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New chromogenic bis(isatin hydrazonyl)calix[4]arenes for dual recognition of fluoride and silver ions

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ABSTRACT

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The design and synthesis of ditopic receptors for selective binding of both cationic and anionic species have become exciting domains of supramolecular chemistry.^{1,2} Macrocyclic compounds such as calixarenes have been employed extensively for this purpose by various workers.³ These versatile ditopic receptors may possess the cation and anion binding sites on the opposite rims⁴ of calixarene structure or together on one^{5,6} side of the calixarene scaffold. At the same time, chromogenic receptors that can undergo a vivid color change upon guest interaction are preferred and constitute an emanating territory of interest.^{7–9} Indeed, colorimetric sensor molecules based on the formation of hydrogen bonding or anion promoted deprotonation of the binding moiety have been shown to be very efficient and highly sensitive.^{10–12}

Amongst the range of commonly occurring anions, fluoride is of special interest due to its proven role in prevention of dental caries^{13,14} and treatment of osteoporosis.¹⁵ On the other hand, amongst important metal ions, silver ion has attracted considerable attention¹⁶ during last few years due to its widespread applications in the organic synthesis, electronics, photography, and imaging industry. However, unlike other transition metal ions there are not many reports on silver ion receptors, probably due to the fact that silver ion does not show a pronounced coordination ability. This in turn makes discrimination of silver from other chemically related cations more difficult.

In this Letter we report the synthesis and evaluation of two new ditopic calix[4]arene based molecular receptors (6-7) bearing isatin hydrazone units in their molecular scaffold for dual colorimetric recognition of Ag⁺ and F⁻. The synthesis of bis(isatin hydrazonyl)calix[4]arenes involved the formation of a schiff base between calixarene derivative 5 and isatin hydrazones 2a and 2b. The choice of isatin hydrazone as chromogenic sensing molecule was driven by the fact that as an indole derivative, isatin could not only serve as an anion sensor based on H-bonding or deprotonation mechanism but it could be linked to the calixarene framework to result in an extended conjugated system to function as a color reporting group. Strong coordination ability of schiff base moiety in the designed receptors further augments the plausibility of their use in metal ion recognition. To the best of our knowledge this is the first report on an isatin functionalized calixarene based molecular receptor for target applications. The designed receptors feature cation binding sites (in the form of hydrazone nitrogens and amide oxygens) and anion binding sites (in the form of amide NH and phenolic OH groups) which facilitate the dual ionic recognition.

New calixarene based dual chromogenic receptors bearing isatin hydrazone units have been synthesized

and evaluated for their ion recognition potential. The synthesized molecular receptors can effectively and

selectively recognize fluoride and silver ions through visible color changes and pronounced bathochromic

shifts in their UV-visible spectra. NMR titration data further support the preliminary conclusions.

Isatin hydrazones **2a** and **2b** were synthesized by reaction of corresponding isatin with hydrazine hydrate in ethanol. The synthesis of receptors **6** and **7** is outlined in Scheme 1. N-alkylation of isatin was carried out by reaction of isatin with propyl bromide and potassium carbonate in DMF. The structures of compounds **6** and **7** were confirmed from their spectroscopic^{17,18} and analytical data. The ¹H NMR spectrum of **6** showed two doublets (4H each) for calixarene methylene bridge protons, two singlets (4H each) corresponding to calixarene aryl ring protons, two doublets (2H each) and two triplets (2H each) corresponding to isatin aryl ring

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Scheme 1. Synthesis of **6** and **7**. Reagents and conditions: (i) ethyl bromoacetate, K₂CO₃, CH₃CN, reflux; (ii) hexamethylenetetramine, trifluoroacetic acid, reflux; (iii) isatin hydrazone, ethanol, reflux.

protons, and two singlets (2H each) corresponding to isatin NH and calixarene OH, while **7** showed all these peaks except for the peak of isatin NH. This was further confirmed by HRMS analysis which showed peaks at 1073.4369 and 1157.5328 corresponding to **6** and **7**, respectively. Additionally, distinct signals at 30.7 and 31.1 for **6** and **7**, respectively in ¹³C NMR spectra confirm symmetric cone conformation for **6** and **7**.

In order to get an insight into the spectroscopic behavior of designed receptors toward cations and anions, UV-visible and ¹H NMR titrations were performed.

In the absence of external analytes, UV–vis spectrum of **6** and **7** in THF could be characterized by absorption peaks at 373 and 369 nm, respectively, which could be attributed to intramolecular charge transfer band. The cation binding and sensing ability of receptor **6** was investigated in detail by following its absorption spectral changes upon addition of various metal perchlorates. Figure S3 (Supplementary data) represents the UV–vis absorption changes upon addition of different transition metal ions (Mn²⁺, Co²⁺, Cu²⁺, Fe²⁺, Ni²⁺, Hg²⁺, Ag⁺, Cd²⁺, and Zn²⁺) to the THF solution of receptor **6** (30 µM). It was found that the UV–vis spectrum of **6** exhibited a considerable red shift ($\Delta \lambda_{max}$ 37 nm) only in the presence of silver ions while other tested cations did not produce any substantial change in the absorption spectrum. Figure S4 (Supplementary data) shows a comparative view when different metal ions were added in 1.5 equiv amount to the THF solution of **6**.

Upon successive addition of silver ion to the solution of receptor **6**, the absorption band at 373 nm decreased while a new peak gradually moving toward longer wavelength and finally reaching a maximum value at 410 nm appeared. Figure 1 exhibits the UV-vis spectral changes for receptor **6** (30 μ M) on gradual addition of silver from 0 to 1.5 mol equiv. This change in absorption spectra was accompanied by a visible color change from pale yellow to



Figure 1. Variation in absorption spectrum of **6** (30 μ M) upon titration with Ag⁺ (0–1.5 equiv). Inset: the color change of **6** upon silver addition.

dark yellow while no other cation gave colorimetric response. Moreover, the absorbance at 410 nm got saturated in the presence of 1 equiv of silver ions, suggesting the formation of a 1:1 complex between **6** and silver ion, which is in good agreement with 1:1 stoichiometry for the silver complex, as confirmed by the Job's plot analysis (Supplementary data, Fig. S9). The corresponding binding constant on the basis of Benesi–Hildebrand plot¹⁹ was calculated to be 8.4×10^3 M⁻¹ (Supplementary data, Fig. S5).

In order to understand the binding mode of **6** with Ag⁺ ion, ¹H NMR titrations were performed in DMSO-*d*₆. Upon addition of 1 equiv of silver to the receptor solution (0.01 M), the chemical shift of amide protons exhibited a downfield shift by $\Delta\delta$ 0.23 ppm from δ 10.795 ppm (Fig. 3). Similarly azo-methine protons (**H**C=N) showed a downfield shift by $\Delta\delta$ 0.18 ppm. These spectral changes suggest that silver ion could be bound by hydrazonyl nitrogens and amide oxygens of **6**.

To ascertain the practical applicability of **6** as a silver selective sensor, competitive experiments were carried out in THF, where in absorption spectra of transition metal ion/silver ion coexisted systems were examined. No significant change in the absorption value was seen even when other metal ions (1 equiv) were present along with silver ion in the receptor solution (Fig. 2). Based on the UV titrations and colorimetric response shown by sensor **6** with Ag⁺, it could be inferred that **6** shows a pronounced selectivity for Ag⁺ ion over other transition metal cations being tested.



Figure 2. Competitive selectivity and sensitivity of **6** for Ag^+ in preference to other related metal ions. Black bar represents the absorbance of **6** in the presence of Ag^+ alone. Gray bar denotes absorbance of Ag^+/M^{n+} coexisting systems.



Figure 3. Partial ¹H NMR spectra of 6 upon addition of 1 equiv of silver ion.

Having established the ability of **6** to interact with cations, we investigated the utility of **7** as a cation sensor under identical conditions. Upon titration with silver (0–2 equiv), the absorption spectrum of **7** too shifted to a longer wavelength but with an isobestic point at 401 nm (Supplementary data, Fig. S15). The corresponding binding constant has been calculated to be $37.5 \times 10^3 \text{ M}^{-1}$.

To quantitatively study the anion sensing ability of **6** in THF, UV–vis monitoring was performed by adding a standard solution of tetrabutylammonium salts of anions. The tested anions included F^- , Cl^- , Br^- , I^- , HSO_4^- , and $H_2PO_4^-$. All the representative anions, except fluoride produced a negligible change in the absorption spectrum of **6** (30 μ M) (Supplementary data, Fig. S6). Addition of fluoride to the receptor solution resulted in an instantaneous change in the absorption band of receptor accompanied by a visible color change displaying higher selectivity of **6** toward fluoride over other commonly occurring anions. It was determined that the UV–vis spectrum of **6** was red shifted to 593 nm ($\Delta\lambda_{max}$ 220 nm) as fluoride ions came in contact with the receptor solution.

Figure S7 (Supplementary data) shows a comparative view when different anions were added in 4 equiv amount to a THF solution of **6**. Figure 4 displays the absorption spectral changes for **6** (30μ M) on gradual addition of fluoride ion from 0 to 4 mol equiv. While, the original absorption peak at 373 nm got gradually weakened, a new bathochromically shifted peak at 593 nm resulted from binding of **6** and F⁻. These spectral changes could be attributed to H-bonding between amide N–H and phenolic O–H of **6** and fluoride ion followed by deprotonation. The interaction was accompanied by a color change of receptor solution from pale yellow to dark



Figure 4. Variation in the absorption spectra of **6** on titration with tetrabutylammonium fluoride (0–4 equiv). Inset: the color change of **6** upon addition of TBAF.

blue. The color change was attributed to the fact that when receptor binds with fluoride ions, the electron density in the supramolecular system increases which in turn enhances the charge transfer interactions between electron rich and deficient moieties.

Interestingly, addition of a protic solvent such as water or methanol resulted in disappearance of the observed color of the complex, suggesting that fluoride–calixarene interaction did not involve covalent bond formation and that H-bonding interactions are indeed involved. The binding stoichiometry between **6** and fluoride was determined to be 1:2 (**6**: F⁻) by Job's plot analysis (Supplementary data, Fig. S10). The associated binding constant calculated by employing modified Benesi–Hildebrand²⁰ equation is 33×10^6 M⁻² (Supplementary data, Fig. S8).

To further evaluate the nature of intermolecular interactions between **6** and fluoride, ¹H NMR spectral changes upon addition of TBAF to DMSO- d_6 solution of **6** (0.01 M) were investigated. The ¹H NMR spectrum of **6** showed a singlet at δ 8.88 ppm corresponding to phenolic protons and a singlet at δ 10.795 ppm corresponding to amide protons. As expected, both N**H** and O**H** protons underwent serious signal broadening followed by disappearance upon addition of TBAF (Fig. 5). These data further confirmed the conclusion that both isatin –CONH and calixarene phenolic OH are involved in the interaction with fluoride as envisaged.

UV-vis titration of **7** with anions under identical conditions revealed the role of isatin NH in anion binding. The absorption spectrum of **7** underwent a red shift from 369 to 588 nm ($\Delta \lambda_{max}$ 219 nm) upon addition of tetrabutylammonium fluoride(TBAF) while other anions did not produce any change. Figure S16 (Supplementary data) shows the UV-vis spectral changes of **7** upon successive addition of fluoride from 0 to 4 equiv. It was determined that **7** with fully N-substituted isatin hydrazonyl functionality shows much less significant UV-vis changes than **6**. Moreover, **7** in the absence of binding amide group shows comparatively little color change upon addition of fluoride. For instance, addition of 1 equiv of TBAF to a 30 μ M solution of **7** in THF results in much smaller color changes compared to the color changes seen with **6**.

The detection limit^{21} of **6** toward fluoride and silver ions was obtained from UV–visible titration experiments. The interaction of **6** with fluoride could be detected down to at least 4.0 μ M, while with silver the detection limit was determined to be 3.98 μ M (Supplementary data, Figs. S11, S12).

To investigate the binding ability of one ion in the presence of its competing ion, two sets of UV–vis binding studies of **6** and **7** were performed with Ag^+ and F^- ions. When **6** Ag^+ complex was titrated with TBAF (0–10 equiv), it was observed that the red shifted absorption maxima of **6** Ag^+ complex underwent a blue shift along with the appearance of a new band around 600 nm. This suggests that silver ions are sequestered out of the receptor as F^- binds with it (Supplementary data, Fig. S17). When **6** F^- was titrated with Ag^+ ,



Figure 5. Partial ¹H NMR spectra of sensor 6 in the presence of 1 equiv of fluoride ion.

it was observed that a band corresponding to **6** and Ag⁺ complexation was formed around 400 nm, but the long wavelength band corresponding to **6** and F⁻ binding did not disappear completely even after addition of 55 equiv of Ag⁺ (Supplementary data, Fig. S18). These observations could be attributed to a stronger interaction of 6 with F⁻ in comparison to that in Ag⁺ because of which F^- is not completely sequestered out of **6**. Upon titration of **7**·Ag⁺ with F⁻, the absorption maxima of **7**·Ag⁺ gradually shifted to smaller wavelength and a new red shifted band developed around 557 nm instead of 588 nm as seen in the absence of Ag⁺. On this basis it was assumed that $7 \cdot Ag^+$ complex could be involved in further complexation with F^- to give a mixed complex. The spectral change reached its limiting value upon addition of 3 equiv of F⁻ (Supplementary data, Fig. S19). In the reverse experiment, upon addition of Ag^+ into $\mathbf{7} \cdot F^-$ complex, the peak at 557 nm was observed again, indicating the formation of a mixed complex. However, when the amount of Ag⁺ was increased beyond 1 equiv, the absorbance at 557 nm decreased and the spectra eventually changed to that of 7 Ag⁺ (Supplementary data, Fig. S20).

In summary, two new bis(isatin hydrazonyl) calix[4]arene based dual receptors 6 and 7 have been designed and synthesized for selective detection of fluoride and silver ions. 6 can be utilized as a visible chemosensor owing to the noticeable color change in the presence of these ions. **6** could bind Ag^+ and F^- while displaying significant bathochromic shifts in UV-vis spectroscopy. While 6 binds Ag⁺ with 1:1 stoichiometry, it binds F⁻ with 1:2 stoichiometry. It interacts with fluoride through amide and phenolic protons while binding of silver takes place through hydrazonyl nitrogens and amide oxygens. Moreover, as expected the absence of isatin NH in 7 interfered with the possible interaction between the receptor and fluoride. Further work to explore utility of isatin hydrazonyl calix[4]arenes is in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013. 01.038.

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- Analytical data for **6**: Yield: 72%; Mp: 190–192 °C; UV (λ_{max} , THF):373 nm, 17. HRMS (ESI-MS) m/z: calcd 1073.4420, found 1073.4369; ¹H NMR (300 MHz, DMSO, δ in ppm): 10.795 (s, 2H, NH, D₂O exchangeable), 8.88 (s, 2H, OH, D₂O exchangeable), 8.43 (s, 2H), 8.1 (d, 2H), 7.8 (s, 4H), 7.38 (t, 2H), 7.24 (s, 4H), 7.0 (t, 2H), 6.86 (d, 2H), 4.9 (s, 4H), 4.38 (d, 4H), 4.31 (q, 4H), 3.66 (d, 4H), 1.30 (t, 6H),1.12(s,18H); ¹³C NMR (300 MHz, DMSO, δ in ppm) 14.04, 30.782, 34.006, 61.013, 71.904, 110.61, 116.732, 122.256, 124.949, 126.142, 129.107, 129.463, 130.096
- 132.481,133.253,144.731,147.529,150.435,156.539,162.79,164.846,169.193.
- Analytical data for 7: Yield: 65%; Mp: 178–180 °C; UV (λ_{max},THF): 369 nm, HRMS (ESI-MS) m/z: calcd 1157.5359, found 1157.5328; ¹H NMR (300 MHz, CDCl₃, δ in ppm): 8.6 (s, 2H, OH, D₂O exchangeable), 8.5 (s, 2H), 8.27 (d, 2H), 7.6 (s, 4H), 7.38 (t, 2H), 7.07 (s, 4H), 6.98 (t, 2H), 6.85 (d, 2H), 4.85 (s, 4H), 4.5 (d, 4H), 4.36 (q, 4H), 3.7 (t, 4H), 3.54 (d, 4H), 1.7 (m, 4H), 1.40 (t, 6H), 1.12 (s, 18H), 0.969 (t, 6H); 13 C NMR (300 MHz, DMSO, δ in ppm) 11.314, 14.152, 20.783, 31.145, 34.156, 41.531, 61.468, 72.151, 108.726, 117.044, 122.650, 125.303, 126.268, 129.348, 130.195, 132.313, 132.605, 132.911, 145.989, 148.358, 150.618, 157.101, 164.665, 169.112.
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