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Design and Synthesis of A Novel Bis-Benzimidazolyl Podand As a Responsive Chemosensors for Anions

H. Eshghi[a,*], M. Rahimizadeh[a], N. Noroozi-Shad[a] and H. Sabet-Sarvestani[a]

[a]*Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad 91775- 1436, Iran*

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A novel podand based anion receptor bearing benzimidazole motifs as recognition sites was designed and synthesized by reaction of 1,7-bis(2'-methylbenzoate)-1,4,7-trioxaheptane and phenylenediamine. The binding properties of anionic guest with this receptor were studied using UV-Vis and fluorescence spectroscopy. These studies revealed that this receptor exhibit selective recognition towards F^- ion among other anions such as HSO_4^-, ClO_4^-, Cl^-, Br^- and I^- in methanol through intermolecular hydrogen bonding of guest and host. Also, we have focused our attention on the receptor-F^- with theoretical computation based on DFT/B3LYP/6-31G(d).

Keywords: Fluorescence, Receptor; UV-Vis spectroscopy, Fluoride, Podand

INTRODUCTION

Complexation between chemosensor and ion makes change in physical properties of the chemosensor. This change is used to both qualitative and quantitative analysis by simple monitoring of an increase or decrease in the absorbance or fluorescence intensities. The optical and photo-physical changes in a molecule are found more valuable in this regard. These receptor molecules exhibit selective response to the specific ions or neutral species to be used as chromosensors. Podands with chromophores as the monitoring sites and a non-cyclic binding site are one of the important class of chemosensors that can be used as sensors for cations, anions and small organic molecules. These open-chain crown ethers allow creating cavities of the appropriate sizes during complexation with metal cations or anions and neutral molecules. In recent years, this unique feature has made these compounds as highly valuable chemosensors among the chemists. Podands are biologically inspired design compounds for naturally occurring ionophores. Some of the podands containing ester, amide or pyrone linkages have also applications in clinical and analytical fields [1-4].

*Corresponding author. E-mail: heshghi@um.ac.ir

Numerous molecules and ionic species are found with widespread use in physiology, medical diagnostics, catalysis and environmental chemistry [5-7].

Anions play important role in many chemical and biological processes; the design and synthesis of receptors capable of binding and sensing anions selectively have drawn considerable attention. The F^- ion is important in clinical treatment for osteoporosis and detection of fluoride toxicity resulting from over accumulation of F^- in bone [8]. There are many anions either used as, or are the products of, the degradation or hydrolysis of chemical warfare agents for example fluoride, which is the decomposition product of Sarin gas found in many nerve agents [9]. Hence, it is highly advantageous to develop high-effective sensors that can detect fluoride anion.

We designed and synthesized new benzimidazole motifs-based molecular receptor **4** for the selective sensing of anions. Then, anion effects on the UV-Vis and fluorescence spectra of receptor **4** were studied by addition of tetrabutylammonium salts ($[Bu_4N]^+X^-$, X = F^-, Cl^-, Br^-, I^-, ClO_4^- and HSO_4^-). The receptor **4** was particularly sensitive as a chemosensor for fluoride ion based on its noticeable UV-Vis and fluorescence responses in the presence of F^- ions. Also, we report a theoretical study on the receptor **4**-F^- complex by using DFT/B3LYP/6-31G(d) calculation [10].

We have focused our attention on the mechanism relating to the hydrogen bonding interaction between this chemosensor and fluoride anion.

EXPERIMENTAL

General Procedures and Materials

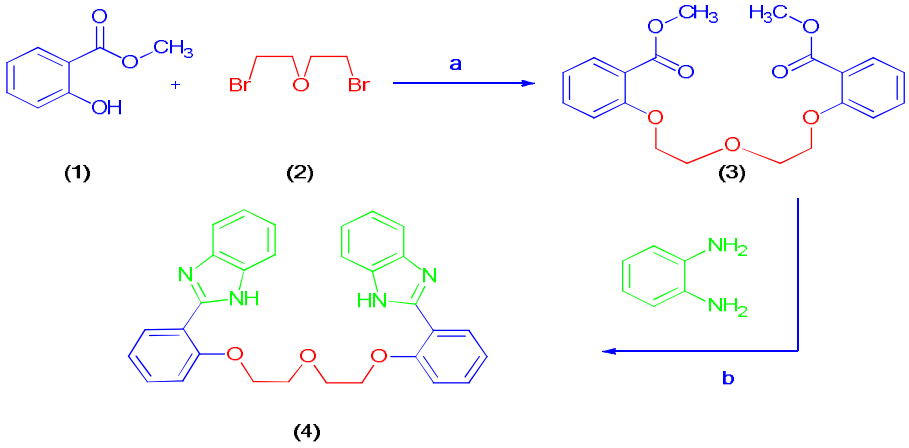
All reagents were obtained commercially and were used without further purification except 1,7-bis(2'-methylbenzoate)-1,4,7-trioxaheptane (**3**), which was synthesized according to our previous reported procedure [11]. ^{1}H NMR spectra were obtained on Bruker-400 MHz Spectrometer. The FT-IR spectra were recorded on AVATAR-370-FTIR ThermoNicolet. CHN elemental analyses were made on elemental Thermo Finnigan Flash EA microanalyses and the results were in good agreement (±0.3%) with the calculated values. The UV-Vis spectra were recorded on a Philips PUB 700 spectrophotometer with a quartz cuvette (path length = 1 cm) at 25 °C. In the UV-Vis titration experiment all the anions were added in the form of tetra-N-butylammonium (TBA) salts purchased from Sigma-Aldrich Company.

Synthesis of 2-(2-(2-(2-(2-(1H-benzo[d]imiazol-2-yl) phenoxy)ethoxy)ethoxy)phenyl)-1H-benzo[d] imidazol (4)

A mixture of 1,7-bis(2'-methylbenzoate)-1,4,7-trioxaheptane (3) (0.374 g, 1 mmol) and 1,2-phenylenediamine (0.216 g, 2 mmol) in polyphosphoric acid (3.26 g) was heated at 120 ºC in an oil bath for 8 h. Upon completion of reaction (monitored by TLC) the solution was cooled to room temperature and poured into crushed ice. Then the solution was neutralized by saturated solution of sodium bicarbonate. Ethyl acetate was then added and the organic layer was separated, and then dried with anhydrous magnesium sulphate. The solvent was evaporated to give brown precipitate. The crude product was purified by recrystallization from ethanol to give **4** (cream-colored precipitate) (Scheme 1). Calc. for $C_{30}H_{26}N_4O_3$: C 73.45%, H 5.34%, N 11.42%. Found: C 73.19%, H 5.29%, N 11.44%; IR (KBr, cm^{-1}) 3337 (N-H, imidazole), 2953-2875 (aliphatic C-H), 1584 (C=N, imidazole), 1279-1241 (C-O-C); ^{1}H NMR δ_H(400 MHz, $CDCl_3$) δ 11.1 (S, 2 H) 8.59 (dd, J_1 = 8 Hz, J_2 = 1.6 Hz, 2H) 7.81 (d, J = 8 Hz, 2H) 7.40 (t, J = 8 Hz, 2H) 7.14-7.28 (m, 6H) 7.09 (t, J = 8 Hz, 2H) 7.02 (d, J = 8 Hz, 2H) 4.42 (m, 4H) 4.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.65, 149.67, 142.97, 133.67, 131.16, 130.36, 122.88, 122.70, 122.30, 119.39, 119.17, 113.71, 110.40, 68.99, 67.52.

Spectroscopic Titration Method

The interactions of receptor **4** with a variety of anions are investigated in a methanol solution through UV-Vis and Fluorescence spectrophotometric titrations. For UV-Vis and Fluorescence spectrophotometric titration of anions, Stock solutions (1.0×10^{-3} M) of the tetrabutylammonium salts of HSO_4^-, ClO_4^-, F^-, Cl^-, Br^- and I^- in methanol and a Stock solution of receptor **4** (1.0×10^{-3} M) were prepared in



Scheme 1. Synthesis of receptor **4**. (a) K_2CO_3, Acetone, reflux. (b) PPA, 120 ºC, 8 h

methanol at 298.2 ± 0.1 K. This solution was used for all spectroscopic studies after appropriate dilution.

RESULTS AND DISCUSSION

The recognition properties of the receptor **4** towards different anions were studied by the UV-Vis and Fluorescence titration.

UV-Vis Study

Chemosensor **4** was titrated by the successive increment of a number of equivalents of F^- and other ions separately and the corresponding UV-Vis absorption spectra were monitored. The effect of F^- concentration on the absorbance intensity of receptor complex with F^- is shown in Fig. 1. Upon addition of fluoride, the band at 310 nm increased minor in intensity and a new peak at 260 nm appeared, that the band at 260 nm progressively increased in intensity with broadening. We believe that at low concentration of anion, F^- ions are surrounded by solvent molecules. But at higher concentration of anion, the F^- can establish hydrogen bonding with the -NH protons of the benzimidazole rings. Additionally, it is possible that the negative charge of anion is dispersed to the π-conjugated system either through intermolecular charge transfer (ICT) or might induce electronic charge in the molecular orbitals of benzimidazole. Similar spectral changes are observed upon the addition of other halogen anion, but the changes are smaller. However, when Cl^-, Br^- and I^- were treated with **4**, the spectra hardly changed even after an excess of the anions was added.

By the same method, receptor **4** was treated with HSO_4^- and ClO_4^-. The addition of HSO_4^- and ClO_4^- did lead to a different spectral change, and the changes were minor. Studying the UV-spectra of $HSO_4^-$and ClO_4^- titrations indicated that upon addition of HSO_4^- and ClO_4^-, the band at 270 nm progressively decreases in absorption (Fig. S5 in Supplementary Data). However, as the Cl^-, Br^- and I^- were titrated into **4**, the spectra were hardly changed even the anions added were excessive.

The selectivity of receptor **4** for F^- anion over other anions was also studied. Variations in the UV-Vis absorption spectra and fluorescence spectra of **4** in methanol (3×10^{-5} M) in the presence of these anions (F^-, Cl^-, Br^-, I^-, HSO_4^- and ClO_4^-) (50 equiv as their tetrabutylammonium salts) are shown in Fig. 2, respectively. It was found that receptor **4** exhibits only an absorption peak at 310 nm in CH_3OH, that a new and blue-shifted absorption is appeared at 260 nm for F^- and 270 nm for HSO_4^- and ClO_4^- ions when these anions are added. Other anions such as Cl^-, Br^- and I^- did not produce any change under the same conditions.

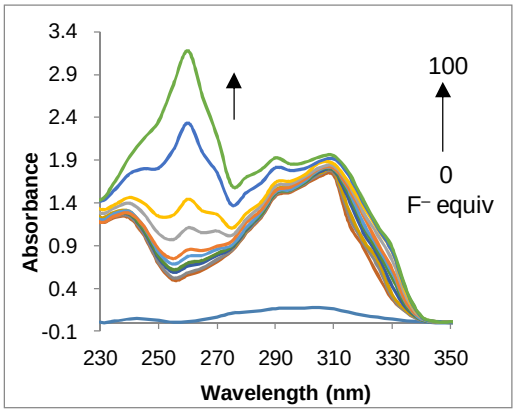


Fig. 1. UV spectral change of receptor **4** ($c = 3 \times 10^{-5}$ M) upon gradual addition of $[Bu_4N]^+F^-$ in methanol.

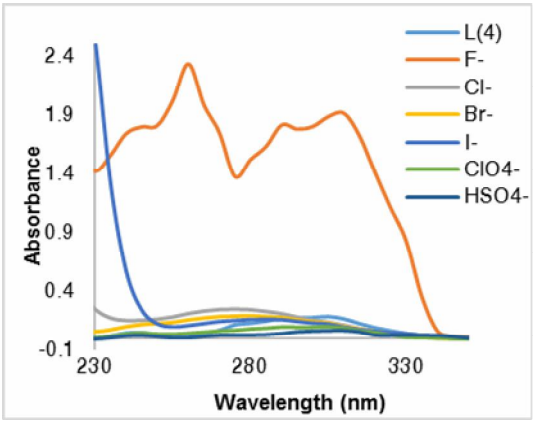


Fig. 2. The absorption spectra of receptor **4** (3×10^{-5} M) in the absence and presence of a 50 equiv. of F^-, Cl^-, Br^-, I^-, HSO_4^-, ClO_4^- anions in CH_3OH.

Through the continuous variation method, the binding stoichiometry of **4**-F^- complex in MeOH was determined using Job's plot experiments. In Fig. 3, the absorbance at 260 nm is plotted against the molar fraction of chemosensor under a constant total concentration. A maximum

absorbance was observed when the molar fraction was 0.5, indicating a 1:1 ratio for the **4**-F^- complex.

Obviously, the recognition function of **4** is selective and strongest for F^-. The reason may be that receptor **4** has the cavity that is proper to F^-, which is a spherical anion, and hence can match the receptor better than that of the trigonal and tetrahedral anions. Also, the basicity of F^- is stronger than HSO_4^- and ClO_4^-. Finally, considering the difference in electronegativity, the ability of F^- binding to H is much stronger than that of Cl^-, Br^-, and I^-.

To understand the interactions between receptor **4** and the F^- anion, the B3LYP/6-31G(d) level using DFT approach was performed (Table. S6 in Supplementary Data). Molecular modeling showed that the anion receptor **4** has a right shape for F^- anion.

The energy minimized structure of receptor **4** and F^- is shown in Fig. 4. The fluoride ion is bridged between the two benzimidazole moieties *via* the NH...F hydrogen bonds. The interatomic distance between the fluoride anion and the benzimidazole NH proton is 1.520 A˚, which is very close to the length of the HF molecule (0.92 A˚) and the N...HF angle is close to linearity (164.4°). The N-H bond lengths are lengthened significantly from 1.008 A˚ in **4** to 1.064 A˚ in the fluoride complex. These bonding parameters clearly show that the involved hydrogen bonds are particularly strong.

Figure 5 illustrates the molecular orbitals of **4.** As shown in Fig. 5, the highest-energy occupied molecular orbital (HOMO) is delocalized over the benzimidazole moieties and the neighboring phenyl rings, whereas the lowest-energy unoccupied molecular orbital (LUMO) is more localized on the core of phenyl rings, which these results indicate intramolecular charge-transfer (ICT) character of the HOMO-LUMO transition.

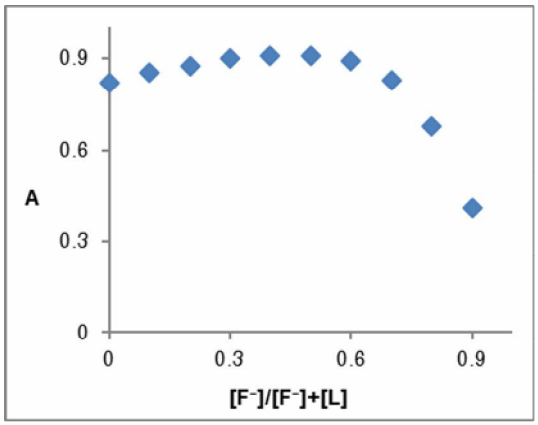


Fig. 3. Job's plot of a 1:1 complex of **4**-F^- complex, where the absorbance at 260 nm was plotted against the mole fraction of F^-.

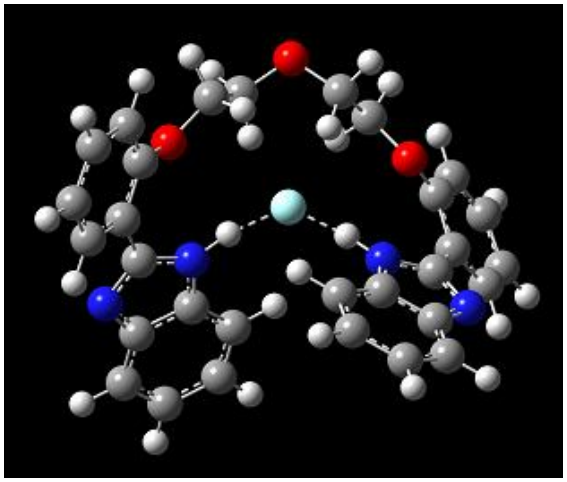


Fig. 4. The optimized structure of 1:1 complex between receptor **4** and F^-. DFT/B3LYP/6-31G(d), Gaussian 09.

Fluorescence Study

Fluorescence spectroscopy studies were carried out to evaluate the ability of **4** to operate as a fluorescent anion sensor (Fig. 6). The receptor **4** displayed a maximum emission at 375 nm when excited at 260 nm. The changes in fluorescence intensity of **4** upon the addition of F^- are shown in Fig. 6. However, Br^-, Cl^-, I^-, HSO_4^- and ClO_4^- in MeOH do not affect the emission spectra, even when present in excess (<100 equiv.). We believe that this is the outcome of a conjunct operation from the difference in size of binding sites and the direct result of the basicity of anions.

Increasing the F^- ion concentration relative to receptor **4** resulted in fluorescence enhancement. It is believed that anion-hydrogen bonding with the receptor will change the photophysical properties of fluorophore because the complexed anion increases the rigidity of the host molecules. Receptors that have N-H functional group

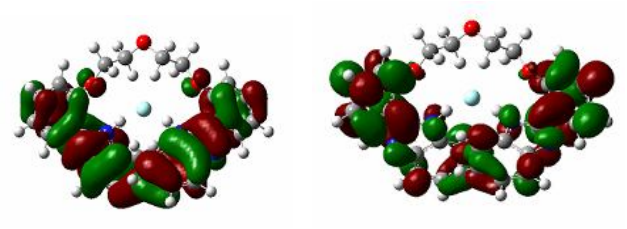


Fig. 5. HOMO (left) and LUMO (right) features of receptor **4** as obtained from DFT/B3LYP/6-31G(d) level calculation.

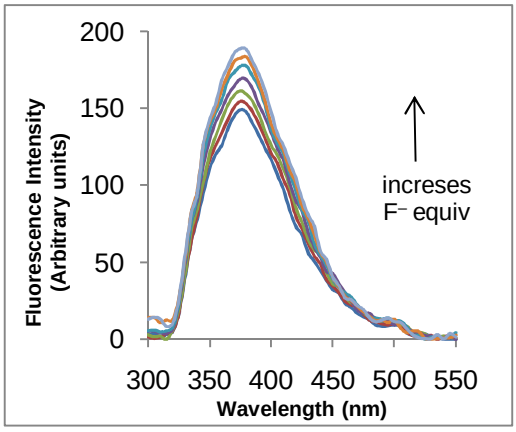


Fig. 6. Fluorescence change of receptor **4** (c = 3 µM) upon gradual addition of $[Bu_4N]^+F^-$ in MeOH (excited at 260 nm).

bound, as chemosensor of F^-, have been reported in various articles [12-16]. In aprotic solvent as the concentration of F^- ion increases the fluorescence intensity decreases. Since, addition of F^- resulted in the deprotonation of N-H to N^-, which has no affinity for F^- ion and this system does not have any rigidity. While in methanol, as a protic solvent, F^- ions are surrounded by hydrogen bonding of solvent which causes a decrease in the basicity of F^-. At this condition F^- ions cannot deprotonate the N-H of functional group. Therefore, as the concentration of F^- ions increases the hydrogen bonding between F^- and N-H of the benzimidazole rings increases, and as a result the fluorescence intensity increases.

CONCLUSIONS

In summary, we designed and synthesized a novel fluorescence probe based on benzimidazole motifs for determination of F^- in a wide range concentration. This compound (chemosensor) displayed a sensor properties and showed sensitivity and selectivity towards F^- in absorption and emission spectrophotometry that resulted in strong hydrogen bond between benzimidazole NH protons and the fluoride anion. Short synthetic route, easy purification, remarkable fluorescence and UV-Vis signal responses, symmetrical bis-acceptor with two active binding sites and high sensitivity to F^- were important features of this novel chemosensore.

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:…….

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