Highly selective recognition of fluoride anion through direct deprotonation of intramolecularly hydrogenbonded phenolic hydroxyl groups

Xiang Zhang, Jie Fu, Tian-Guang Zhan, Liyan Dai, Yingqi Chen, Xin Zhao

PII: S0040-4039(13)01160-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.07.021
Reference: TETL 43219

To appear in: *Tetrahedron Letters*

Received Date: 3 May 2013
Revised Date: 23 June 2013
Accepted Date: 3 July 2013

Please cite this article as: Zhang, X., Fu, J., Zhan, T-G., Dai, L., Chen, Y., Zhao, X., Highly selective recognition of fluoride anion through direct deprotonation of intramolecularly hydrogenbonded phenolic hydroxyl groups, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.07.021

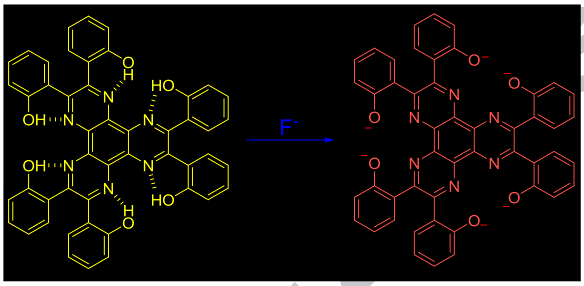
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Highly selective recognition of fluoride anion through direct deprotonation of intramolecularly hydrogen–bonded phenolic hydroxyl groups

Leave this area blank for abstract info.

Xiang Zhang, Jie Fu, Tian-Guang Zhan,
Liyan Dai,* Yingqi Chen, Xin Zhao*



Tetrahedron Letters
journal homepage: www.elsevier.com

Highly selective recognition of fluoride anion through direct deprotonation of intramolecularly hydrogen–bonded phenolic hydroxyl groups

Xiang Zhang[a], Jie Fu[b], Tian-Guang Zhan[b], Liyan Dai[a*], Yingqi Chen[a], Xin Zhao [b*]

[a]*Department of Chemical and Biological Engineering, Zhejiang University, Hangzhou 310027, China*
[b]*Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

ARTICLE INFO

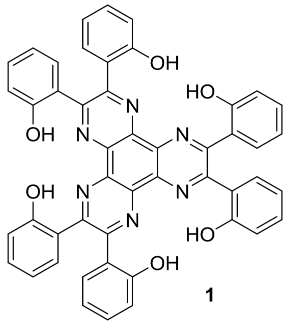
Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Recognition
Fluoride
Phenol
Deprotonation
Hexaazatriphenylene

ABSTRACT

A novel chemosensor for fluoride anion has been developed. This sensor, constructed by merging six phenolyl units into a hexaazatriphenylene (HAT) core, could recognize F^- visually and spectroscopically with high selectivity over other anions, which was demonstrated by naked-eye experiment and UV–vis absorption spectroscopy study.

Chemosensors capable of selectively and efficiently detecting fluoride anion have gained considerable attention in the past decades because of the duplicitous effects of fluoride anion in biological systems.[1] While it exhibits beneficial effect on dental care and has been widely adopted in the treatment of osteoporosis,[2] excessive fluoride ions intake may lead to fluorosis, urolithiasis, and even cancer.[3] In this context, a vast number of fluoride anion sensors with various chemical structures have been developed and different working models that utilize the changes of color (naked-eye), UV–vis absorption, fluorescence emission, or electrochemical property have been established. Among the various fluoride anion sensors developed in the past decades, the use of NH unit, including urea/thiourea[4], pyrrole/indole[5], and amide[6], to bind fluoride anion via hydrogen-bonding interaction, has been extensively studied and well documented. In contrast, very little attention has been paid to hydroxyl-based system,[7] although hydroxyl group can also be excellent hydrogen-bonding donor and its proton even exhibits more acidity compared to the proton of NH unit. The reason might be attributed to low recognition selectivity of OH when it binds to anions through hydrogen–bonding. Herein we report a hexaazatriphenylene (HAT)-phenol hybrid chemosensor (**1**) which displays a high degree of F^- discrimination both in organic solvent and aqueous mixture by direct deprotonation of phenolic OHs. The high selectivity was revealed to originate from the formation of intramolecular hydrogen bonds between the phenolic OHs and nitrogen atoms of HAT core. As a result, the formation of intermolecular hydrogen bonds between OH units and anions should be weakened dramatically (or even prevented) and only deprotonation of OHs by F^- could occur.



1

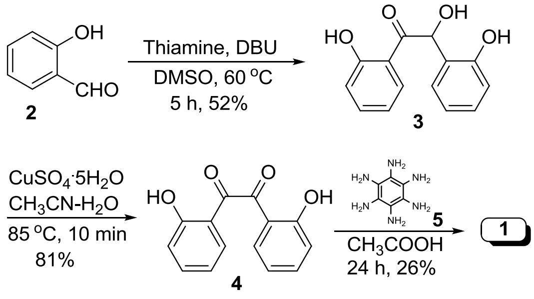
The synthesis of sensor **1** is shown in Scheme 1. 2,2'-Dihydroxy-benzoin (**3**) was firstly obtained in 52% yield through benzoic condensation of salicylaldehyde (**2**) and then **3** was oxidized to generate diketone **4** in 81% yield. Refluxing a mixture of **4** and hexamine **5**[8] in glacial acid afforded **1** in 26% yield (see Supplementary materials for details).

Single crystals of **1** suitable for X-ray crystallographic analysis were grown by slowly diffusing petroleum ether into a solution of **1** in acetone.[9] As shown in Figure 1, the six phenolic OH groups are intramolecularly hydrogen-bonded with the nitrogen atoms of HAT core. The distances between these

---

* Liyan Dai. Tel.: 0086-571-87952693; fax: 0086-571-87952693; e-mail: dailiyan@zju.edu.cn.

* Xin Zhao. Tel.: 0086-21-54925023; fax: 0086-21-64166128; e-mail: xzhao@mail.sioc.ac.cn.



Scheme 1. Synthesis of compound **1**.

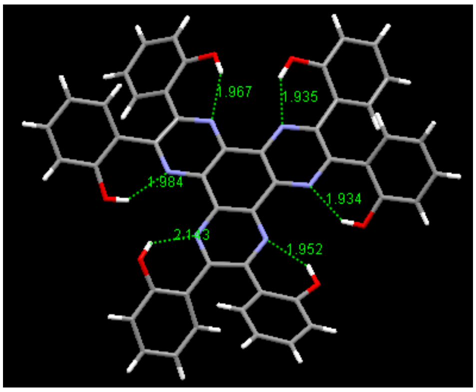


Figure 1. The crystal structure of **1**.

hydrogen atoms and nitrogen atoms are in the range of 1.94–2.14 Å, notably shorter than the sum of their van der Waals radii (d_0=2.65 Å, d/d_0=0.73–0.81). Such short bond lengths suggest that these intramolecular hydrogen bonds are quite strong and thus might prevent the OH units from forming intermolecular hydrogen bond with external hydrogen-bonding acceptors such as anions. Furthermore, it is also found that all the phenolyl units twisted out of the HAT plane, as a result of the steric effect between the hydrogen atoms of the adjacent phenolyl units.

Naked-eye experiment was first carried out in DMSO. As depicted in Figure 2, distinctive color change of the solution of **1** from pale yellow to reddish orange was observed upon the addition of 5 equiv of tetra-n-butylammonium fluoride (TBAF). In sharp contrast, no obvious color change could be detected by naked-eye even in the presence of up to 100 equiv of AcO^-, $H_2PO_4^-$, Cl^-, Br^-, I^-, NO_3^-, ClO_4^-, and HSO_4^-, demonstrating a high selectivity of **1** towards F^- over other anions. Such significant color change facilitates its application as a colorimetric sensor for F^-.

It was found that compound **1** was fluorescence silent, which might be attributed to the charge transfer between electron-deficient HAT core and electron-rich phenol units. Fluorescence emission could not be turned on upon the addition of anions. Therefore, the recognition behavior of **1** was further investigated using UV–vis spectroscopy. The solution of **1** in DMSO exhibited a maximum absorption peak at 377 nm. Upon incremental introduction of F^- in the form of TBAF salt, this peak decreased gradually and concomitant increases of an absorption band in the range of 250-325 nm was observed (Figure 3a). Moreover, gradual increase of absorption in the range of 430-500 nm was also simultaneously observed. All these results clearly indicated that fluoride anions interacted with sensor **1**, resulting in the dramatic UV-vis absorption change of the sensor.

The selectivity of **1** towards different anions was then investigated by treating **1** with excessive F^-, Cl^-, Br^-, I^-, HSO_4^-, NO_3^-, ClO_4^-, AcO^-, and $H_2PO_4^-$ in DMSO, respectively. Upon the addition of 50 equiv of F^- into a DMSO solution of **1**, its absorbance at 377 nm declined dramatically from 0.98 to 0.18 (Figure 3b). In contrast, for the other anions, even for AcO^-, and $H_2PO_4^-$ from which fluoride is hard to be discriminated, the spectral changes of **1** were quite small when they were introduced into the solution of **1** respectively. The dramatic difference clearly indicates a high sensing selectivity of **1** towards F^- over other anions.

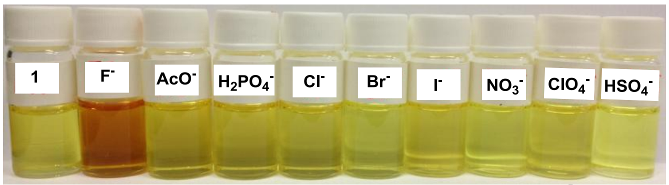


Figure 2. Photo of the solutions of **1** (5×10^{-4} M in DMSO) before and after the addition of F^- (5 equiv) and other anions (100 equiv), respectively.

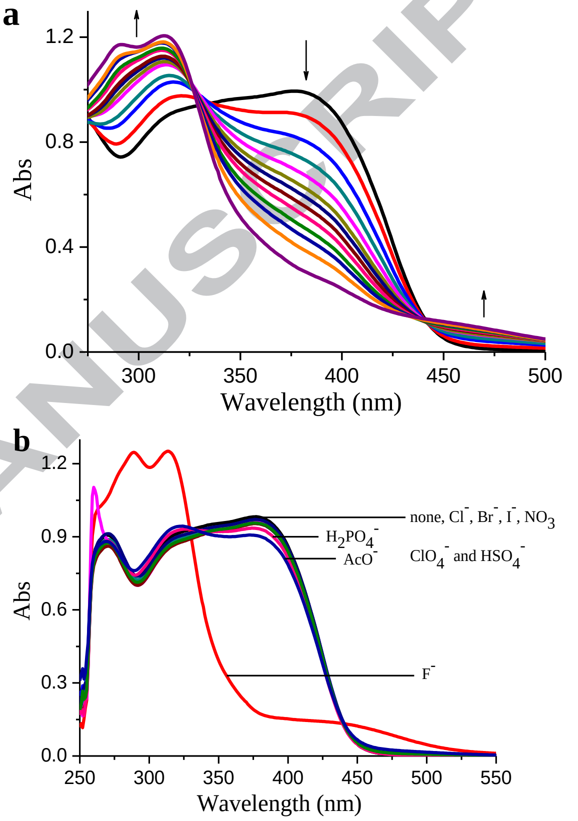


Figure 3. (a) UV–vis spectral of sensor **1** (2.5×10^{-5} M in DMSO) upon the addition of 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 30, and 50 equiv of F^-, and (b) UV–vis spectral of sensor **1** (2.5×10^{-5} M in DMSO) upon the addition of 50 equiv of different anions.

It was reported that recognition of F^- in aqueous phase is extremely difficult because of the strong hydration of fluoride anion by water molecules,[1] In order to explore the recognition capability of **1** in aqueous mixture, UV-vis titration of **1** with F^- in a DMSO–H_2O (9:1, v/v) binary solvent was also recorded. As exhibited in Figure 4a, progressive addition of F^- into a solution of **1** in DMSO–H_2O (9:1, v/v) leads to quite similar spectra change as that observed in DMSO, suggesting similar interacting pattern between **1** and F^- in DMSO with or without the presence of water. Similarly, while the introduction of F^- resulted in considerable UV–vis absorption change of **1** in DMSO–H_2O (9:1, v/v), its absorption band exhibited almost no change upon the addition of even 1000 equiv of the other anion tested above (Figure 4b), indicating the excellent selectivity towards F^- was still kept in the presence of water.

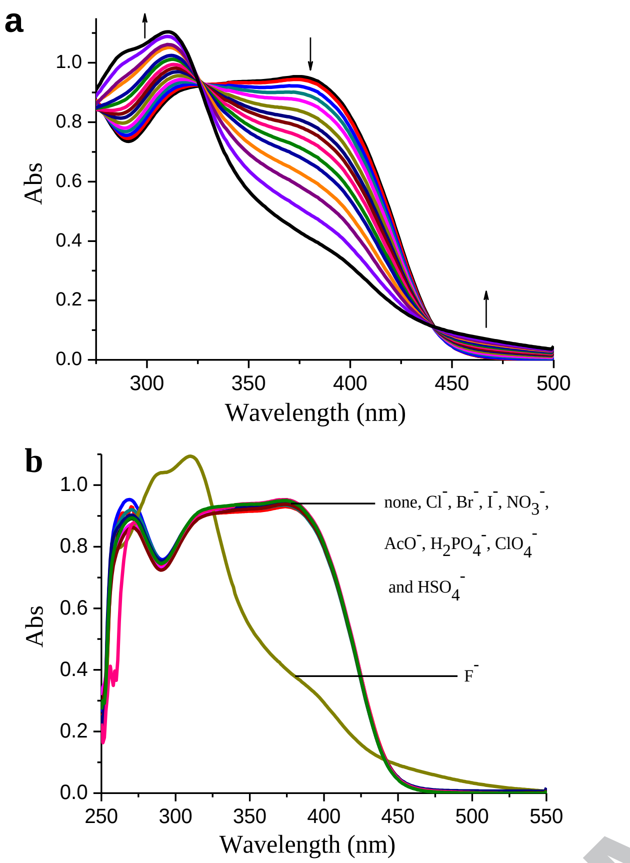


Figure 4. (a) UV–vis spectral of sensor **1** (2.5×10^{-5} M in DMSO–H_2O (9:1, v/v)) upon the addition of 0, 10, 30, 60, 100, 150, 200, 300, 400, 500, 700 and 1000 equiv of F$^-$, and (b) UV–vis absorption changes of **1** (2.5×10^{-5} M in DMSO–H_2O (9:1, v/v)) upon the addition of 1000 equiv of different anions.

To further probe the recognition mechanism between F$^-$ and sensor **1**, ^{1}H NMR dilution and titration experiments were performed. ^{1}H NMR dilution experiment in DMSO-d_6 (0.1–10 mM) revealed that no concentration-dependent shifts of the signals of **1** were observed in the whole concentration range examined, suggesting that no dimerization or other higher order aggregation of **1** existed under the experimental condition. Upon the addition of F$^-$ (0.25 equiv), the signal of phenolic OH protons broadened first and then disappeared completely when only 0.5 equiv of F$^-$ was added. The protons of the aromatic rings consistently displayed continuous upfield-shifts with the increase of the concentration of fluoride. Furthermore, a signal (16.1 ppm) corresponding to HF$_2^-$ appeared when 10 equiv of fluoride was introduced (Figure 5, inset).[10] These phenomena strongly suggested that deprotonation of phenolic OH by F$^-$ occurred once fluoride was introduced. This result is different from the examples reported in the previous literatures,[4b,11] which usually involve a two-stepwise mechanism, this is, formation of hydrogen bond between NH(or OH) and F$^-$ first and then deprotonation of the NH (or OH) by excessive F$^-$. In this case, there was no hydrogen-bonding step but direct deprontonation. This should be attributed to the strong intramolecular hydrogen-bonding interaction in sensor **1** which prevents its phenolic OHs from forming stable intermolecular hydrogen bond with fluoride anion. As a result, direct deprotonation of OHs by F$^-$ occurs due to its high basicity. The deprotonation of hydroxyl groups was further ascertained by ^{1}H NMR titration experiment of **1** with OH$^-$, a strong Brønsted base instead of a hydrogen-bonding acceptor, which showed similar ^{1}H NMR spectra change as that of F$^-$ (Figure S1, Supplementary Information). For the other anions, their basicities are not high enough to deprotonize the OHs. Since the formation of intermolecular hydrogen bonds with **1** is blocked, the interaction between them and **1** should be very weak, which leads the high selectivity to fluoride anion. This assumption was supported by a control experiment using Cl$^-$, an anion that was reported capable of forming hydrogen bond with free phenolic OH.[12] The chemical shift of the hydroxyl proton of **1** displayed almost no change upon the addition of 10 equiv of Cl$^-$, suggesting no detectable hydrogen-bonding exists between chloride anion and the hydroxyl units (Figure S2, Supplementary Information). Other basic anions such as CO$_3^{2-}$ and HCO^{3-} were also examined. Upon the addition of 50 equiv of them, decline of absorbance of **1** at 377 nm was also observed. However, the decreasing extents caused by CO$_3^{2-}$ and HCO^{3-} were not as large as that by F$^-$, indicating that **1** still exhibited selectivity towards F$^-$. Neutral basic species such as n-butylamine was also tested. Upon the addition of n-butylamine, the absorption spectrum of **1** just exhibited very small change, indicating an excellent selectivity between F$^-$ and neutral basic species (Figure S3, Supplementary Information).

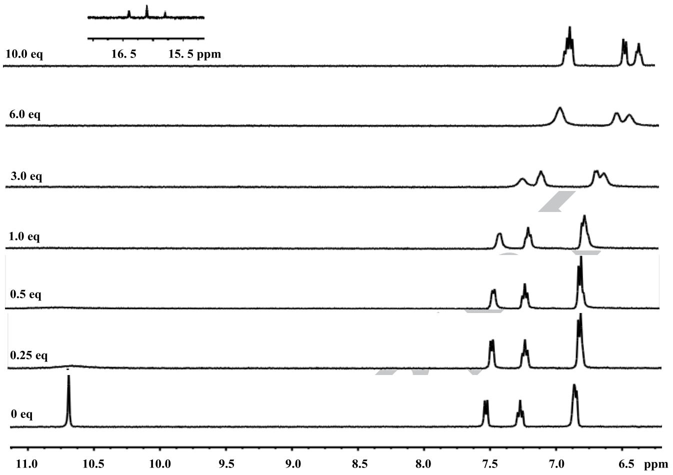


Figure 5. Partial ^{1}H NMR spectra (400 MHz) of **1** upon the addition of F$^-$ in DMSO-d_6 at 25 °C.

In summary, we have developed a novel chemosensor for highly selective recognition of fluoride anion. Thanks to the high acidity of the phenolic OH units and the strong intramolecular hydrogen bonds formed between them and HAT core, the formation of intermolecular hydrogen-bonding between the OHs and anions was blocked and thus only direct deprotonation of OHs by F$^-$ could occur, which led to a high selectivity to fluoride over other anions. While most fluoride sensors have mainly been constructed by employing NH unit as hydrogen-bonding donor to bond F$^-$, this work demonstrates that the use of OH could also be a promising way to construct sensors for F$^-$ detection. One advantage of the use of phenolic OH is that the deprotonation of hydroxyl unit usually results in multiplex responses of the sensors due to the generation of phenolic anion. Taking this advantage, more phenolic OH-based F$^-$ sensors are anticipated in the near future.

Acknowledgments

We thank NSFC (No. 21172249) for financial support.

Supplementary data

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

References and notes

1. Cametti, M; Rissanen, K. *Chem. Soc. Rev.* **2013**, *42*, 2016–2038.
2. (a) Kirk, K. L. *Biochemistry of the Elemental Halogens and Inorganic Halides*,p58, Plenum, New York, 1991; (b) Hetrick, E. M.; Schoenfisch, M. H. *Annu. Rev. Anal. Chem.* **2009**, *2*, 409–433.

3. (a) Kleerekoper, M. *Endocrinol. Metab. Clin. North Am.* **1998**, *27*, 441-452; (b) Ayoob, S.; Gupta, A. K.; *Crit. Rev. Environ. Sci. Technol.* **2006**, *36*, 433–487; (c) Riggs, B. L. *Bone and Mineral Research, Annual 2, Elsevier,* Amsterdam, 1984; (d) Bassin, E. B.; Wypij, D.; Davis, R. B. *Cancer Causes Control* **2006**, *17*, 421–428.
4. (a)Amendola, V.; Fabbrizzi, L.; Mosca, L. *Chem. Soc. Rev.* **2010**, *39*, 3889–3915; (b) Li, A.-F.; Wang, J.-H.; Wang, F.; Jiang, Y.-B. *Chem. Soc. Rev.* **2010**, *39*, 3729–3745; (c) Liu, W. X.; Jiang, Y. B. *J. Org. Chem.* **2008**, *73*, 1124–1127; (d) Jose, D. A.; Kumar, D. K.; Gnagguly, B.; Das, A. *Org. Lett.* **2004**, *6*, 3445–3448.
5. (a) Gale, P. A.; Sessler, J. L.; Král, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140–5141; (b) Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17–55; (c) Liu, X.-M.; Zhao, Q.; Song, W.-C.; Bu, X.-H. *Chem. Eur. J.* **2012**, *18*, 2806–2811; (d) Chang, K.-J.; Moon, D.; Lah, M. S.; Jeong, K. S.; *Angew. Chem. Int. Ed.* **2005**, *44*, 7926–7929.
6. (a) Shang, X.-F.; Xu, X.-F.; Lin, H.; Shao, J.; Lin, H.-K. J. *Inclusion phenom. Macrocycl. Chem.* **2007**, *58*, 275-281; (b) Kang, S. O.; Powell, D.; Bowman-James, K. *J. Am. Chem. Soc.* **2005**, *127*, 13478–13479; (c) Kang, S. O.; Powell, D.; Day, V. W. Bowman-James, K. *Angew. Chem. Int. Ed.* **2006**, *45*,1921–1925.
7. (a) Lee, C.; Lee, D. H.; Hong, J.-I. *Tetrahedron Lett.* **2001**, *42*, 8665–8668; (b) Devaraj. S.; Saravanakumar,D.; Kandaswamy, M. *Tetrahedron Lett.* **2007**, *48*, 3077–3081; (c) Luxami, V. Kumar, S. *Tetrahedron Lett.* **2007**, *48*, 3083–3087; (d) Chen, C.-F.; Chen, Q.-Y. *New. J. Chem.* **2006**, *30*, 143–147.
8. Xiao, Z.-Y.; Zhao, X.; Jiang, X.-K.; Li, Z.-T. *Langmuir* **2010**, *26*, 13048–13051.
9. The crystal structure has been deposited at the Cambridge Crystallographic Data Center and assigned the deposition number CCDC 937305.
10. Shenderovich, I. G.; Limbach, H.-H.; Smirnov, S. N.; Tolstoy, P. M.; Denisov, G. S.; Golubev, N. S. *Phys. Chem. Chem. Phys.* **2002**, *4*, 5488–5497.
11. (a) Boiocchi, M.; Boca, L. D.; Gómez, D. E.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *J. Am. Chem. Soc.* **2004**, *126*, 16507–16514; (b) Jose, D. A.; Kar, P.; Koley, D.; Ganguly, B.; Thiel, W.; Ghosh, H. N.; Das, A. *Inorg. Chem.* **2007**, *46*, 5576–5584.
12. Winstanley, K. J.; Sayer, A. M.; Smith, D. K. *Org. Biomol. Chem.* **2006**, *4*, 1760-1767.