Revisiting β-dicyanovinyl substituted calix[4]pyrrole : toward the chemodosimetric detection of hydrazine in solution

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Abstract

Calix[4]pyrrole derivatives are usually used to recognize charged species or polar guests through non-covalent interactions, but the chemodosimetric approach remains scarce in the literature. In this study, the selective chemodosimetric detection and quantification of hydrazine, a hazardous pollutant commonly used in industy, was performed using UV-spectroscopy with a repurposed β-dicyanovinyl substituted calix[4]pyrrole sensor. The selectivity of the chemodosimeter towards hydrazine was evaluated in acetonitrile with various nucleophiles (nitrogen-containing compounds and a thiol). In addition, the influence of several parameters (time, water content, and temperature) on hydrazine detection by the sensor was evaluated. This study allows for the sensing of hydrazine with a limit of detection (LOD) of 1.3 mg/L and a linear response in the 10-1000 µM range. The ability to detect hydrazine with the naked eye has also been demonstrated. This paper reports one of the first chemodosimetric approach employed with calix[4]pyrrole to detect and quantify a neutral molecule, namely hydrazine.

Introduction

Hydrazine, a small covalent molecule, is regarding as a hazardous environmental pollutant and being a carcinogenic chemical has proved to be highly toxic for both humans and animals.[1] The continuous exposure to hydrazine leads to nose, throat, and eye irritation, dizziness, nausea, pulmonary edema, etc., which in turn proves fatal for kidneys, liver and central nervous system in human beings.[2] As a matter of the fact, U.S based Environmental Protection Agency (EPA) has marked hydrazine as potential carcinogen and fixed an Immediately Dangerous to Life and Health (IDLH) value of 50 ppm in air.[3] By virtue of widespread use of hydrazine in industries (pharmaceuticals, polymers, dyes etc.)[4], hydrazine pollution in water and air has become a major concern globally. Indeed, it was reported that upon exposure to about 0.1 ppm hydrazine in air, the urine of Japanese workers contains an average of 2.7 ppm of hydrazine.[5] It is also expected to find concentrations above 10 ppm in urine in case of an event-level exposure.[6] Thus, there arises a need to efficiently monitor the level of hydrazine in air, water, human fluids and other related systems. To date, numerous conventional analytical methods have been employed for the detection of hydrazine like chromatography, spectrophotometric flow injection, and electroanalytical methods.[7–9] However, naked eye and UV-visible detection are particularly attractive because they are generally cheap, fast, selective, and reliable, even if the detection limit is not as low as other methods such as molecular fluorescence spectroscopy[10–13]. Analytical methods utilizing optical signatures and supramolecular sensors/receptors have been of great interest to the scientific community in recent years.[14,15] Among the diverse supramolecular receptors available, the tetrapyrollic macrocyclic receptor known as calix[4]pyrrole (C4P) has shown a promising role in the recognition of diverse analytes[16]. C4P possess a built-in recognition site able to recognize anions or polar guests, while its functionalization at the level of meso-carbon or pyrrole allow to achieve cation or ion-pair recognition throught non-covalent interactions.[17–19] To date, the use of calix[4]pyrrole scaffold for chemodosimetric detection (i.e. detection with significant chemical transformation involving both breaking and forming of the covalent bonds[20]) of non-charged molecules is still scarce[21]. In this study, we repurposed a β-dicyanovinyl substituted C4P preliminary designed for the recognition of cyanide anion in order to achieve the naked eyed and spectroscopic detection of hydrazine in acetonitrile (ACN) and acetonitrile-water mixture.

Material and Methods

NMR spectra were recorded on a Bruker Ascend 400 spectrometer operating at 400 MHz and 101 MHz for ^{1}H and ^{13}C respectively. Traces of residual solvent were used as the internal standard. High-resolution mass spectrometry spectra (HRMS) were recorded in the positive mode using an Agilent 6540 Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) LC/MS system equipped with an Agilent Jet Stream dual electrospray source. UV-Vis measurements were performed at a fixed temperature using a Varian Cary 3500 UV-Vis spectrophotometer equipped with a compact Peltier apparatus. A quartz suprasil 100-QS TO 10 mm pathlength cuvette was used.

Synthetic procedure for compound 3: To a clear low melting mixture (5.00 g) of *L*-(+)-tartaric acid (TA) and N,N'-dimethyl urea (DMU) in the ratio of 3:7 at 70 ^{o}C, was added freshly distilled pyrrole (5.00 ml, 72.07 mmol, 1 equiv) and acetone (26.69 ml, 360.34 mmol, 5 equiv). The reaction mixture was stirred at 70 ^{o}C for 4-5 h and was monitored by TLC. After the completion of reaction, the warm reaction mixture was diluted with water (20 ml). The reaction mixture was cooled to room temperature, filtered through a sintered glass funnel and the solid material was washed with water (4 x 20 mL). The crude product was purified by silica gel column chromatography using (5% EtOAc:petroleum ether). The first eluted fraction was the desired compound **3** (4.64 g, 60% yield, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 4H), 5.93 (d, J = 2.4 Hz, 8H), 1.54 (s, 24H).^{13}C NMR (101 MHz, $CDCl_3$) δ 138.67, 102.93, 35.61, 29.09; HRMS (ESI, Q-TOF) m/z: calculated for $C_{28}H_{36}N_4$ $[M+H]^+$ 429.3013, found: 429.3021**.** The spectral data is in accordance with the literature[22].

Synthetic procedure for compound 4: In a dried two-necked 50 ml round bottomed flask, $POCl_3$ (0.52 ml, 5.60 mmol) was added dropwise at 0 °C under an inert nitrogen atmosphere to dry DMF (0.43 ml, 5.60 mmol) with vigorous stirring. After some time, dry CH_2Cl_2 (5 ml) was added to this reaction mixture and left for stirring at 0 °C for 45 minutes under inert atmosphere to obtain a Vilsmeier reagent. This prepared reagent was later on added dropwise at 0º C under inert atmosphere to a stirred solution of compound 3 (2.40 g, 5.60 mmol) in dry CH_2Cl_2 (100 ml) prepared in another two-necked 250 ml round bottomed flask. The solution turns dark red and was left for stirring at 0 °C for 2 h. After the completion of the reaction, the reaction mixture was thoroughly washed with saturated aqueous Na_2CO_3 and NaCl. The organic contents were extracted in CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated over vacuum to afford crude red solid. This crude mixture was later on subjected to column chromatography (SiO_2, CH_2Cl_2 followed by 5% CH_2Cl_2:ethyl acetate) to get pure **4** (0.537 g, 21% yield, white solid). ^1H NMR (500 MHz, $CDCl_3$) δ 10.09 (s, 1H), 7.35 (s, 2H), 6.96 (s,1H), 6.47 (s,1H), 6.0 – 5.83 (m, 7H), 1.73 (s, 6H), 1.53 (d, s, 12H), 1.49 (s, 6H). The spectral data is in accordance with the literature[23].

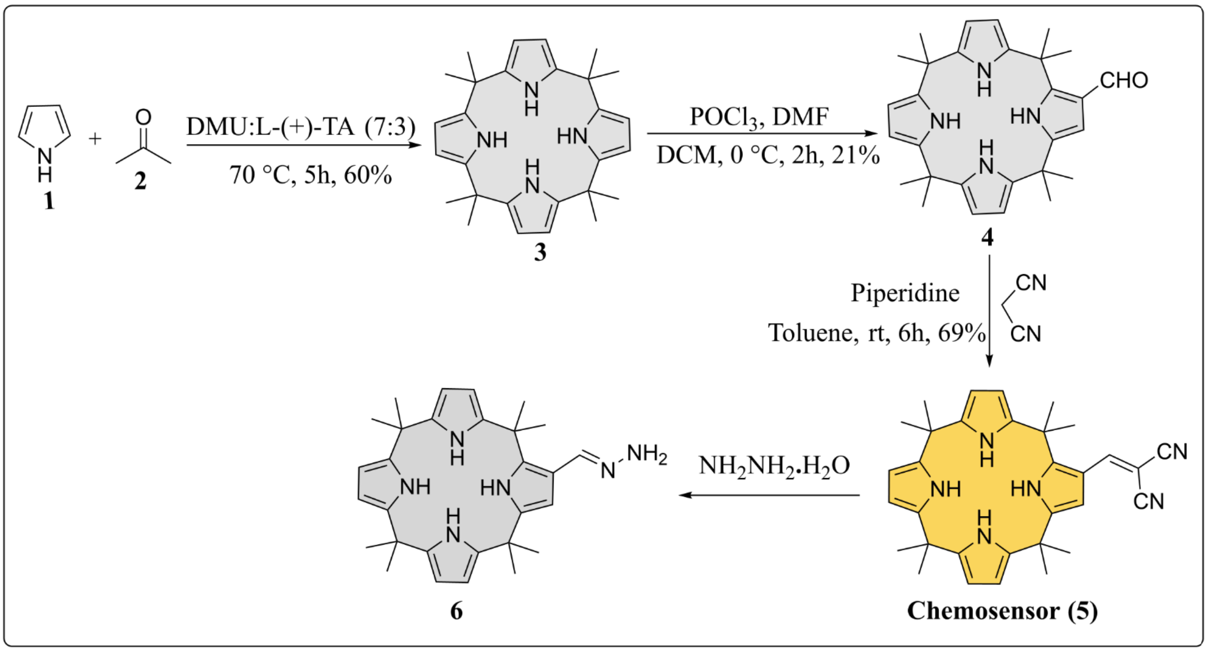
Synthetic procedure for chemodosimeter 5: In a dried two-necked 50 ml round bottomed flask, compound **4** (0.50 g, 1.10 mmol) and malononitrile (89 µl, 1.60 mmol) were dissolved in 18 ml of toluene at room temperature. To this stirred solution, piperidine (0.15 ml, 1.52 mmol) was added and left for stirring at room temperature for 6 h. After the reaction gets completed, the organic contents were extracted in CH_2Cl_2, dried over anhydrous Na_2SO_4, and concentrated over vacuum to afford the crude mixture. This crude mixture was then subjected to column chromatography (SiO_2, pure CH_2Cl_2) to afford pure sensor **5** (381 mg, 69% yield) as a yellowish solid. ^1H NMR (400 MHz, CDCl3) δ 7.95 (s, 1H), 7.42 (bs, 1H), 7.26 (bs, 1H), 7.20 (bs, 1H), 6.95 (d, J=2.7 Hz, 1H), 6.88 (bs,1H), 5.95-6.02 (m,4H), 5.91 (m,1H), 5.85 (m, 1H), 1.68 (s, 3H), 1.55 (s, 3H), 1.53 (s, 3H), 1.50 (s, 3H). The spectral data is in accordance with the literature[24].

UV-spectroscopy analysis : For UV spectroscopy analysis, a stock solution of sensor **5** was prepared in pure acetonitrile at 1.10^{-3} M and then diluted to 10 µM (10 mL). Stock solutions of nucleophilic compounds were also prepared in pure acetonitrile at 1.10^{-1} M. An aliquot of the nucleophilic compounds (100 equivalents) was added to the 10 µM solution of sensor **5** and then UV spectra were recorded every 10 minutes during 2 hours. For calibration curves, 7 solutions of compound **5** at a concentration of 10 µM in acetonitrile were incubated in a water bath at 25 °C. Every two minutes, a known concentration of hydrazine (i.e. 10 equiv. for solution 2, 20 equiv. for solution 3, 40 equiv for solution 4 etc.) was added to each individual solution. The two minutes interval between hydrazine addition allow the operator to fill the UV cuvette and record UV spectra at known time interval of 1, 2 and 4 hours.

Results and discussion:

1) synthesis and characterization

The synthesis of sensor **5** is described in Scheme 1. First, octamethylcalix[4]pyrrole **3** was obtained from the condensation of pyrrole with acetone following a green procedure employing a deep eutectic solvent.[22] Then compound **4** and **5** were obtained according to previously published procedures.[23,24] The ^{1}H NMR spectra in $CDCl_3$ is in accordance with the literature (Figures S1-2).



Scheme 1. Synthesis of β-vinyl substituted calix[4]pyrrole (sensor **5**) and its reaction with hydrazine

2) NMR investigation

Prior to UV-spectroscopy studies, the reaction of sensor **5** with hydrazine was investigated by ^{1}H NMR spectroscopy. The addition of an excess hydrazine to a solution of sensor **5** in CD_3CN led after a few minutes to a change in color from yellow to almost colorless. The aromatic part of the ^{1}H NMR spectrum of sensor **5** and its reaction product with hydrazine are presented in Figure 1. It can be seen that the reaction produce a single new product, presenting a significant upfield shift of the proton present on the pyrrole bearing the sensing arm ($\Delta\delta$ = 0.69 ppm) and a slight shielding of vinylidene singlet proton at 8.12 ppm ($\Delta\delta$ = 0.008) ppm. These observations are in agreement with the previously published literature employing the dicyanovinyl group as sensing unit.[25] Moreover, the proposed structure of compound **6** was consistent with the high resolution mass spectrometry experiment (Figure S4).

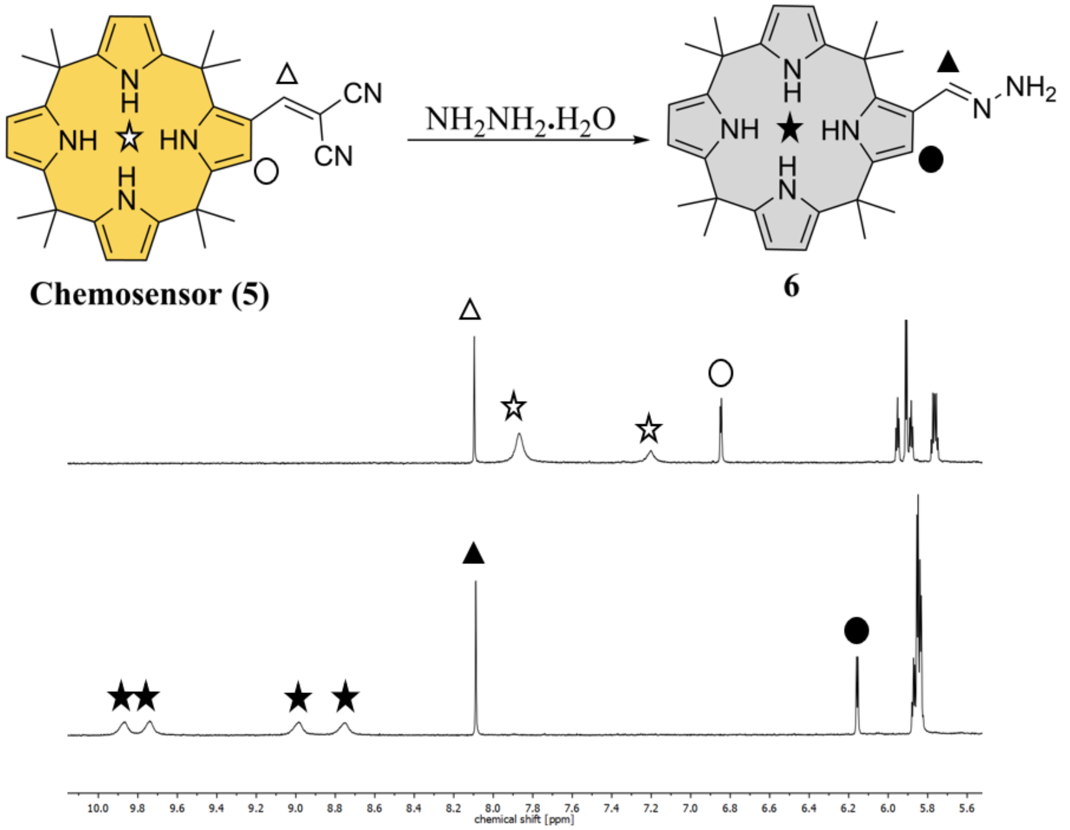


Figure 1 : Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298K) of sensor **5** before (top) and after (bottom) addition of an excess of hydrazine. (full spectra are provided in Figure S5)

3) Study of selectivity

The recognition behavior of sensor **5** was firstly studied by UV-spectroscopy in pure acetonitrile towards various nucleophilic compounds (hydrazine, ammonia, propylamine, diethylamine, triethylamine, pyrrole, aniline, and 2-mercaptoethanol). The UV spectrum of sensor **5** presents a maximum absorption at 373 nm, which is similar to previously published data[24] recorded in an ACN-DMSO (3%) mixture and possesses a molar extinction coefficient of 19303 $L.mol^{-1}.cm^{-1}$ (Figure S6). This value should allow the observation of reasonably low concentration of analytes.[26]

As expected from the NMR experiments, the addition of 100 equivalents of hydrazine to a solution of sensor **5** at 10 µM in ACN led to a decrease in absorbance at 373 nm (Figure 2) with the emergence of an isobestic point at 298 nm. It is important to note that the reaction between the dicyanovinyl group of sensor **5** and hydrazine was time-dependant. To take into account the dependency of the UV response on time, UV spectra were acquired every 10 minutes for 2 hours for each nitrogen-containing compounds (Figures S7-13). To our delight, the addition of 100 equivalents of other nucleophilic compounds did not significantly modify the absorption spectra of sensor **5** after 60 or 120 minutes (Figure 3A), indicating that sensor **5** was highly selective towards hydrazine. A competition experiment was also performed (Figure 3B). In this experiment, Sensor 5 was exposed to 100 equivalents of the 7 competing nucleophiles (ammonia, propylamine, diethylamine, triethylamine, pyrrole, aniline, and 2-mercaptoethanol) and a UV spectra was recorded after an incubation time of 2h. A modest decrease in absorbance intensity of 8% was observed. Then 100 equivalents of hydrazine were added to the previous solution and allow to react for 2 more hours. As expected, a drastic decrease in absorbance intensity was observed, indicating that sensor 5 is selective towards hydrazine. This selectivity could be attributed to the stronger nucleophilicity of hydrazine compared to other tested nucleophiles[27]. Kinetic studies indicate that the reaction between hydrazine and calixpyrrole **5** is pseudo-first order (Figure S14)

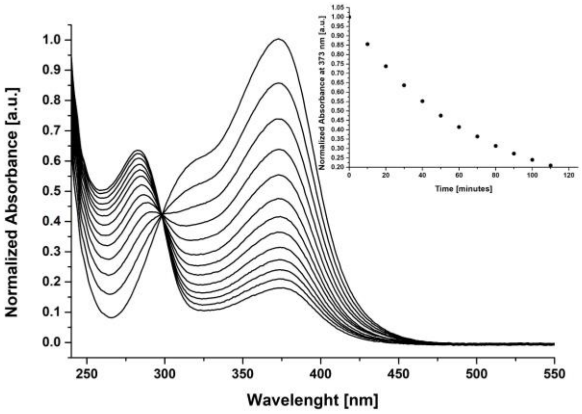


Figure 2: UV absorption of sensor **5** (1.10^{-5}M, 25 °C) upon addition of 100 equivalents of hydrazine in acetonitrile. Spectra acquired every 10 min. Inset: variation of absorbance at 373 nm

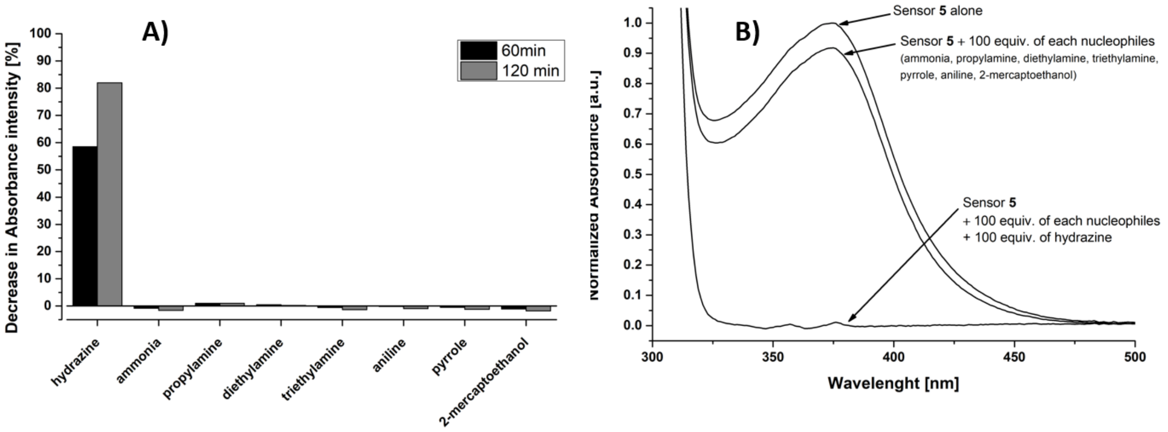


Figure 3: A) Variation of UV absorption at 373 nm of sensor **5** (1.10^{-5}M, 25 °C) upon addition of 100 equivalents of different competing nucleophiles in pure acetonitrile. B) UV spectra of sensor **5** alone, then 2h after addition of 100 equivalents of each competing nucleophiles and finally 2h after addition of 100 equivalent of hydrazine.

This great selectivity was also demonstrated at a higher concentration (Figure 4). Addition of 100 equivalents hydrazine to a 1 mM solution of sensor **5** lead to a complete bleaching after less than 90 seconds that can be perceived by naked eye.

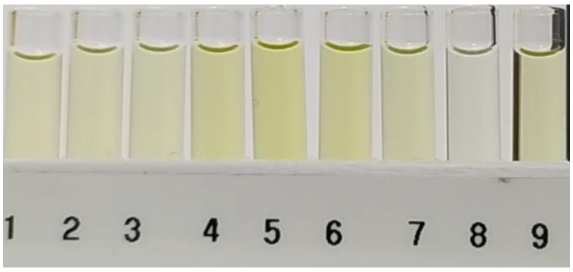


Figure 4: Color change of sensor **5** (1 mM) in acetonitrile in the presence of 100 equivalent of nucleophiles. 2-mercaptoethanol (1), pyrrole (2), aniline (3), triethylamine (4), diethylamine (5), propylamine (6), ammonia (7), hydrazine (8), sensor **5** alone (9). Picture was taken 90s after hydrazine addition.

4) Study of the influence of water

The influence of water on the detection capacity of sensor **5** was evaluated by measuring the maximum absorbance of a solution of calixpyrrole at 10 µM in the presence of 100 equivalents of hydrazine with different percentages of water at 25 °C. The addition of water led to a slight red shift in the maximum absorption, reaching 376 nm for 40% of water. It can be observed on Figure 5 (and Figure S15-20) that the response decreases with an increasing amount of water. This can be explained by the lower nucleophilicity of hydrazine in water compared to acetonitrile.[28] The same type of response decrease can be observed to a lesser degree by adding a polar protic solvent such as ethanol in acetonitrile instead of water (Figure S21). This lower decrease could be explained by the fact that ethanol is a less effective hydrogen bond donor than water. Nevertheless, the detection capacity of sensor **5** in presence of water can be easily restored by enhancing the reaction rate by increasing the temperature to 50 °C (Figure 5). This finding would allow the use of sensor **5** for the detection of environmental samples on aqueous media.

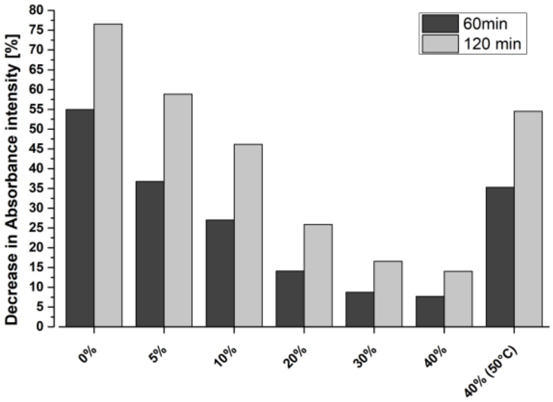


Figure 5: Variation of UV absorption at maximum absorption of sensor **5** (1.10^{-5}M, 25°C or 50°C) upon addition of 100 equivalents of hydrazine in acetonitrile containing increasing water content.

5) **Analytical performance towards hydrazine**

In order to evaluate the analytical performance of sensor **5**, calibration curves were constructed by monitoring the absorbance at 373 nm with increasing amounts of hydrazine (0 to 100 equiv.). To take into account the time dependency of the reaction between calixpyrrole and hydrazine, 7 individual solutions of compound **5** at a concentration of 10 µM were prepared and incubated in a water bath at 25 °C. Then, an increasing amount of hydrazine was added to each solution with a time interval of 2 minutes in order to allow the operator to fill the UV cuvette and record the UV spectra. A series of solutions were analyzed after 1, 2, and 4 hours. The calibration curves are shown in Figure 6 A and Figure S22.

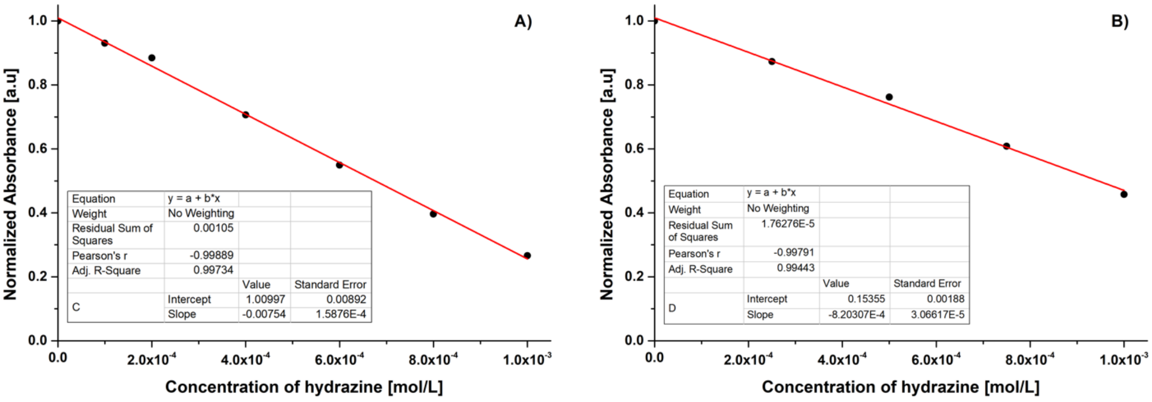
One can observe that good correlation coefficients were obtained after 1 and 2 hours. After 4h, high hydrazine concentrations (i.e. 80 and 100 equiv.) start to reach a plateau that derive from linearity and therefore do not allow accurate quantification of hydrazine. However, the first 5 points of the calibration curve remained aligned, with a good correlation coefficient. In our hand, the best result was achieved after 2 hours of incubation (Figure 6 A) with a correlation coefficient of 0.997. The same methodology was employed in an ACN-water 40% mixture with an incubation time of 2 hours at 50 °C. A representative calibration curve is depicted on figure 6B, which shows a good correlation coefficient of 0.994.

The limit of detection (LOD) and limit of quantification (LOQ) were deduced from the calibration curves according to the following equations[29]:

LOD = 3.3 x σ / slope

LOQ = 10 x σ / slope

with σ = the standard deviation of y-intercept of the regression line



Equation	y = a + b*x		
Weight	No Weighting		
Residual Sum of Squares	0.00105		
Pearson's r	-0.99889		
Adj. R-Square	0.99734		
		Value	Standard Error
C	Intercept	1.00997	0.00892
	Slope	-0.00754	1.5876E-4

Equation	y = a + b*x		
Weight	No Weighting		
Residual Sum of Squares	1.76276E-5		
Pearson's r	-0.99791		
Adj. R-Square	0.99443		
		Value	Standard Error
D	Intercept	0.15355	0.00188
	Slope	-8.20307E-4	3.06617E-5

Figure 6 : Calibration curves for hydrazine monitoring in the range 10-1000 µM obtained after 2h of incubation. A) in acetonitrile, 25°C B) ACN-Water 40%, 50°C

LOD was evaluated at 4.10^{-5} M (1.3 mg/L) and LOQ at 1.2.10^{-4}M (3.9 mg/L) in 100% acetonitrile solution. In 40% water solution, LOD and LOQ were evaluated at 2.5 mg/L and 7.5 mg/L respectively.

Conclusion

In conclusion, we have successfully repurposed a β-dicyanovinyl-substituted calix[4]pyrrole chemodosimetric sensor initially designed for the sensing of cyanide anion in order to achieve the spectroscopic detection of hydrazine. It is one of the first time that chemodosimetric approach was used with calixpyrrole for the detection of a covalent analyte. Sensor **5** proved to be highly selective towards hydrazine among other competing aliphatic or aromatic amino compounds (ammonia, propylamine, diethylamine, triethylamine, pyrrole, aniline) and 2-mercaptoethanol. The sensing capacities were evaluated by UV-spectroscopy in pure acetonitrile and in acetonitrile-water mixtures with up to 40% water. Calibration curves obtained after an incubation time of 2 hours at 25°C in pure acetonitrile or 2 hours at 50°C for ACN-water 40% mixture proved to be linear in the 10-1000 µM range. Limit of detection of sensor toward hydrazine were estimated at 4.10^{-5}M (1.3 mg/L) and $7.5.10^{-5}$M (2.5 mg/L) in pure acetonitrile and ACN-water 40% mixture respectively. Finally, sensor **5** was employed for the naked-eye detection of hydrazine, which is the only compound studied that induce a total bleaching of the yellow solution. The chemodosimetric approach used in this study could be exploited in the future for the design of mutitopic receptors based on calix[4]pyrroles thanks to the presence of a responsive side arm and the pyrrole cavity.

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Conflicts of interest

There are no conflicts to declare.

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