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Cooperative Recognition of a Copper Cation and Anion by a Calix[4]arene Substituted at the Lower Rim by a β-Amino-α,β-Unsaturated Ketone

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Abstract: We report herein a new ditopic calix[4]arene receptor 25,27-bis-{[4-amino-4-(1-naphthyl)-2-oxo-3-butenyl]oxy}-26,28-dihydroxycalix[4]arene (**2**) for the simultaneous complexation of anionic and cationic species. The host molecule 25,27-bis{[3-(1-naphthyl)-5-isoxazolyl]methoxy}-26,28-dihydroxycalix[4]arene (**1**) was synthesised first and was followed by a [$Mo(CO)_6$]-mediated ring-opening reaction to give the target receptor **2**. The binding properties of ligands **1** and **2** towards metal ions in CH_3CN were investigated by UV/Vis and fluorescence spectroscopies. The results showed that both ligands **1** and **2** were highly selective for Cu^{II} ions. Upon titration with Cu^{II}, the fluorescence of **1** was severely quenched, whereas **2** showed strong fluorescence enhancement because the metal ions help to lock the conformation of the fluorophores. During the complexation of **2** with Cu^{II}, the Cu^{II} was reduced to Cu^{I} by the free phenolic OH of **2**, whereas the phenol was oxidised by Cu^{II}, after which it assisted in the trapping of Cu^{I}. Ditopic behaviour was observed for the complex **2**·Cu^{I}, which showed further enhancement of its fluorescence intensity upon complexation with anions such as acetate or fluoride.

Keywords: calixarenes · dipolar reactions · ditopic receptor · fluorescence · inclusion compounds

Introduction

In the last decade, the design and synthesis of new ditopic ligands for the simultaneous complexation of cationic and anionic species has gained much attention in calixarene chemistry.[1] The specific recognition of metal ions or anions plays an important role in biological systems and environmental protection. For example, it is known that copper ions, despite being an essential biological trace element, are toxic to organisms, even at submicromolar concentrations. On the other hand, carboxylate anions are biologically important because of their roles in determining the antibiotic activities of the vancomycin family.[2] Thus, many chemosensors have been designed for the sensitive and specific recognition of copper ions[3] and carboxylate anions.[4]

Most calix[4]arene-based fluorescent sensors have been designed based on their photophysical changes upon ion binding, and the mechanisms include photoinduced electron transfer (PET),[5] photoinduced charge transfer (PCT),[6] metal-to-ligand charge transfer (MLCT)[7] and excimer/exciplex formation.[8] As part of our continuing interest in the design and synthesis of chromo-[9] and fluorogenic chemosensors,[10] we report herein a ditopic calix[4]arene receptor 25,27-bis-{[4-amino-4-(1-naphthyl)-2-oxo-3-butenyl]oxy}-26,28-dihydroxycalix[4]arene (**2**) with naphthalene pendants as the fluorophore and β-amino-α,β-unsaturated ketone units as the cooperative cationic and anionic recognition sites. The complexation of the carboxylate or fluoride anions of receptor **2** can only proceed when a Cu^{II} ion is present in the calix[4]arene lower rim cavity; conversely, without a Cu^{II}, no binding of the anion was detected.

Results and Discussion

The synthesis of calix[4]arenes 25,27-bis{[3-(1-naphthyl)-5-isoxazolyl]methoxy}-26,28-dihydroxycalix[4]arene (**1**) and **2** and model compounds 5-(2,6-dimethyl-phenoxymethyl)-3-

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naphthalen-1-ylisoxazole (**3**) and 4-amino-1-(2,6-dimethylphenoxy)-4-naphthalen-1-yl-3-buten-2-one (**4**) are shown in Scheme 1. Precursor **1** was obtained through 1,3-dipolar cycloaddition[11] of 25,27-dipropargyloxy-26,28-dihydroxycalix[4]arene with 1-napthyl hydroximoyl chloride in the presence of excess Et_3N in toluene at reflux to afford **1** in 80% yield. Subsequent N–O bond cleavage of the isoxazole units by a $[Mo(CO)_6]$-mediated ring-opening reaction[12] led to the formation of target receptor **2**, which was obtained in 52% yield. Model compounds **3** and **4** were synthesised by following the same synthetic strategy as calix[4]arenes **1** and **2**, and they were obtained in 69 and 76% yield, respectively. The structures of compounds **1**–**4** were confirmed by ^1H and ^{13}C NMR spectroscopy, mass spectrometry and HRMS. The structures of calix[4]arenes **1** and **2** were further confirmed by single-crystal X-ray analysis (Figure 1).

The fluorescence spectra of compounds **1**–**4** are shown in Figure 2. Ligand **1** displayed weak monomer and strong excimer emission bands at 345 and 404 nm, respectively, whereas model compound **3** only showed a strong monomer emission band at 345 nm. The results implied that a π–π interaction of the two pendant naphthalenes of ligand **1** should have occurred in CH_3CN. However, the two naphthyl groups of ligand **1** were separated in the solid state (see the X-ray structure in Figure 1). In contrast, very weak emission of ligand **2** and model compound **4** was observed, which might be attributed to the flexibility of the β-amino-α,β-unsaturated ketone unit and a PCT process between its amino group and naphthalene.

The binding properties of ligands **1** and **2** were then assessed by the addition of 10 equivalents of perchlorate salts of Li^I, Na^I, K^I, Ag^I, Ca^{II}, Pb^{II}, Hg^{II}, Cu^{II}, Ni^{II} and Cr^{III} in CH_3CN, and their fluorescence intensity changes are shown in Figure 3. Among the ten metal ions tested, only Cu^{II} caused dramatic fluorescence quenching towards ligand **1**. In sharp contrast, a significant fluorescence enhancement for ligand **2** was also found only for Cu^{II}. These results imply that the recognition of Cu^{II} by ligands **1** and **2** might have different mechanisms.

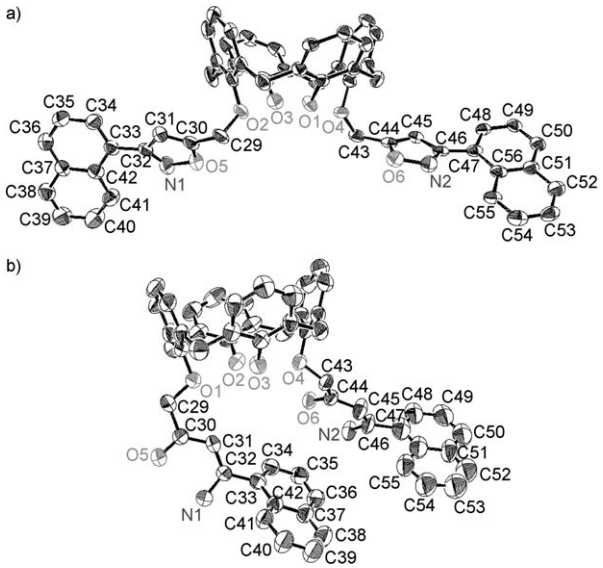
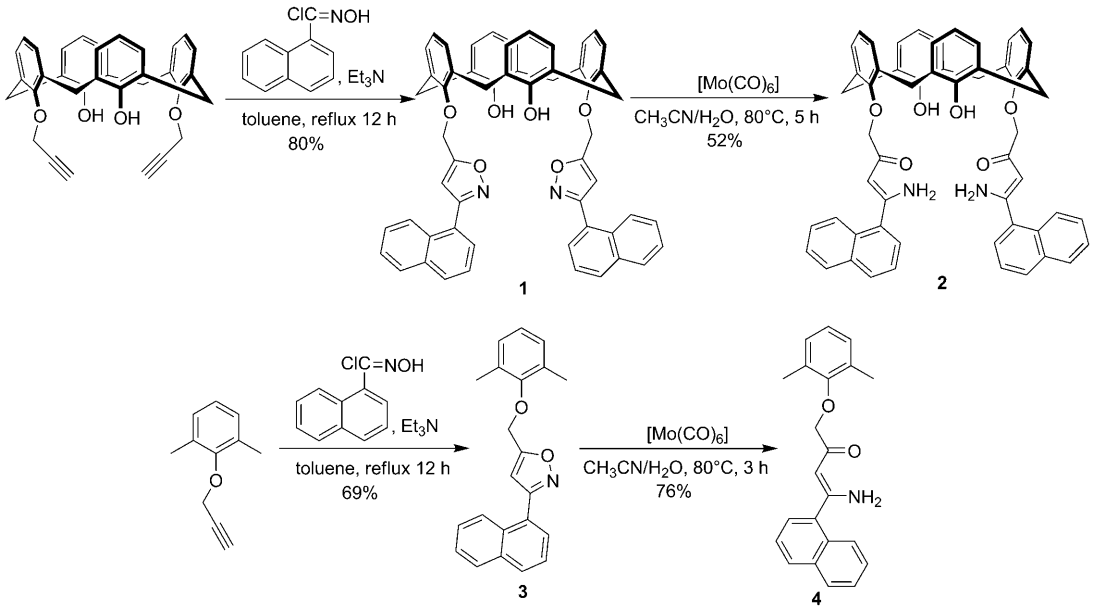


Figure 1. Single-crystal X-ray structures of calix[4]arenes a) **1** and b) **2**.

The UV/Vis spectra of ligand **1** in the presence of Cu^{II} showed a new absorption band at approximately 430 nm (Figure 4a), which is characteristic of a MLCT band between Cu^I and the phenolic OH on the lower rim.[13] Thus, Cu^{II} might have been reduced to Cu^I by the phenolic OH groups of calix[4]arene **1**, and the oxidised phenols may help to trap the reduced Cu^I.[10b] The autoreduction of Cu^{II} by phenol has been well documented.[14] Upon titration of



Scheme 1. Synthesis of calix[4]arenes **1** and **2** and model compounds **3** and **4**.

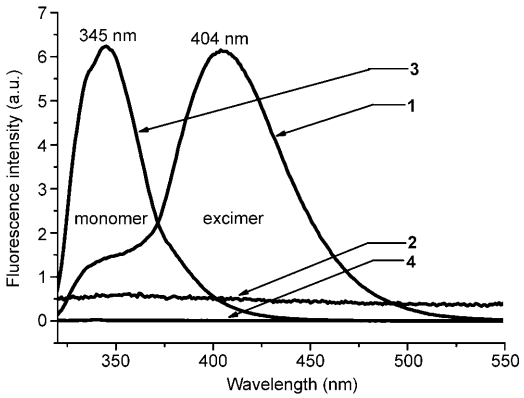


Figure 2. Fluorescence emission spectra of **1**–**4** in CH_3CN (20 μM, excitation wavelength = 285 nm).

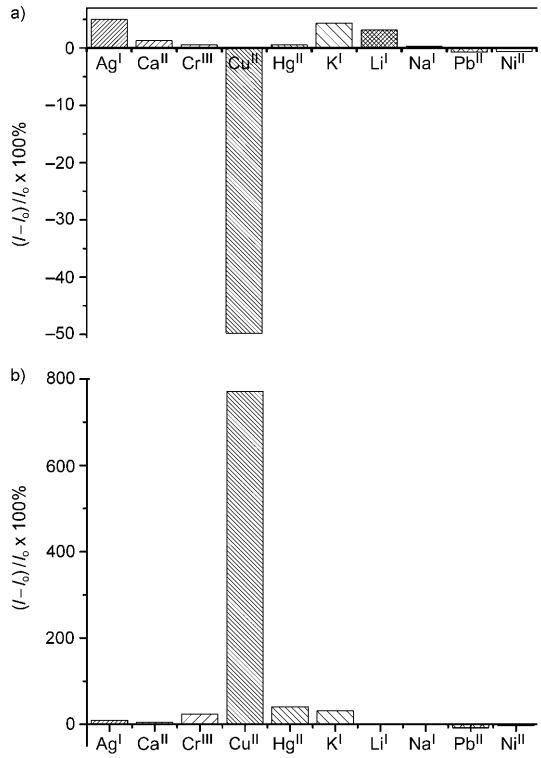
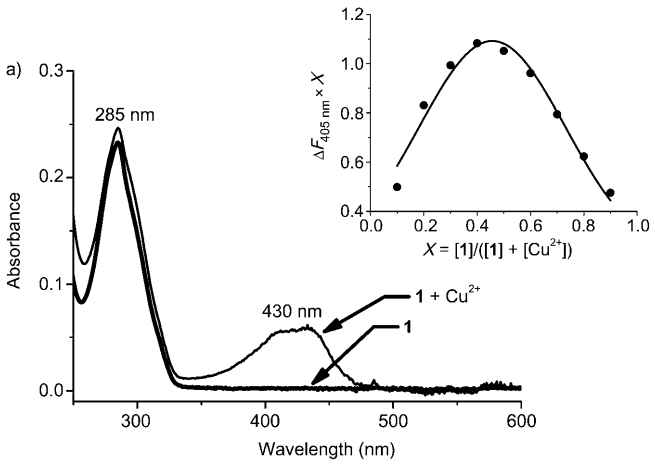


Figure 3. Fluorescence changes of ligands a) **1** and b) **2** with the addition of metal perchlorates (10 equiv) in CH_3CN (20 μM, excitation wavelength = 285 nm).



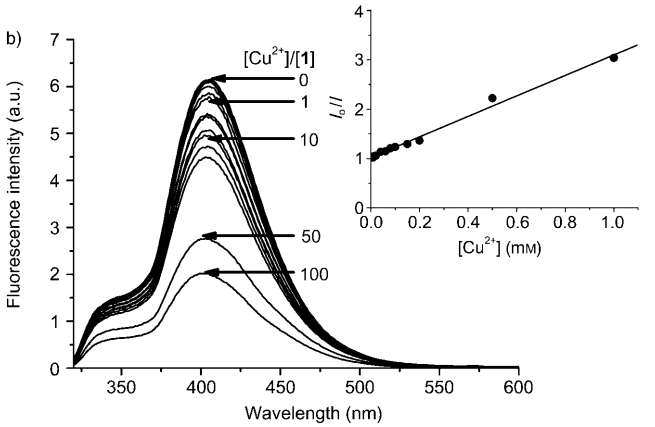


Figure 4. a) UV/Vis spectrum of ligand **1** before and after adding $Cu(ClO_4)_2$ (10 equiv) in CH_3CN (20 μM). The inset is a Job plot of a 1:1 complex of **1** and Cu^{II}, in which the difference in fluorescence intensity (ΔF) at 405 nm was plotted against the mole fraction of **1** at a total concentration of 20 μM in CH_3CN. b) Fluorescence quenching of **1** with various equivalents of $Cu(ClO_4)_2$ in CH_3CN (20 μM, excitation wavelength = 285 nm). The inset is a Stern–Volmer plot of **1** with $Cu(ClO_4)_2$ in CH_3CN (20 μM), in which the fluorescence intensity (I_o/I) at 405 nm was plotted against the concentration of Cu^{II} (intercept = 1.02, slope = 2.08×10^3, $K_a = 2.08 \times 10^3\ M^{-1}$, $R^2 = 0.990$).

Cu^{II} into the solution of ligand **1**, both the monomer and excimer emissions of **1** were quenched, which was presumably owing to the combination of 1) a heavy atom effect;[15] 2) a reverse PET[16] from naphthalene units to the nitrogen atoms in the isoxazole rings, the electron density of which might have been decreased by metal ion complexation; and 3) an inner filter effect[17] due to the broad absorption band at 430 nm. From the fluorescence titration experiment, the association constant (K_a) of ligand **1** with Cu^{II} was calculated to be $2080\ M^{-1}$ in CH_3CN,[18] and the binding ratio, which was calculated from the Job plot, was 1:1 (see Figure 4).

In contrast to the titration of ligand **1** with Cu^{II}, which showed fluorescence quenching, the titration of ligand **2** with Cu^{II} showed dramatic enhancement of the monomer emission at 343 nm, but a small increase in the excimer emission at 450 nm (Figure 5b). Furthermore, the UV/Vis spectrum of ligand **2** showed a bathochromic shift from 315 to 438 nm upon addition of Cu^{II} (Figure 5a). The formation of a new absorption band at 438 nm is reminiscent of a MLCT band between Cu^{I} and the phenolic OH on the lower rim of ligand **2**.[13,14] A similar broad absorption band for a Cu^{I} tetrahedral complex has also been reported, which was ascribed to a MLCT band.[19] The autoreduction of Cu^{II} to Cu^{I} was reported in the copper ion complexation of a bis-β-ketoimine-substituted calix[4]arene.[13a] The formation of Cu^{I} in **2** was further confirmed by cyclic voltammetry, in which the oxidation potential of the Cu^{I}/Cu^{II} couple was detected at +0.60 V in CH_3CN, whereas the free host **2**

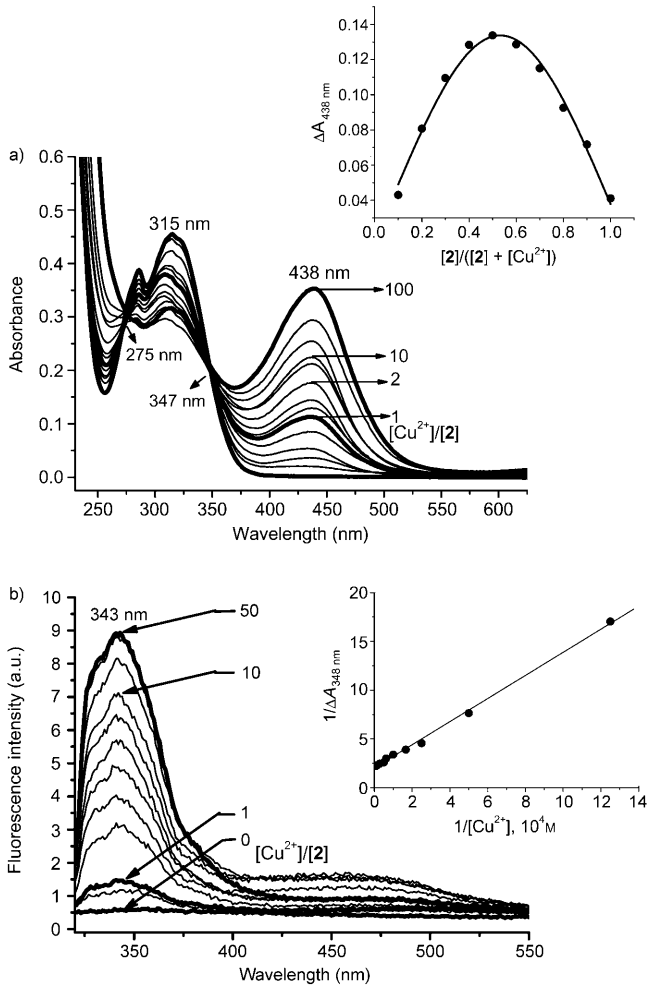


Figure 5. a) UV/Vis and b) fluorescence emission spectra of ligand **2** with various equivalents of $Cu(ClO_4)_2$ in CH_3CN (20 μM, excitation wavelength = 285 nm). The inset in a) is a Job plot of a 1:1 complex of **2** and Cu^{II}, in which the difference in absorbance at 438 nm was plotted against the mole fraction of **2** at a total concentration of 20 μM in CH_3CN. The inset in b) is a Benesi–Hildebrand plot of **2** with $Cu(ClO_4)_2$ in CH_3CN (20 μM), in which the reciprocal of the differences in absorption at 438 nm were plotted against the reciprocal concentrations of Cu^{II} (intercept = 2.03, slope = 1.18×10^{-4}, $K_a = 1.72\times10^4\,M^{-1}$, $R^2 = 0.9976$).

showed an oxidation potential of +0.83 V versus an Ag/AgCl electrode (see Figure S9 in the Supporting Information).[19b]

The monomer emission band ($\lambda_{max} = 343$ nm) of ligand **2** dramatically increased upon adding Cu^{II}. The observation of such a chelation-enhanced fluorescence (CHEF) is mainly because metal ion complexation helps to lock the conformational movement of β-amino-α,β-unsaturated ketones. It is expected that such a complexation should also cause the two distal naphthalenes to overlap more and lead to an enhancement of the excimer emission. However, the enhancement of excimer emission was unexpectedly small, which was presumably due to an inner filter effect[17] of the broad absorption band at 438 nm. From the titration experiments, the K_a[20] value of ligand **2** with Cu^{II} was calculated to be $17\,200\,M^{-1}$ and the binding ratio calculated from the Job plot was 1:1 (Figure 5). The binding ability of ligand **2** towards Cu^{II} was eight times greater than that of ligand **1**. Furthermore, the ESI^+ mass spectrum showed a peak at *m*/*z* 905.4 for $C_{56}H_{46}CuN_2O_6$ (calculated *m*/*z* 905.3), which supported the formation of **2**·Cu^I.

In addition to the UV/Vis absorption and fluorescence changes, ^1H NMR titration spectra of **2** with Cu^{II} also support the observation that the β-amino-α,β-unsaturated ketones of ligand **2** participate in the autoreduction of Cu^{II} and its complexation with Cu^I. Figure 6 shows the ^1H NMR spectra of ligand **2** in $[D_3]CH_3CN$ in the presence of different concentrations of Cu^{II} ions. The proton signals were still relatively sharp, even after adding more than one equivalent of paramagnetic Cu^{II} ions, which implied that the Cu^{II} ions had been reduced to diamagnetic Cu^I. All of the proton signals were affected upon adding Cu^{II}, especially the upfield shift ($\Delta\delta \approx 0.51$ ppm) of the methylene bridge protons at $\delta =$ 4.84 ppm and the downfield shift ($\Delta\delta \approx 0.50$ ppm) of the α,β-unsaturated protons (H_b) at $\delta = 6.86$ ppm. In addition, the amino protons (H_c and H_d) disappeared, and this was accompanied by the formation of a 1:1:1 triplet signal at $\delta =$ 6.70 ppm with $J = 53$ Hz, which was probably due to the splitting of a metal-bound nitrogen atom.[21] The phenolic OH signal was buried in the multiplet of naphthyl protons at approximately 8.3–8.4 ppm, so it was difficult to monitor its changes. Based on all of the information obtained from ^1H NMR, UV/Vis and fluorescence spectra as well as cyclic voltammograms upon adding Cu^{II} ions to ligand **2**, we propose that the β-amino-α,β-unsaturated ketone moieties coordinated with Cu^I ions and prefer to adopt a tetrahedral coordination geometry.[22] The phenolic OH on the lower rim of calix[4]arene might also assist in the coordination with Cu^I (see Scheme 2). In this way, the cone conformation of calix[4]arene was distorted by the tetrahedral geometry to make the two pendant naphthalenes overlap, resulting in the enhancement of the excimer emission. To clarify whether ligands **1** and **2** can bind to Cu^I ions directly, we have also studied their binding abilities towards Cu^I ions by using UV/Vis and fluorescence titration experiments; however, no change was observed (Figure S10 in the Supporting Information), suggesting that only the oxidised, but not the free phenols, help to trap the Cu^I ions.

To study the ditopic binding ability of ligand **2**, from the outset we investigated its recognition properties towards various anions (F^-, Cl^-, Br^-, I^-, HSO_4^-, $H_2PO_4^-$, NO_3^- and CH_3COO^-) using tetrabutylammonium as a countercation in CH_3CN. No significant changes in the absorption or fluorescence of **2** were observed when anions were added. However, it was expected that the copper complex of ligand **2** might be able to show ditopic binding behaviour towards anions. Indeed, the **2**·Cu^I complex showed selective ditopic behaviour with CH_3COO^- and F^- anions (Figure S11 in the Supporting Information). The monomer emission of **2**·Cu^I was further enhanced by the addition of CH_3COO^-, whereas no excimer emission was observed, as shown in Figure 7a. The absorption band at 438 nm for **2**·Cu^I was broadened and

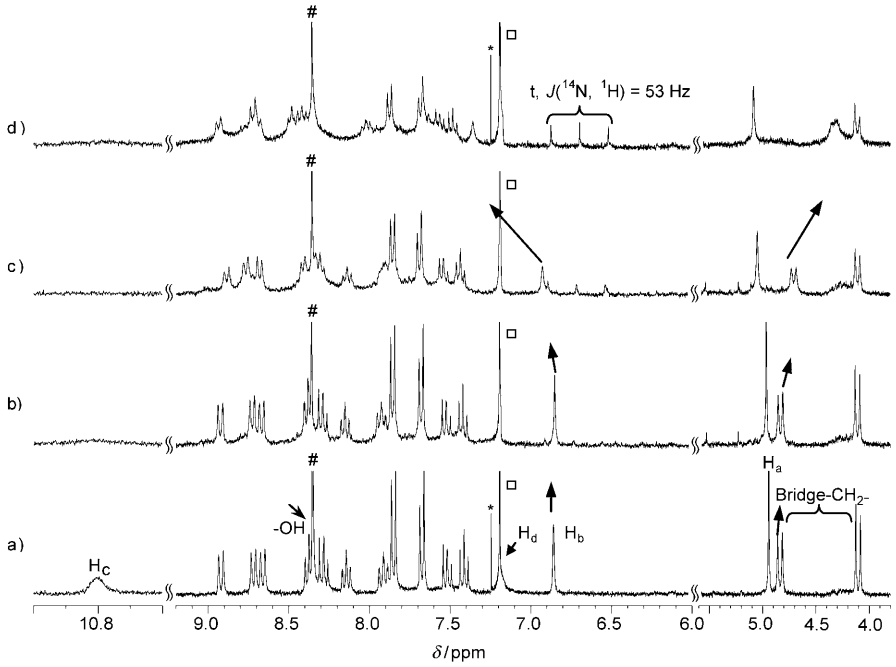
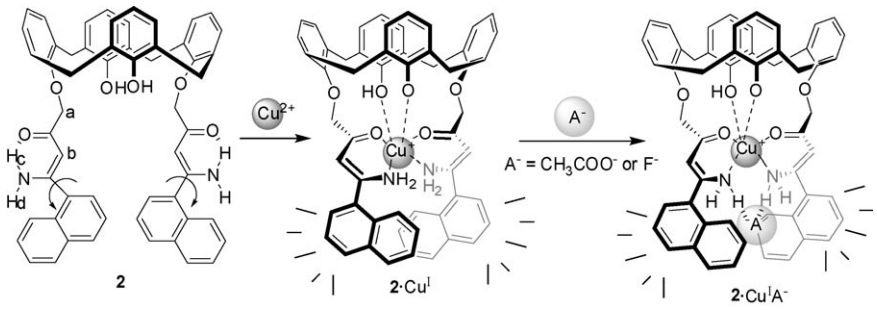


Figure 6. ^{1}H NMR spectra of ligand **2** in [D$_3$]CH$_3$CN (0.65 mM) in the presence of different amounts of Cu(ClO$_4$)$_2$: a) 0, b) 0.5, c) 1.0 and d) 2.0. (#=internal $CHCl_3$ signal, □=external standard $CHCl_3$ and *=the signal due to an impurity).



Scheme 2. Possible binding mode of **2**·Cu^I and **2**·Cu^{I}A$^-$.

enhanced by the addition of CH_3COO^- (Figure S12 in the Supporting Information). The enhancement of UV/Vis absorption and monomer emission of complex **2**·Cu^I by the addition of anions suggests that the anions may be bound both through the hydrogen bonds of the acidic protons on the nitrogen atoms of the β-amino-α,β-unsaturated ketone moieties, as well as through the electrostatic force between the ion pairs.[23] The anion that was bound to with the amino group of **2**·Cu^I should reduce its participation in PET quenching of the naphthalene, and thus enhance the fluorescence emission. Moreover, no excimer emission was observed owing to the insertion of anions that caused the two naphthalenes to move away from each other. Similarly, the fluorescence intensity of **2**·Cu^I was enhanced by the addition of F^- (Figure 7b), but to a lesser extent.

The absorption band of **2**·Cu^I at 441 nm was also broadened and enhanced by the addition of F^- ions (Figure S14 in the Supporting Information). From these titration experiments, the association constants of **2**·Cu^I with CH_3COO^- and F^- were calculated to be 159000 and 59900 M^{-1}, respectively (Figures S13 and S15 in the Supporting Information).[20] The ditopic complexation was further supported by visualising the colour change from yellow to beige (Figure 8). We had hoped to obtain structural information of the ditopic complex by using ^{1}H NMR titration results; however, upon addition of AcO^- into the **2**·Cu^I solution, some precipitates immediately formed (even though the concentration was as low as 0.65 mM in CD_3CN), therefore, the chemical shift changes could not be observed. It should be noted that no such precipitation was observed in the UV/Vis titration experiments of **2**·Cu^I with AcO^-.

We also investigated the ditopic binding properties of model compound **4**, which also showed selective binding with Cu^{II} (Figure S16 in the Supporting Information). However, its absorption spectra, upon adding various amounts of Cu^{II}, showed a hypochromic effect and a hypsochromic shift (14 nm) with isosbestic points at 275 and 345 nm. The fluorescence intensity of **4** was gradually enhanced upon adding Cu^{II} ions (Figure 9). From this titration experiment, the association constant[20] for **4**·Cu^I was calculated to be 30600 M^{-1} and the binding ratio calculated from the Job plot was 1:1 (Figure S17 and 18 in the Supporting Information). However, in sharp contrast with ligand **2**, compound **4** did not show the broad absorption band at 441 nm, which is characteristic of a MLCT band of the tetrahedral complex between Cu^I and the oxidised **2**. For compound **4**, reduction of Cu^{II} to Cu^I was also confirmed by cyclic voltammetry, which showed an oxidation potential of Cu^I to Cu^{II} at +0.57 V (Figure S19 in the Supporting Information). Note that in addition to the phenolic OH,[14] the amino groups of β-amino-α,β-unsaturated ketones of calix[4]arene **2** might also be involved in the autoreduction of Cu^{II}.[24] The binding of Cu^I with **4** was supported by ^{1}H NMR titration experiments (Figure S20 in the Supporting Information). Furthermore, the formation of **4**·Cu^I was confirmed by analysis of the ESI$^+$ mass spectrum, which showed a peak at m/z 393.9 for $C_{22}H_{21}CuNO_2$ (**4**·Cu^I).

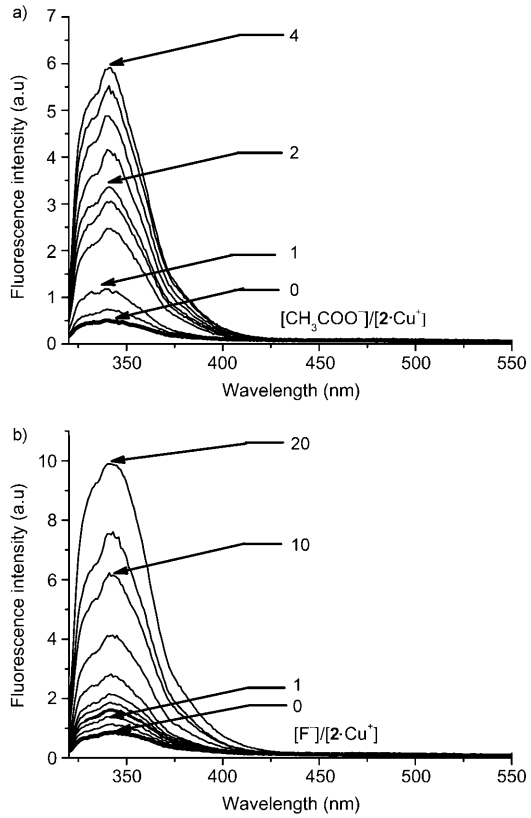


Figure 7. Fluorescence spectra of **2**·Cu^{I} with various amounts of a) CH_3COO^- and b) F^- in CH_3CN (20 μM, excitation wavelength = 285 nm).

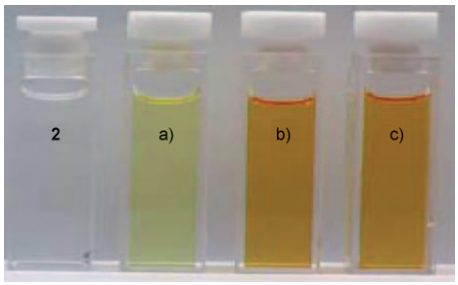


Figure 8. Visual changes for ligand **2** in CH_3CN (20 μM) in the presence of 10 equivalents of a) Cu^{II}, b) Cu^{II}/CH_3COO^- and c) Cu^{II}/F^-.

Although ligand **4** has a higher binding constant towards Cu^{II} than ligand **2**, no selective ditopic recognition of **4**·Cu^{I} with any anions was observed.

Finally, the formation of Cu^{I} species in the titration of ligands **1** and **2** with Cu^{II} ions was supported by EPR spectroscopy in CH_3CN at 77 K, which displayed a 79 (**1**/Cu^{II} = 1:1) and 100% (**2**/Cu^{II} = 0.5:1) decrease in the intensity of the initial Cu^{II} EPR signal (Figure 10).

To confirm whether the two hydroxyl groups on the lower rim of calix[4]arene **2** participated in the complexation with Cu^{I}, we also synthesised 25,27-bis{[4-amino-4-(1-naphthyl)-2-oxo-3-butenyl]oxy}-26,28-dipropoxycalix[4]arene (**6**) in

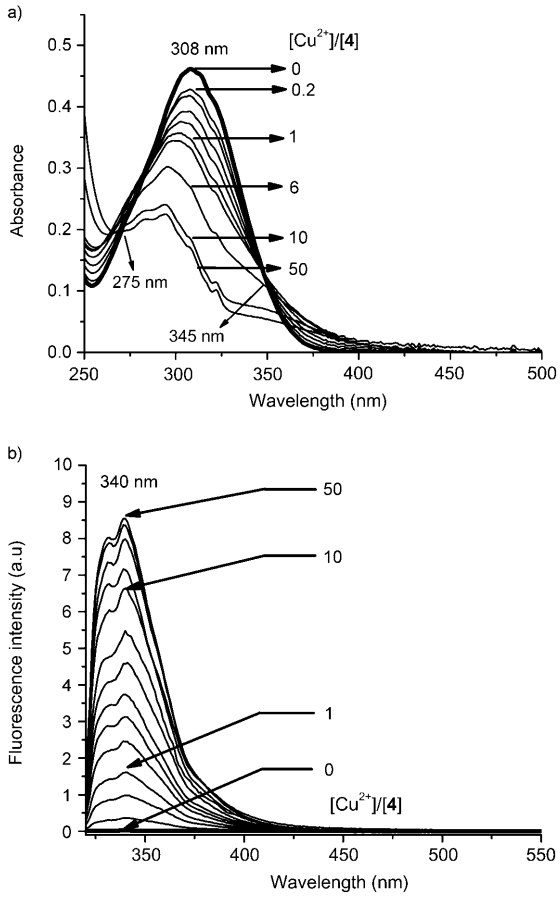


Figure 9. a) UV/Vis and b) fluorescence emission spectra of **4** with various amounts of $Cu(ClO_4)_2$ in CH_3CN (20 μM, excitation wavelength = 285 nm).

which the two hydroxyl groups were converted to propyl ethers.[25] The syntheses of calix[4]arenes 25,27-bis{[3-(1-naphthyl)-5-isoxazolyl]methoxy}-26,28-dipropoxycalix[4]arene (**5**) and **6** are shown in Scheme 3. The propyl ether protected calix[4]arene **5** was obtained by the alkylation of phenolic OH groups on calix[4]arene **1** in the presence of sodium hydride and propyl iodide. The $[Mo(CO)_6]$-mediated ring-opening reaction of calix[4]arene **5** gave the target calix[4]arene **6** in 30% yield.

The UV/Vis spectra of calix[4]arene **6**, upon adding various equivalents of Cu^{II}, showed only a small bathochromic shift (λ_{max} from 308 to 310 nm in Figure 11a). This observation is quite different from the large bathochromic shift observed for ligand **2** (Figure 5a), as well as the hypochromic and hypsochromic (blue) shifts observed for model compound **4** (Figure 9a) when they were treated with Cu^{II}. Furthermore, both the monomer (λ_{max} = 341 nm) and excimer (λ_{max} = 476 nm) emission bands of calix[4]arene **6** dramatically increased upon adding Cu^{II} ions (Figure 11b). The excimer emission band (λ_{max} = 476 nm) could be clearly observed because there was no MLCT absorption band at approximately 430 nm, and therefore, no disturbance by an inner filter effect (see above). Based on these results, we

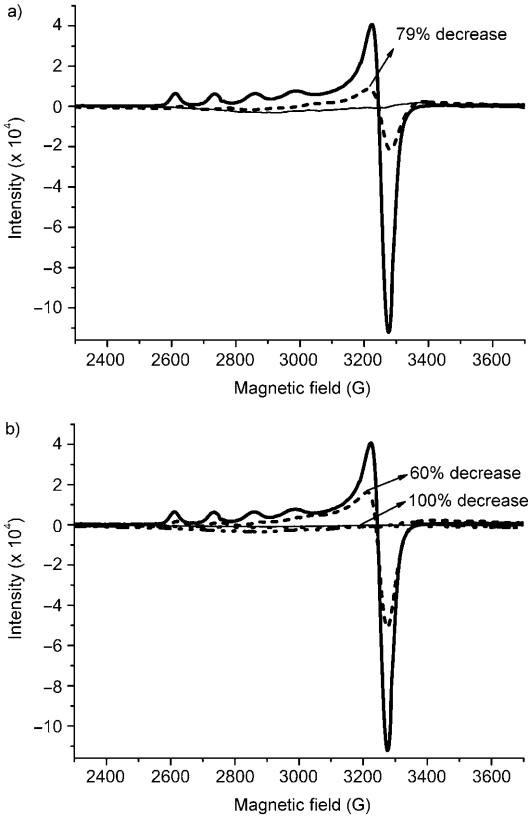
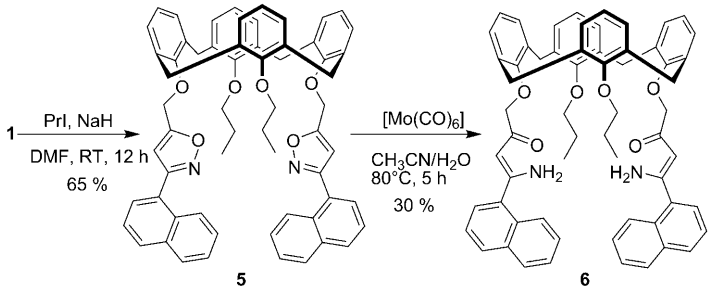


Figure 10. EPR spectra of $Cu(ClO_4)_2$ (5 mM) after adding different amounts of a) ligand **1** (——$=Cu^{2+}$, – – –$=Cu^{2+}+1.0$ equiv of **1** and ——=**1**) and b) ligand **2** in CH_3CN (——$=Cu^{2+}$, – – –$=Cu^{2+}+0.2$ equiv of **2**, –•–•–$=Cu^{2+}+0.5$ equiv of **2**, -----$=Cu^{2+}+1.0$ equiv of **2** and ——= **2**) at 77 K, recorded at X-band with microwave power = 20 mW and microwave frequency = 9.5 GHz.



Scheme 3. Synthesis of calix[4]arenes **5** and **6**.

conclude that the two hydroxyl groups of ligand **2** must have participated in the complexation with Cu^{I} (as depicted in Scheme 2), and resulted in the formation of the MLCT absorption band around 430 nm. For protected calix[4]arene **6**, complexation with Cu^{II} can be achieved by coordination of the two α,β-unsaturated β-aminoketones. Accordingly, the conformational freedom near the fluorophores of **6** was locked, which led to the dramatic enhancement of its fluorescence intensity. From the fluorescence titration experiments, the K_a value of calix[4]arene **6** with Cu^{II} was calculated to be 18000 M^{-1} by using a Benesi–Hildebrand plot.

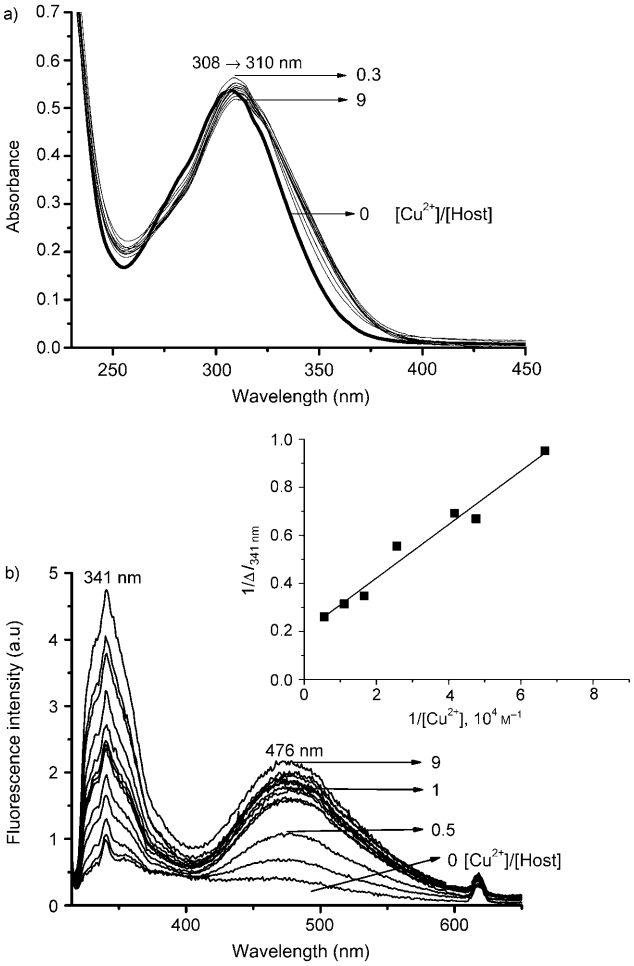


Figure 11. a) UV/Vis and b) fluorescence emission spectra of **6** (20 μM) with various equivalents of $Cu(ClO_4)_2$ in cosolvent $CHCl_3/CH_3CN$ (v/v = 1:93, excitation wavelength = 308 nm). The inset in b) is a Benesi–Hildebrand plot of **6** with $Cu(ClO_4)_2$ in cosolvent $CHCl_3/CH_3CN$ (v/v = 1:93), in which the reciprocal of the differences in fluorescence intensity at 341 nm were plotted against the reciprocal of the concentrations of Cu^{II} (intercept = 0.1996, slope = 1.11×10^{-5}, $K_a = 1.8\times10^4$ M^{-1} and $R^2 = 0.965$).

Conclusion

We have designed and synthesised highly Cu^{II} selective, chromogenic and fluorogenic calix[4]arene chemodosimeters **1** and **2**. Upon titration with Cu^{II}, ligand **1** showed a dramatic fluorescence quenching phenomenon (on–off), whereas **2** showed a strong enhancement in fluorescence (off–on) due to complexation-induced rigidity of the molecules and diminished PCT. It is important to note that autoreduction of Cu^{II} to Cu^{I} was observed during complexation of both ligands **1** and **2**. Furthermore, ditopic behaviour was observed for the calix[4]arene complex **2**·Cu^{I}, which showed further enhancement of its fluorescence intensity upon complexation with anions such as acetate or fluoride. Although model

compound **4** also showed selective binding with Cu^{II}, which was accompanied by autoreduction of Cu^{II} to Cu^{I}, complex **4**·Cu^{I} did not show any ditopic behaviour towards anions.

Experimental Section

General information: ^1H and ^{13}C NMR spectra were recorded on 300 and 500 MHz instruments. Mass spectra were obtained on a GC–MS instrument. HRMS were recorded on a high-performance mass spectrometer. Column chromatography was performed by using SiO_2 (silica gel 60, 230–400 mesh). UV/Vis spectra were recorded by using a spectrophotometer with a diode array detector with the resolution set at 1 nm. Fluorescence spectra were recorded on a luminescence spectrophotometer. Cyclic voltammetry was performed on solutions in CH_3CN by using platinum working and counter electrodes, a Ag/AgCl reference electrode and Bu_4NPF_6 as the electrolyte. Electrolysis was performed by replacing the platinum electrode with a platinum coil.

Synthesis of 1: Excess triethylamine (4 mol equiv) was slowly added to a well-stirred solution of 25,27-dipropargyloxy-26,28-dihydroxycalix[4]arene (1 mol equiv) and 1-naphthyl hydroximoyl chloride (3.5 mol equiv) in toluene. The reaction mixture was stirred at reflux for 12 h, diluted with dichloromethane, washed with water and dried over $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified over a silica gel column, which gave the cycloadduct **1** as a yellow solid (80%). M.p. 196–198°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.37$ and 4.26 ($J = 13.2$ Hz, 8H; ABq), 5.21 (s, 4H), 6.65–6.72 (m, 6H), 6.83 (d, $J = 7.5$ Hz, 4H), 7.06 (d, $J = 7.5$ Hz, 4H), 7.22–7.27 (m, 2H), 7.38–7.60 (m, 8H), 7.81–7.84 (m, 4H), 8.31–8.34 ppm (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 31.2$, 68.1, 105.8, 119.3, 125.1, 125.5, 126.0, 126.2, 126.2, 127.0, 127.8, 127.9, 128.5, 128.6, 129.2, 130.3, 130.7, 133.0, 133.7, 151.2, 152.9, 162.6, 166.9 ppm; FAB-MS: m/z: 840 $[M+2]^+$; HRMS (FAB) calcd for $C_{56}H_{42}N_2O_6$: 838.3045; found: 838.3056.

X-ray crystal data for 1: $C_{57.5}H_{43.5}Cl_{4.5}N_2O_6$; $M = 1017.97$; monoclinic; $a = 38.7769(19)$, $b = 17.9986(9)$, $c = 15.1865(7)$ Å; $\alpha = 90$, $\beta = 112.227(1)$, $\gamma = 90°$; $V = 9811.5(8)$ Å^3; space group $C2/c$; $Z = 8$; $\rho_{calcd} = 1.378$ Mg m^{-3}; crystal dimensions $0.30 \times 0.25 \times 0.22$ mm^3; $T = 150(2)$ K; λ ($Mo_{K\alpha}$) $= 0.71073$ Å; $\mu = 0.324$ mm^{-1}; 38976 reflections collected; 8647 independent reflections ($R_{int} = 0.0660$); 644 parameters refined on F^2; $R_1 = 0.1424$, $wR_2[F^2] = 0.3038$ (all data); GOF on $F^2 = 1.030$; $\Delta\rho_{max} = 1.536$ e Å^{-3}. CCDC-707767 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of 2: A solution of **1** (1 mol equiv) and molybdenum hexacarbonyl (1.5 mol equiv) in CH_3CN (18 mL) containing water (3 drops) was heated at reflux at 80°C for 5 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography to give the expected product **2** as a yellow solid (52%). M.p. 212–214°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.05$ (d, $J = 13.0$ Hz, 4H), 3.80 (d, $J = 13.0$ Hz, 4H), 4.20 (s, 4H), 6.11 (s, 2H), 6.25 (brs, 2H), 6.57 (t, $J = 7.4$ Hz, 2H), 6.61–6.66 (m, 4H), 6.75 (d, $J = 7.4$ Hz, 4H), 6.88 (d, $J = 7.4$ Hz, 2H), 7.11 (t, $J = 7.8$ Hz, 2H), 7.30–7.38 (m, 4H), 7.58 (d, $J = 6.2$ Hz, 4H), 7.81 (d, $J = 8.2$ Hz, 4H), 8.30 (d, $J = 8.4$ Hz, 2H), 10.38 ppm (s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 30.9$, 78.8, 93.7, 118.6, 124.9, 125.2, 125.4, 125.6, 126.0, 126.3, 127.5, 128.0, 128.2, 128.8, 129.4, 130.0, 132.8, 133.4, 135.7, 151.7, 152.6, 163.4, 191.2 ppm; FAB-MS: m/z: 844 $[M+2]^+$; HRMS (FAB) calcd for $C_{56}H_{46}N_2O_6$: 842.3356; found: 842.3346.

X-ray crystal data for compound 2: $C_{58}H_{49}N_3O_6$; $M = 884.00$; triclinic; $a = 11.0578(5)$, $b = 14.6102(5)$, $c = 16.1385(7)$ Å; $\alpha = 114.299(2)$, $\beta = 91.656(2)$, $\gamma = 94.592(3)°$; $V = 2363.18$ Å^3; space group $P\bar{1}$; $Z = 2$; $\rho_{calcd} = 1.242$ Mg m^{-3}; crystal dimensions $0.25 \times 0.20 \times 0.10$ mm^3; $T = 295(2)$ K; λ ($Mo_{K\alpha}$) $= 0.71073$ Å; $\mu = 0.081$ mm^{-1}; 12911 reflections collected; 7918 independent reflections ($R_{int} = 0.0786$); 605 parameters refined on F^2; $R_1 = 0.2745$; $wR_2[F^2] = 0.3748$ (all data); GOF on $F^2 = 1.090$; $\Delta\rho_{max} = 0.502$ e Å^{-3}. CCDC-707768 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of 3: A mixture of 1,3-dimethyl-2-prop-2-ynyloxybenzene (1 mol equiv), 1-naphthyl hydroximoyl chloride (1.5 mol equiv) and excess triethylamine (4 mol equiv) in toluene was heated at reflux for 12 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography to give compound **3** as a brownish-yellow viscous liquid (69%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.36$ (s, 6H), 5.05 (s, 2H), 6.70 (s, 1H), 7.00–7.08 (m, 3H), 7.53–7.58 (m, 3H), 7.73 (d, $J = 7.0$ Hz, 1H), 7.91–7.98 (m, 2H), 8.36–8.39 ppm (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 16.7$ (CH_3), 65.1 (CH_2), 105.4 (CH), 125.1 (CH), 125.6 (CH), 126.0 (CH), 126.7 (CH), 127.1 (C_q), 127.5 (CH), 128.2 (CH), 128.9 (CH), 129.5 (CH), 130.7 (C_q), 131.4 (CH), 134.2 (C_q), 155.6 (C_q), 163.1 (C_q), 168.6 ppm (C_q); EIMS: m/z: 329 $[M]^+$; HRMS: m/z: calcd for $C_{22}H_{19}NO_2$: 329.1416; found: 329.1417.

Synthesis of 4: A solution of **3** (1 mol equiv) and molybdenum hexacarbonyl (1.5 mol equiv) in CH_3CN (18 mL) containing water (3 drops) was heated at reflux at 80°C for 3 h. After the reaction was complete, the solvent was removed under reduced pressure, and the residue obtained was purified by column chromatography to give the expected product **4** in 76% yield as a yellow solid. M.p. 101–103°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.2$ (s, 6H), 4.37 (s, 2H), 5.53 (brs, 1H), 5.98 (s, 1H), 6.89–7.01 (m, 3H), 7.48–7.61 (m, 4H), 7.88–7.94 (m, 2H), 8.25–8.28 (m, 1H), 10.31 ppm (brs, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$,): $\delta = 16.3$ (CH_3), 75.4 (CH2), 94.1 (CH), 124.0 (CH), 125.0 (CH), 125.0 (CH), 125.6 (CH), 126.4 (CH), 127.0 (CH), 128.5 (CH), 128.8 (CH), 130.1 (CH), 130.8 (C_q), 133.7 (C_q), 135.4 (C_q), 155.4 (C_q), 163.1 (C_q), 195.1 ppm (C_q); EIMS: m/z: 331 $[M]^+$; HRMS: m/z: calcd for $C_{22}H_{21}NO_2$: 331.1572; found: 331.1567.

Synthesis of 5: Propyl iodide (20 mol equiv) was added to a well-stirred solution of **1** (1 mol equiv) and NaH (30 mol equiv) in DMF (25 mL) and was stirred for 12 h at room temperature. When the reaction was complete, water was added to quench the reaction. The solution was diluted with CH_2Cl_2 and extracted with water to remove DMF and base, and the organic layer was dried over $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified over a silica gel column, which gave the adduct **5** in 65% yield as a white solid. M.p. 86–88°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.81$ (t, $J = 7.4$ Hz, 6H), 1.73–1.80 (m, 4H), 3.14 (d, $J = 13.5$ Hz, 4H), 3.62 (t, $J = 7.2$ Hz, 4H), 4.30 (d, $J = 13.5$ Hz, 4H), 5.50 (s, 4H), 6.15–6.28 (m, 6H), 6.43 (s, 2H), 6.90 (t, $J = 7.4$ Hz, 2H), 7.03 (d, $J = 7.4$ Hz, 4H), 7.43–7.48 (m, 6H), 7.62 (d, $J = 6.0$ Hz, 2H), 7.82–7.88 (m, 4H), 8.16–8.19 ppm (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): 10.5 (CH_3), 23.2 (CH_2), 31.2 (CH_2), 64.8 (CH_2), 77.3 (CH_2), 106.0 (CH), 122.3 (CH), 123.2 (CH), 125.2 (CH), 125.6 (CH), 126.2 (CH), 126.9 (CH), 127.6 (CH), 127.6 (CH), 128.4 (CH), 129.1 (CH), 130.1 (CH), 131.0 (C_q), 133.1 (C_q), 133.7 (C_q), 137.1 (C_q), 155.4 (C_q), 155.7 (C_q), 162.4 (C_q), 169.0 ppm (C_q); FAB-MS: m/z: 923 $[M+H^+]$.

Synthesis of 6: A solution of compound **5** (1 mol equiv) and molybdenum hexacarbonyl (3 mol equiv) in CH_3CN (10 mL) containing water (3 drops) was heated at reflux at 80°C for 5 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography to give the expected product **6** as a yellow solid (30%). M.p. 240–242°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = -0.27$ (t, $J = 6.8$ Hz, 6H), 1.32–1.40 (m, 4H), 3.07 (d, $J = 13.7$ Hz, 4H), 3.55 (t, $J = 8.0$ Hz, 4H), 4.20 (s, 4H), 4.32 (d, $J = 13.7$ Hz, 4H), 5.23 (brs, 2H), 5.94–5.96 (m, 6H), 6.16 (t, $J = 7.6$ Hz, 2H), 6.78 (t, $J = 7.4$ Hz, 2H), 6.94 (d, $J = 7.4$ Hz, 4H), 7.25–7.48 (m, 8H), 7.79–7.83 (m, 4H), 8.03–8.06 (m, 2H), 10.27 ppm (brs, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 8.73$ (CH_3), 22.7 (CH_2), 31.0 (CH_2), 76.2 (CH_2), 78.8 (CH_2), 94.2 (CH), 121.6 (CH), 122.6 (CH), 124.9 (CH), 125.0 (CH), 125.4 (CH), 126.4 (CH), 127.0 (CH), 127.5 (CH), 128.3 (CH), 129.0 (CH), 129.8 (CH),130.0 (CH), 133.0 (C_q), 133.5 (C_q), 135.1 (C_q), 135.4 (C_q), 136.8 (C_q), 154.7 (C_q), 157.8 (C_q), 163.3 ppm (C_q); FAB-MS: m/z: 950 $[M+Na^+]$.

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