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Optical Chemosensor for Ag^{+}, Fe^{3+}, and Cysteine: Information Processing at Molecular Level

Manoj Kumar,* Rajesh Kumar, and Vandana Bhalla

Department of Chemistry, UGC-Center for Advance Studies-1, Guru Nanak Dev University, Amritsar, Punjab, India

mksharmaa@yahoo.co.in

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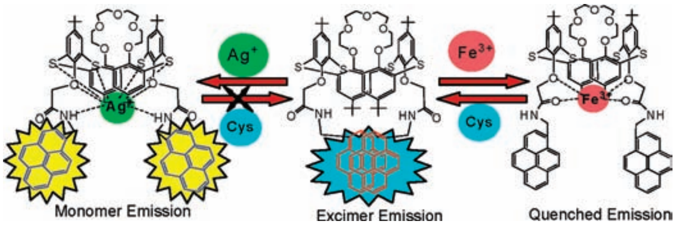
ABSTRACT



A thiacalix[4]arene based chemosensor 3 bearing two pyrene groups has been synthesized which demonstrates ratiometric sensing with Ag^{+} and fluorescence quenching with Fe^{3+} ions in mixed aqueous media. The '*in situ*' prepared Ag^{+} and Fe^{3+} complexes showed high selectivity toward cysteine. The molecular switching between three chemical inputs (Ag^{+}, Fe^{3+}, cysteine) results in various molecular logic gates which have been integrated sequentially to generate a sequential information processing device.

Among biologically important metal ions, the Ag^{+} and Fe^{3+} ions have received considerable attention due to their widespread applications. The silver ions are well-known because of their antimicrobial activities[1] and various applications in electronic, photographic, and imaging industries.[2] The excess of silver ions leads to bioaccumulation and toxicity,[3] inactivation of sulfhydryl enzymes,[4] and irreversible darkening of the skin. On the other hand, the trivalent form of iron is an essential element in the human body and provides the oxygen-carrying capacity of heme and acts as a cofactor in many enzymatic reactions. It plays an important role in many biological processes at the cellular level ranging from oxygen metabolism to DNA and RNA synthesis.[5] Iron is indispensable for most organisms, and both its deficiency and excess result in various pathological disorders.[6]

In view of the role played by these ions in day to day life, the development of techniques for sensing and monitoring of these ions is in great demand. Fluorescence signaling is one of the best choices due to its high detection sensitivity and simplicity which translates molecular recognition into tangible fluorescence signals.[7] A number of fluorescence sensors for zinc,[8a] mercury,[8b] and copper[8c] have been

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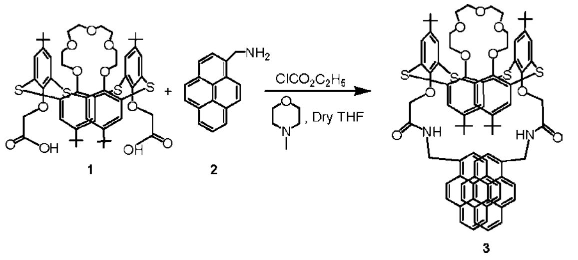
Scheme 1. Synthesis of Compound **3**



reported, but there are few reports in the literature for fluorogenic sensing of Ag^+ [9] and Fe^{3+} [10] in mixed aqueous media.

Earlier, from our laboratory,[8b,c,11] we have reported ratiometric sensors for Hg^{2+} [8b] and Cu^{2+} ions.[8c] The ratiometric fluorescent probes have an important feature of permitting signal rationing and increase the dynamic range and providing built in correction for environmental effects.[7] In the present manuscript, we have prepared a new fluorescent ratiometric chemosensor **3** for Ag^+ which until now has remained rare,[9a−e] because silver normally quenches fluorescence by electron transfer and intersystem crossing processes.[9d] In the presence of Ag^+ ions, compound **3** undergoes fluorescence quenching at 470 nm and fluorescence enhancement at 377 nm. On the other hand, compound **3** shows complete quenching of monomer and excimer emission bands in the presence of Fe^{3+} ions. The '*in situ*' prepared Ag^+ and Fe^{3+} complexes of compound **3** showed remarkable selectivity toward cysteine[12] which plays a crucial role in a variety of fundamental physiological processes in organisms.[13] A deficiency of cysteine leads to many diseases, such as a hematopoiesis decrease, leucocyte loss, psoriasis, etc.[14] Cysteine is also a potential neurotoxin[15] and a biomarker for various medical conditions.[16] Thus, compound **3** shows fluorogenic sensing toward Ag^+, Fe^{3+}, and cysteine. In addition, it behaves as an information processing device at 470 nm with cysteine in the presence of Ag^+ and Fe^{3+} ions.

Thus, the reaction of diacid **1** with 2.0 mol equiv of 1-pyrenemethylamine in the presence of ethylchloroformate (2.6 mol equiv) and *N*-methymorpholine (2.6 mol equiv) furnished thiacalix[4]arene derivative **3** in 66% yield (Scheme 1 and Supporting Information, pp S1−S3). The structure of thiacalix[4]arene receptor **3** was confirmed by its spectroscopic and analytical data.

The binding behavior of compound **3** was investigated toward different cations and amino acids by fluorescence and ^{1}H NMR spectroscopy. The fluorescence spectrum of compound **3** gave weak monomer and strong excimer emission of the pyrene group at 377 and 470 nm, respectively, when excited at 344 nm (Figure 1a). The formation of a strong excimer band indicates that the two pyrene moieties are stacked together. Upon addition of increasing amounts of Ag^+ (1−300 equiv) as its perchlorate salt to the solution of receptor **3**, there was a ratiometric response with significant monomer enhancement at 377 nm and excimer quenching at 470 nm (Figure 1a). The relative intensity ratio of monomer to excimer emission (I_{377}/I_{470}) of the free ligand was 0.36 and it increased by 14-fold to 5.11 (Figure 2) with addition of Ag^+ ions which was attributed to formation of the **3.Ag**$^+$ complex. The quenching in excimer emission is due to conformational change that takes place during the binding of silver with nitrogen atoms. In this changed conformation it is not possible for the pyrene groups to stack together. The binding modes of receptor **3** with silver were evaluated by ^{1}H NMR spectroscopy. It was found that on addition of 1 mol equiv of Ag^+ ion to receptor **3**, significant downfield shifts of 0.23, 0.23, and 0.25 ppm were observed for protons of OCH_2, NCH_2 of pyrene arms, and aromatic protons (ArH) of the thiacalix[4]arene moiety, respectively (Supporting Information, Figures S10 and S11), which indicates that Ag^+ is interacting with nitrogens of pyrene arms and sulfur atoms of the thiacalix[4]arene moiety of receptor **3**. On the other hand, the addition of increasing amounts of Fe^{3+} ions (300 equiv) to the solution of

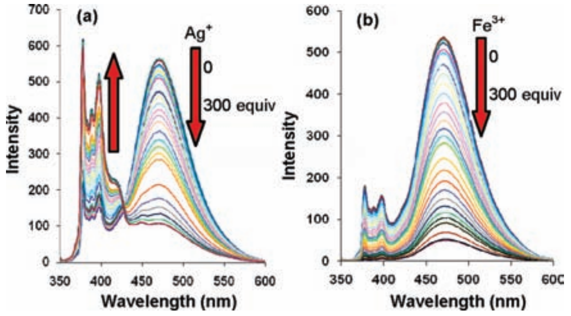


Figure 1. Fluorescence emission spectra of receptor **3** (5.0 μM) upon various additions of (a) Ag^+ (0−300 equiv) and (b) Fe^{3+} (0−300 equiv) in 10% aqueous ethanol.

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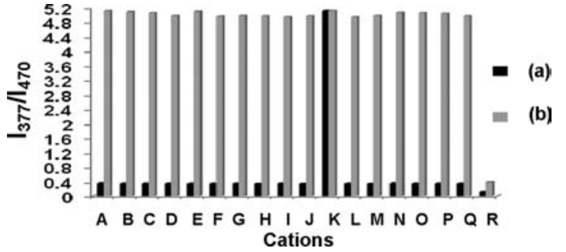

Figure 2. (a) Ratiometric selectivity of **3** (5.0 μM) toward Ag^+ upon addition of different caions and (b) competitive ratiometric selectivity of **3** (5.0 μM) toward Ag^+ in the presence of different cations in 10% aqueous ethanol. A = **3**, B = Li^+, C = Na^+, D = K^+, E = Ba^{2+}, F = Mg^{2+}, G = Ni^{2+}, H = Cu^+, I = Cu^{2+}, J = Zn^{2+}, K = Ag^+, L = Cd^{2+}, M = Hg^{2+}, N = Pb^{2+}, O = Co^{2+}, P = Mn^{2+}, Q = Fe^{2+}, R = Fe^{3+}.

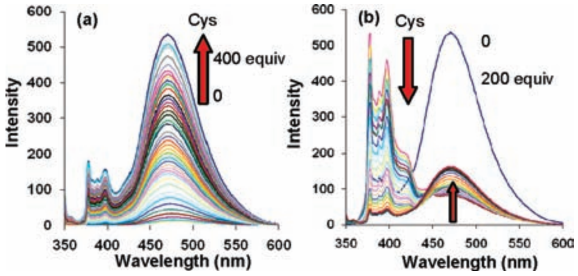

Figure 3. Fluorescence emission spectra of (a) **3.Fe**$^{3+}$ complex and (b) **3.Ag**$^+$ complex upon addition of cysteine (0−400 and 0−200 equiv, respectively) in 10% aqueous ethanol.

compound **3** results in significant quenching in the monomer and excimer emission (Figure 1b). The quenching in monomer emission induced by Fe^{3+} was attributed to reverse PET from pyrene units to the carbonyl oxygen[17] of which the electron density diminished upon iron binding. The quenching in excimer emission in the presence of Fe^{3+} ions is due to conformational changes of two pyrene-appended arms. The carbonyl groups turn inward from an outward orientation to bind the Fe^{3+} ions which prevent the stacking and $\pi-\pi$ interactions between two pyrene units (Supporting Information, Figure S11). Under the same conditions as those used above for Ag^+ and Fe^{3+}, we also tested the fluorescence response of compound **3** to other metal ions such as Li^+, Na^+, K^+, Ba^{2+}, Mg^{2+}, Ni^{2+}, Cu^+, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Pb^{2+}, Co^{2+}, Mn^{2+}, and Fe^{2+}; in addition to Ag^+ and Fe^{3+}, no significant fluorescence change of **3** occurred in the presence of (500 equiv) of these cations (Figure 2 and Supporting Information, Figure S12). Fitting the changes in the fluorescence spectra of **3** with Ag^+ and Fe^{3+} ions using the nonlinear regression analysis program SPECFIT[18] gave the best fit and demonstrated that a 1:1 stoichiometry of the host and guest (Ag^+ and Fe^{3+}) was the most stable species in the solution with binding constants ($\log \beta_{11}$) of 7.32 ± 0.06 and 9.8 ± 0.04 M^{-1}, respectively. The MALDI-TOF mass spectrum of the **3.Ag**$^+$ complex (*m*/*z* at 1529.3) and method of continuous variation (Job's plot) was also used to prove the 1:1 stoichiometry (Supporting Information, Figures S13 and S14).

Further, we studied the behavior of '*in situ*' prepared ferric and silver complexes of receptor **3** toward different amino acids and found that these complexes have pronounced selectivity toward cysteine (Supporting Information, Figure S15). The addition of increasing amounts of cysteine to the solution of the **3.Fe**$^{3+}$ complex (Figure 3a) results in a complete revival of fluorescence emission indicating that Fe^{3+} is being completely removed from the **3.Fe**$^{3+}$complex by cysteine. The fluorescence was quenched again when Fe^{3+} was titrated to the solution of the **3.Fe**$^{3+}$**.Cys** complex, indicating that the receptor **3** showed an interesting reversible "On-Off" switchable behavior with Fe^{3+} and cysteine (Supporting Information, Figure S16). On the other hand, upon addition of cysteine (200 equiv) to the solution of the **3.Ag**$^+$ complex, a significant quenching in the monomer emission (Figure 3b) was observed, but there was a small revival of excimer emission. This indicates that cysteine in not able to remove the Ag^+ ion from the **3.Ag**$^+$ complex and hence prevents the stacking of two pyrene moieties.

Recently, there has been a significant development in the supramolecular systems which behave as molecular logic gates.[19] These systems convert the chemically encoded information as input into fluorescent signals as output which results in the development of molecular level electronic and photonic devices for information processing and computation.[19] Numerous chemical systems have been mimicked into various electronic devices such as identification tags for small objects,[20] molecular keypad locks,[21] and demultiplexers[22] performing digital operations. However, there are only a few reports where information storage devices (Write-Read-Erase) have been developed at a molecular level.[23]

Thus, depending on the three chemical inputs (Ag^+, Fe^{3+}, cysteine), the receptor **3** can switch between different fluorescence emission states, i.e. "on" (strong fluorescence emission) or "off" (quenched fluorescence emission), which display "Write-Read-Erase-Read" behavior with the help of

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Table 1. Truth Table for Memory Unit for Two Input Signals *In*F and *In*C, Where 0 and 1 Indicate *Off* and *On* Signal

reset(*in* F)	set(*in* C)	*out* 1ME channel[a]	*out* 2EE channel[b]
0	0	0	1
1	0	0	0
0	1	0	1
1	1	0	1

[a] ME channel: monomer emission at λ 377 nm. [b] EE channel: excimer emission at λ 470 nm.

binary logic.[19] The three chemical inputs of Ag^+, Fe^{3+}, and cysteine are designated as *In*A, *In*F, and *In*C, respectively. For a reversible "On-Off" switch between Fe^{3+} and cysteine (Table 1), the sequential logic operations are represented by two inputs: Set (*In*C) and Reset (*In*F) as a function of a memory element. The reversible and reconfigurable sequences of Set/Reset logic operations in a feedback loop demonstrate the memory feature with "Write-Read-Erase-Read" functions with the optical output signal at the excimer channel (Figure 4a and b). The strong emission at the excimer channel was considered as a high output memory state, and the system "writes" and saves "logic state 1" when the Set input was high (*In*C = 1). The encoded information is "read" out optically as the excimer emission. The stored information was "erased" by the Reset input (*In*F = 1) with significant quenching in the excimer emission and system write and save "logic state 0". For precise control over the "On-Off" states of compound **3**, many write-erase cycles were conducted, and it was found that it exhibits multiple "rewriting" ability without any degradation in fluorescence emission during the state (On−Off) transition (Supporting Information, Figure S17). Further, Figure 4b defines the bistability behavior, "On-Off" state, of compound **3** and also reveals the nonvolatile nature of the memory effect. This behavior is extensively used in microprocessors for memory elements of integrated logic circuits.[19b] On the other hand, the irreversible"On-Off" switch of two inputs "*In*A and *In*C" produces a simple logic circuit and did not show any memory effect due to the irreversibe nature of the molecular switch (Supporting Information, Table S1, Figure S18).

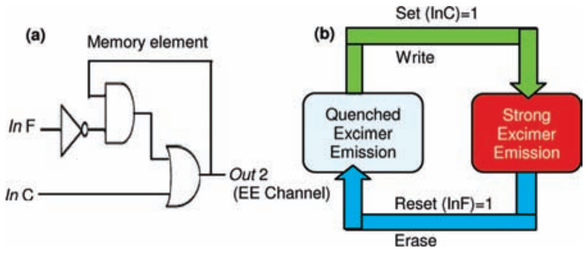

Figure 4. (a) Sequential logic circuit which displays the memory unit and (b) feedback loop showing reversible logic operations for memory element with "Write-Read-Erase-Read" functions.

Table 2. Truth Table for Memory Device for Three Input Signals *In*A, *In*F, and *In*C, where 0 and 1 Indicate *Off* and *On* Signal

reset		set		
(*in* A)	(*in* F)	(*in* C)	*out* 1MEchannel[a]	*out* 2EEchannel[b]
0	0	0	0	1
0	1	0	0	0
0	0	1	0	1
1	0	0	1	0
0	1	1	0	1
1	0	1	0	0
1	1	0	0	0
1	1	1	0	1

[a] ME channel: monomer emission at λ 377 nm. [b] EE channel: excimer emission at λ 470 nm.

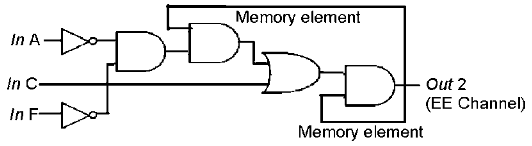

Figure 5. Sequential logic circuit displaying memory unit with three input strings *In*A, *In*F, and *In*C at excimer chanel.

Further, the "Write-Read-Erase-Read" function of the memory element was evaluated for three input combinations (*In*A, *In*F, and *In*C, Table 2). The output at the monomer channel (ME) turned *on* (Supporting Information, Figure S19a) by integration of NOR and AND operations at λ 377 nm. However, the output at the excimer channel reveals the complexity of the operations performed for the three input memory device (Figure 5). The eight combinations of three chemical inputs (*In*A, *In*F, and *In*C) are integrated through a series of Set/Reset operations involving logic operations to produce an information processing device. With strong emission at the excimer channel, the system "writes" and saves logic state "1" when the Set input is high (*In*C = 1) and subsequently it was "erased" by Reset inputs (*In*A or *In*F = 1) and save logic state "0" (Supporting Information, Figure S19b). Further, the three input combination shows a multiple "rewriting" ability with many write-erase cycles, bistability behavior (On−Off state), and nonvolatile nature of memory effect.

In conclusion, we demonstrate that chemosensor **3** for selective detection of Ag^+, Fe^{3+}, and cysteine generates "Write-Read-Erase" functions in the feedback loop with these three chemical inputs.

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Supporting Information Available: $^1H/^{13}C$ NMR, FAB mass, selectivity graphs, fluorescence spectra, and logic gates of different ionic inputs. This material is available free of charge via the Internet at http://pubs.acs.org.

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