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Highly selective recognition of the Al(ClO$_4$)$_3$ molecule by a mono-pyrene substituted thiacalix[4]arene chemosensor†

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A mono-pyrene substituted thiacalix[4]arene chemosensor (TCA-Py) was successfully synthesized in satisfactory yield. Fluorescence analysis revealed that TCA-Py exhibited a high recognition selectivity toward the Al(ClO$_4$)$_3$ molecule due to the synergy between the Al^{3+} cation and ClO$_4^-$ anion. This unique ability to recognise an entire inorganic molecule broadens the field of molecular recognition.

Molecular recognition is one of the most important branches of supramolecular chemistry.[1, 2] Generally, molecular recognition events include the recognition of cations, anions, gases, organic molecules or biomolecules.[3-5] To the best of our knowledge, the recognition of an entire inorganic molecule is rare. Numerous macrocyclic compounds, such as crown ethers,[6, 7] cyclodextrins,[3] cucurbiturils,[8] resorcinarene[9] and calixarenes,[10] have proved to be the excellent candidates for molecular recognition due to their unique cavities which provide the recognition capability. However, for their respective functionalized derivatives, most of the recognition events occur at the appended functional groups rather than in the cavity.[5, 9-11] Such functionalization can lead to the loss of the greatest advantage of the macrocyclic host, *i.e.* the cavity. In order to retain the advantage of the thiacalix[4]arene (**TCA**) cavity, herein, we have designed a mono-pyrene substituted thiacalix[4]arene derivative (**TCA-Py**), which not only preserves the recognition capability of the thiacalix[4]arene

cavity, but is also capable of monitoring the recognition behaviour via fluorescence.

TCA-Py was synthesized in two steps by using the parent macrocyclic scaffold thiacalix[4]arene as the starting material in satisfactory yield (Scheme 1). Introduction of the mono-propargyl at the thiacalix[4]arene (**TCA-CCH**) is the key step in the synthetic route. Since four identical phenol functionalities are present in the skeleton, di- or tetra-substituted derivatives are normally the main products for calix[4]arenes and thiacalix[4]arenes. Current approaches for mono-propargyl-substitution at a calix[4]arene are either poor yielding,[12, 13] or complicated synthetic processes.[14] Lakouraj *et al.* have reported the only synthesis of a mono-propargyl-substituted thiacalix[4]arene derivative.[15] Unfortunately this method was not successful in our hands. Hence, an efficient synthetic method for mono-substituted thiacalix[4]arene derivatives is highly
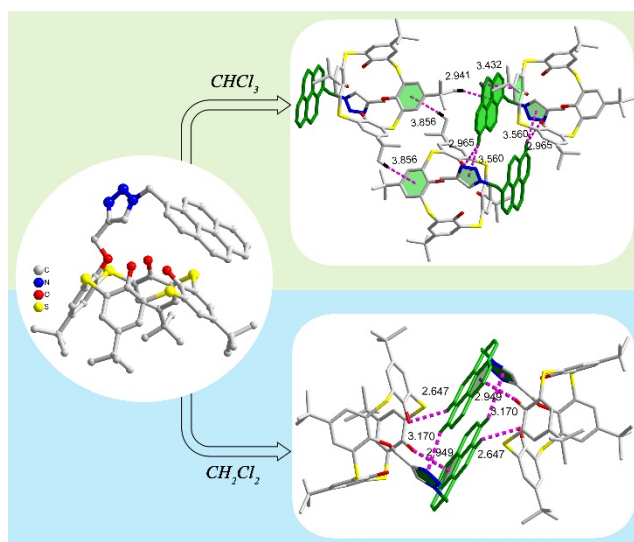

Figure 1. Single-crystal structure of **TCA-Py** which obtained from CHCl$_3$/EtOH or CH$_2$Cl$_2$/EtOH mixture solution. The detail non-covalent interaction of pyrene moiety. The hydrogen atoms and solvent molecule are omitted for clarity.

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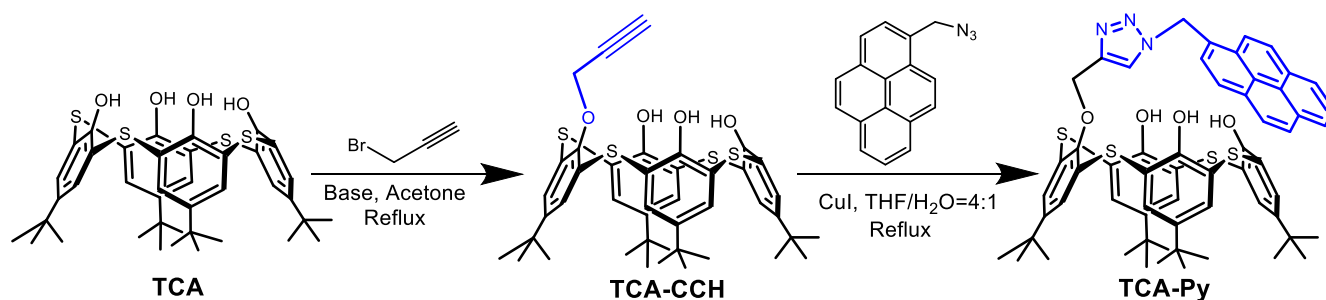
Scheme 1. Synthetic route to mono-pyrene-substituted thiacalix[4]arene derivative (**TCA-Py**).

desirable. To this end, the experimental protocol and reaction conditions were re-optimized (Table S1). Carbonates of alkali metals, such as Na, K and Cs, are usually employed as the base for the condensation of a calix[4]arene with 3-bromoprop-1-yne (BrCH$_2$CCH). Na$_2$CO$_3$ failed to function in the reaction, while the use of K$_2$CO$_3$ yielded a mixture of mono-substituted product (29-38%), tetra-substituted byproduct (2-37%) and unreacted starting material (8-20%), regardless of the reaction conditions employed (Scheme S1, ESI). It seemed that increasing the alkaline strength of the carbonate salt is beneficial to converting **TCA** to the substituted products. In addition, the degree of substitution is governed by the ratio between BrCH$_2$CCH and **TCA**. Therefore, a higher yield and better purity of the desired product was achieved when Cs$_2$CO$_3$ was utilized as the base and the final mol ratio of BrCH$_2$CCH and Cs$_2$CO$_3$ was just slightly over **TCA**. In the optimized protocol, BrCH$_2$CCH and Cs$_2$CO$_3$ were carefully added to **TCA** in several small portions during the reaction to maintain an excess of **TCA** for as long as possible, affording 70% of **TCA-CCH** and no tetra-substituted byproduct. Following the efficient preparation of **TCA-CCH**, the **TCA-Py** sensor was easily obtained by Click chemistry. The structures of **TCA-CCH** and **TCA-Py** were fully verified by ^{1}H/^{13}C NMR spectroscopy and mass spectrometry (Figs. S1 ~ S9, ESI).

Figure 2. Fluorescence spectra (λ_{ex} = 344 nm) of sensor **TCA-Py** (10 μM, EtOH/CH$_2$Cl$_2$/H$_2$O = 94/1/5) with or without 10 equiv. of the various guests. Inset: The colour changes of sensor **TCA-Py** with or without Al(ClO$_4$)$_3$ under UV light.

X-ray crystallographic analysis further confirmed the molecular structure of **TCA-Py**. **TCA-Py** crystal can be easily obtained from a CHCl$_3$/EtOH or CH$_2$Cl$_2$/EtOH mixed solution. A classic cone conformation was observed (Fig. 1). The pyrene moiety folded and oriented to the cavity like a cap of the **TCA** cup. Closer inspection revealed that there are a plenty of C···H···π, O···H···π and hydrogen bonding interactions around the pyrene moiety. These short-range interactions can efficiently absorb the energy from the excited state of the pyrene moiety, which might be the main reason for the non-fluorescence of the guest-free **TCA-Py** sensor (Fig. 2). Interestingly, solvent molecules (such as CH$_2$Cl$_2$ or CHCl$_3$) are readily embedded into the cavity of **TCA-Py** promoted by aromatic-π interactions, indicating that introduction of the mono-pyrene substituent does not interfere with the host-guest molecular recognition capability of the thiacalix[4]arene cavity (Figs. S12&13, ESI).

The recognition properties of sensor **TCA-Py** with guests (the perchlorate of Li$^+$, Na$^+$, K$^+$, Rb$^+$, Cs$^+$, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Pb^{2+}, Co^{2+}, Cu^{2+}, Ni^{2+}, Zn^{2+}, Mn^{2+}, Cd^{2+}, Fe^{3+}, Al^{3+} and Cr(NO$_3$)$_3$) were evaluated by fluorescence analysis (Fig. 2). Sensor **TCA-Py** is almost non-fluorescence, however the addition of different guests results in different fluorescence responses. For example, the addition of Li$^+$, Na$^+$, K$^+$, Rb$^+$, Cs$^+$, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Pb^{2+}, Zn^{2+}, Mn^{2+}, Cd^{2+}, Al^{3+} or Cr^{3+} induces a different degree of fluorescence enhancement, whilst addition of Co^{2+}, Cu^{2+}, Ni^{2+} or Fe^{3+} induces a different degree of fluorescence quenching. In other words, sensor **TCA-Py** exhibited a high affinity towards all of the tested guests. This may be attributed to the presence of the **TCA-Py** cavity, which possesses excellent recognition capability. The introduction of the non-macrocyclic reference sensor **Ref.-Py** (Scheme S2, ESI), which comprises one unit of **TCA-Py** and no cavity, further confirmed the recognition capability originated from the thicalix[4]arene cavity. Without the cavity, no detectable fluorescence changes can be observed under the same test conditions (Fig. S14, ESI). Although the addition of all guests results in changes of the monomer emission of **TCA-Py**, only the addition of Al^{3+} induced the appearance of a dramatic excimer emission (Fig. 2). This suggests that sensor **TCA-Py** possesses high selectivity for the recognition of Al^{3+} among the tested guests based on the excimer emission spectra. The combination of monomer emission and excimer emission resulted in a cyan colour which was obviously different from the blue colour for the monomer emission of pyrene (Fig.2 inset). As a consequence, it is possible to directly recognize Al^{3+} by the naked eye.
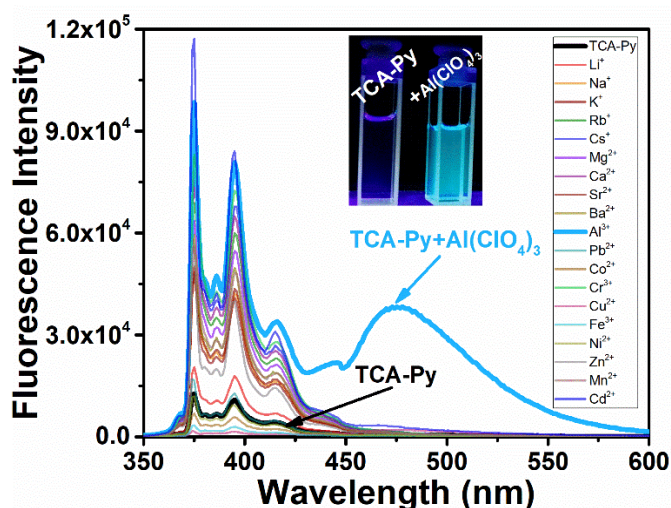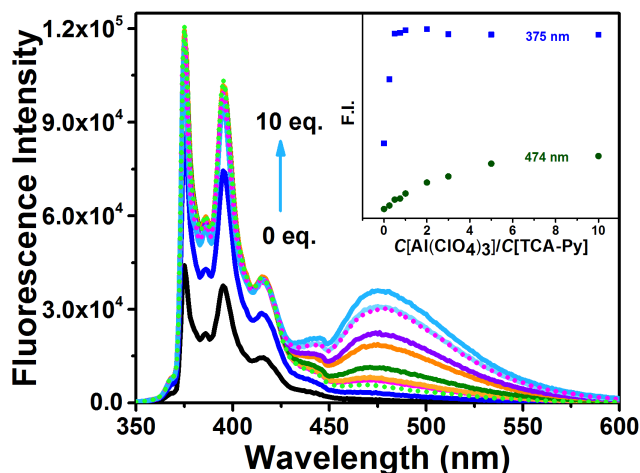
Figure 3. Fluorescence spectra changes of sensor **TCA-Py** (10 µM) solution upon addition of $Al(ClO_4)_3$ (solid line, 0−10 equiv.; pink short dot line, 20 equiv.; green short dot line, 50 equiv.). Inset: the plot of fluorescence intensity (at 375 nm or 474 nm) of sensor **TCA-Py** as a function of $Al(ClO_4)_3$ concentration.

Initially, we thought that this sensor was only a simple chemosensor for ion recognition. However, fluorescence titration experiments revealed an unexpected recognition behaviour for **TCA-Py** toward $Al(ClO_4)_3$ (Fig. 3). Upon the addition of $Al(ClO_4)_3$ (0 to 1.0 equiv.), only an acute fluorescence enhancement of the monomer emission (375 nm) was observed, which was similar to the addition of other cations (Fig. 2). However, on continued addition of $Al(ClO_4)_3$ (1.0 to 10 equiv.) no further significant fluorescence change of the monomer emission was observed, but rather a dramatic fluorescence enhancement of the excimer emission (474 nm). As we know, the monomer emission is a characteristic of the pyrene itself, whilst the excimer emission is a characteristic of the intermolecular π-π stacking of pyrene.[16] Hence, this suggests that the recognition process for $Al(ClO_4)_3$ can be separated into two sequential processes: first is the monomer emission enhancement, followed by the excimer emission enhancement. The addition of $AlCl_3$ as a control experiment further confirmed our hypothesis. Under the same conditions, upon addition of 10 equiv. of $AlCl_3$ only monomer emission fluorescence enhancement resulted (Fig. S15, ESI), which implied that the cation Al^{3+} only contributed to the monomer emission. Thus, the later appearance of the excimer emission was attributed to the presence of the ClO_4^- anion. However, use of other perchlorate salts did not exhibit similar phenomenon (Fig. 2). Additionally, when we first added 10 equiv. $AlCl_3$ to **TCA-Py**, the monomer emission was enhanced as expected. However, on the subsequent addition of a chlorate anion source, such as $NaClO_4$, we cannot observe the excimer emission enhancement (Fig. S16a). On the other hand, when we first added 10 equiv. $NaClO_4$, and then added $AlCl_3$, we also only observed the monomer emission enhancement (Fig. S16b). This may be due to the affinity of $AlCl_3$ toward **TCA-Py** being higher than $Al(ClO_4)_3$ toward **TCA-Py** given that the binding constant of the **TCA-Py**-$AlCl_3$

complex ($1.56 \times 10^8 \pm 2484$ M^{-1}, Fig. S17) is higher than the **TCA-Py**-$Al(ClO_4)_3$ complex ($2.35 \times 10^5 \pm 243$ M^{-1}, Fig. S18).
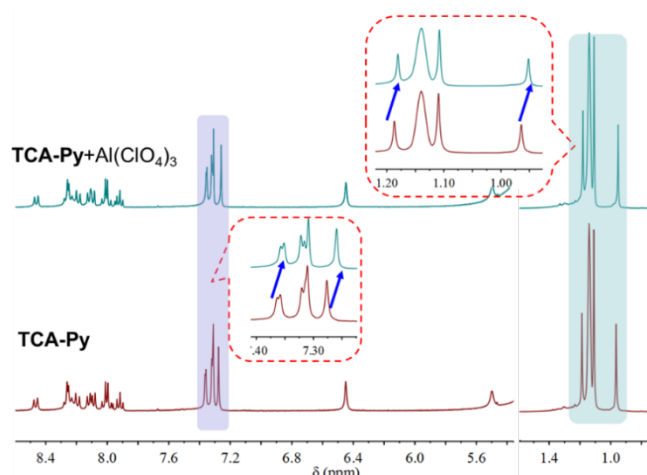

Figure 4. ^{1}H NMR spectral changes of sensor **TCA-Py** (4×10^{-3} M) on addition of 10 equiv. $Al(ClO_4)_3$ (400 MHz, EtOD:CDCl$_3$:D$_2$O = 470:10:25).

This was further confirmed by the gradually addition of $AlCl_3$ to the **TCA-Py**-$Al(ClO_4)_3$ complex which resulted the excimer emission decreasing (Fig. S16c). Consequently, we can conclude that only the simultaneous presence of both the Al^{3+} cation and ClO_4^- anion without strong competitive ion interference results in both the monomer emission and excimer emission enhancement, i.e. the presence of the entire $Al(ClO_4)_3$ molecule is a prerequisite for the observed behaviour. We speculate that the recognition process of $Al(ClO_4)_3$ is as follow: firstly the addition of Al^{3+} disrupted the efficient molecular interaction of pyrene moiety in **TCA-Py** (Fig. 1) which resulted in the pyrene fluorescence reverse. Next, the further presence of ClO_4^- induced a weak π-πstacking process for the **TAC-Py**-Al^{3+} complex. And finally complete the unique recognition behaviors, recognition an entire inorganic molecular $Al(ClO_4)_3$.

^{1}H NMR spectroscopic titration experiments further revealed the detail recognition mechanism of sensor **TCA-Py** with $Al(ClO_4)_3$. The addition of $Al(ClO_4)_3$ resulted in the aromatic proton signals of the **TCA** cavity (7.28~7.36 ppm) and the corresponding t-Bu proton signals (0.96~1.19 ppm) shifting up-field, which suggested that the binding site was in the cavity of **TCA-Py** (Fig. 4). This also explains why **Ref.-Py** with a similar structure but no cavity, exhibited a lack of recognition capability toward any of the tested guests (Fig.S14, ESI). No significant changes of the pyrene proton signals were observed on comparing the **TCA-Py** and **TCA-Py**+$Al(ClO_4)_3$ spectra. However, the pyrene related proton signals in Figure 4 were found to be similar to previously reported pyrene excimer NMR spectra,[16] indicating the existence of the pyrene excimer in both the **TCA-Py** and **TCA-Py**+$Al(ClO_4)_3$ systems during the NMR experiments. This could be attributed to excimer formation by aggregation caused due to the relative high concentration of **TCA-Py** for NMR test. On examining the fluorescence titration results, a plausible recognition mechanism for sensor **TCA-Py** with $Al(ClO_4)_3$ is proposed, as shown in Figure 5. The Al^{3+} was first captured by the cavity of **TCA-Py** through cation-π

interactions, with the benzene rings of the cavity adjusting to a face-to-face conformation in order to accommodate the guest.
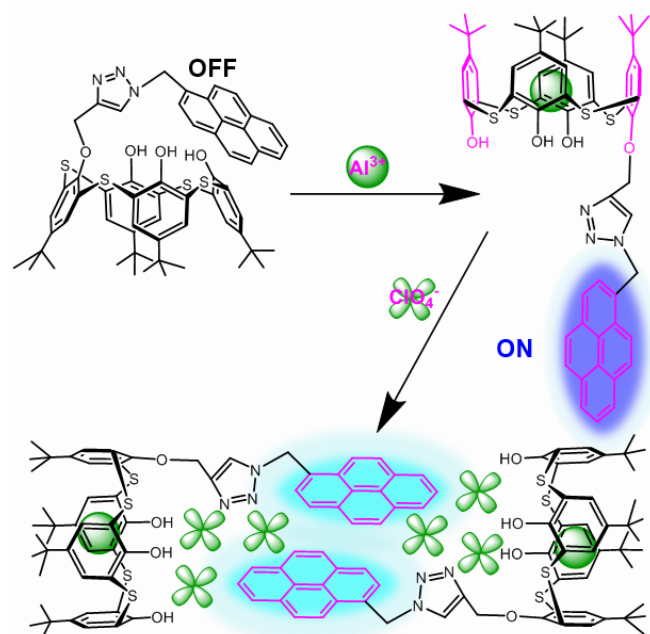

Figure 5. Plausible recognition mechanism for sensor **TCA-Py** with Al(ClO₄)₃.

The shielding effect was enhanced in this more compact conformation, which led to the chemical shifts of the benzene rings moving up-field. The conformational changes disrupted the previous interaction between pyrene and the benzene rings of the **TCA** cavity, which induced the recovery of the pyrene fluorescence (ON). Each **TCA** cavity captures only one molecule of Al^{3+}, which is consistent with the 1:1 binding stoichiometry for Al^{3+} to **TCA-Py** as revealed by the fluorescence titration experiments. The positively charged **TCA-Py**-Al^{3+} complex associates with nearby ClO_4^- anions to achieve a charge balance. Moreover, the anion ClO_4^- further induces **TCA-Py**-Al^{3+} complex aggregation leading to the formation of a dimer via weak π-π stacking of the pyrene moiety, which resulted in the excimer emission. A similar dimer formation mechanism has been confirmed by Kalyani *et. al.* which further supports our hypothesis.[17]

In conclusion, we report in this work a novel mono-pyrene substituted thiacalix[4]arene derivative **TCA-Py** with unique recognition properties. Under the optimized synthetic conditions, **TCA-Py** was readily obtained in two steps in satisfactory yield. Fluorescence analysis revealed that **TCA-Py** exhibited a high recognition selectivity toward Al(ClO₄)₃ due to the synergy between the Al^{3+} cation and ClO_4^- anion. The presence of only Al^{3+} or ClO_4^- did not result in such a phenomenon, which suggested the recognition event involves the entire Al(ClO₄)₃ molecule.

Conflicts of interest

There are no conflicts to declare.

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