (TOF-SIMS) Parameters

The solid samples were firstly dissolved in dichloromethane then filtered; the liquid parts were used for TOF-SIMS analyses. For each sample a volume of 20 μL was deposited on silicon substrate. All experiments and analyses were done in triplicate.

The analyses were performed by TOF-SIMS V mass spectrometer (ION-TOF GmbH, Munster, Germany) in the Lebanese Atomic Energy Commission-NCSR (Lebanon). The instrument was equipped with bismuth and argon clusters sources and a reflectron time-of-flight analyzer. Bi_3^+ clusters ion beam at 25 keV hitting the sample

surfaces with a 45° angle of incidence were selected for the analyses [28]. The spectroscopy mode, also called high current bunched mode was chosen for the analyses with a spatial resolution of 2 μm and $M/\Delta M$ (Full Width at Half Maximum) 2000-8000 [29]. The secondary ions were extracted and post-accelerated to 10 keV before hitting a single micro-channel plate detector. For each sample, three replicates were analyzed. Areas of 500 μm * 500 μm (256*256 pixels) in positive and negative emission modes were explored using a primary ion dose intensity of 5×10^{11} ions/ cm^2 for each polarity. Mass spectra were processed using Surface Lab 6.8 software (ION-TOF GmbH, Münster, Germany) and internally calibrated using H^+ , H_2^+ , H_3^+ , C^+ , CH^+ , CH_3^+ , C_2H_3^+ and C_3H_5^+ in positive mode and H^- , C^- , CH^- , C_2^- , C_2H^- , C_3^- , C_3H^- , C_4^- and C_4H^- in negative mode, respectively.

Conflicts of interest

There are no conflicts to declare

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