Pergamon

Tetrahedron Letters 42 (2001) 2805–2808

TETRAHEDRON LETTERS

Fluorescent anion receptors with iminoylthiourea binding sites—selective hydrogen bond mediated recognition of CO_3^{2-}, HCO_3^- and HPO_4^{2-}

Gunther Hennrich,[a,*] Helmut Sonnenschein[b] and Ute Resch-Genger[a,*]

[a]*Federal Institute for Materials Research and Testing (BAM), Richard-Willstätter-Straße 11, 12489 Berlin, Germany*
[b]*Institute for Nonclassical Chemistry, Permoserstraße 15, 04303 Leipzig, Germany*

Received 22 February 2001; accepted 23 February 2001

Abstract—A number of structurally simple, fluorescent sensor molecules based on the iminoylthiourea/1,2,4-thiadiazole unit are presented, which display extraordinarily strong fluorescence enhancement selectively upon complexation of HCO_3^-, CO_3^{2-} and HPO_4^{2-}.

Selective recognition and sensing of anions by artificial host molecules is of considerable importance in the field of supramolecular chemistry.[1] Anion recognition in biological systems is achieved via hydrogen bonding by highly preorganized proteins with sterically well defined complexation sites in the interior of the protein.[2] The complexation properties of such receptor proteins for anions can be mimicked by chemically sophisticated macrocyclic hosts with well preorganized binding sites.[3] Also, with structurally more simple acyclic receptors, good selectivities in anion binding have been achieved due to the suitable orientation of the H-donor functions employed.[3a,4] In any case, recognition and discrimination between different anions can only be successful if the receptor can provide suitable coordination sites.[5] Among a variety of possible H-bond donor groups, the amide[6] and (thio)urea[7] motif have proven to be very useful in neutral anion binding receptors.

Besides electroactive sensor molecules,[8] a method of great practical relevance to the monitoring of successful complexation is the use of chromoionophores or fluorescent devices.[9] Here, anion complexation induces changes in the spectroscopic properties of the host molecule or the receptor assembly, ideally leading to an analyte specific visible color change, a spectral shift in the emission spectrum, and an enhancement of the emission intensity.[10]

In this paper we present a series of fluorescent anion receptors based on the redox active 1,2,4-thiadiazole/iminoylthiourea system.[11] The synthesis of the iminoylthioureas (reduced form) **1** and **3** from 1-naphthoyl-guanidine and the respective mono- or diisothiocyanate is straightforward as well as their oxidative conversion into the 1,2,4-thiadiazoles (oxidized form) **2** and **4** (Fig. 1).[†]

* Corresponding authors. Present address: Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, TX 78712, USA (G.H.). Tel.: 512-471-5580; fax: 512-471-7791; e-mail: g.hennrich@mail.utexas.edu

† Compound **1**: Mp 266–270°C. ^{1}H NMR ($CDCl_3$): δ_H=7.24–7.71 (10H, m, Ph, Naph), 7.94–7.97 (2H, m, Naph), 8.14–8.21 (4H, m, Naph), 8.57–8.60 (2H, m, Naph), 9.8 (2H, bs, N*H*), 10.3 (2H, bs, N*H*), 11.8 (2H, bs, N*H*), 14.5 (2H, bs, N*H*); ^{13}C NMR ($CDCl_3$): δ_C=124.63, 124.75, 126.27, 126.40, 127.28, 128.86, 129.01, 130.37, 134.01, 134.48, 135.47, 136.94, 149.57 (Ph, Naph), 155.42 (-*C*=NH), 170.28 (-*C*=O), 177.22 (-*C*=S). HRMS found: 619.1697; calcd for $[C_{32}H_{26}N_8O_2S_2+H]^+$: 619.1698. R_f=0.71 (*n*-hexane–ethyl acetate, 2:1). Compound **2**: Mp 211–214°C. ^{1}H NMR (DMSO-d_6): δ_H=7.29–7.74 (12H, m, Ph, Naph), 7.93–8.20 (6H, m, Naph), 10.6–11.4 (4H, m, -N*H*); ^{13}C NMR (DMSO-d_6): δ_C=114.29, 118.04, 118.66, 124.80, 124.92, 125.82, 126.28, 126.57, 126.00, 128.34, 129.69, 130.34, 133.09, 133.32, 133.68, 135.02 (Ph, Naph), 158.87 (-*C*=N-), 166.92 (-*C*=O), 177.64 (-*C*-S-). HRMS found: 613.1221; calcd for $[C_{32}H_{22}N_8O_2S_2-H]^-$: 613.1229. R_f=0.15 (*n*-hexane–ethyl acetate, 1:2). Compound **3**: Mp 124–127°C. Found: C, 69.00; H, 4.41; N, 13.57; calcd for $C_{23}H_{18}N_4OS$: C, 69.35; H, 4.52; N, 14.07%. ^{1}H NMR (DMSO-d_6): δ_H=7.7.48–8.08 (14H, m, Naph), 9.09, 9.61, 10.35–10.55, 12.24, 14.87 (4 H, bs, N*H*); ^{13}C NMR (DMSO-d_6): δ_C=121.95, 123.36, 124.79, 125.44, 125.93, 126.46, 126.80, 127.39, 127.97, 128.42, 129.50, 131.85, 133.16, 133.62, 135.27 (Naph), 156.51 (-*C*=NH), 170.63 (-*C*=O), 179.64 (-*C*=S). MS (FAB) *m*/*z* (%) 397, ([M–H]$^-$, 100%), 327 (88), 271 (31), 211 (26). R_f=0.39 (*n*-hexane–ethyl acetate, 2:1). Compound **4**: Mp 227–230°C. ^{1}H NMR (DMSO-d_6): δ_H=7.47–8.21 (14H, m, Naph), 10.94 (1H, s, -N*H*), 11.36 (1H, s, -N*H*); ^{13}C NMR (DMSO-d_6): δ_C=117.83, 121.79, 124.92, 124.99, 125.88, 126.14, 126.28, 126.43, 126.98, 128.33, 128.39, 129.73, 130.36, 133.10, 133.61, 133.90, 135.22 (Naph), 158.81 (-*C*=N-), 166.84 (-*C*=O), 180.43 (-*C*-S-). HRMS found: 395.0974; calcd for $[C_{23}H_{16}N_4OS-H]^-$: 395.0987. R_f=0.50 (toluene–ethyl acetate, 1:1).

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00324-0

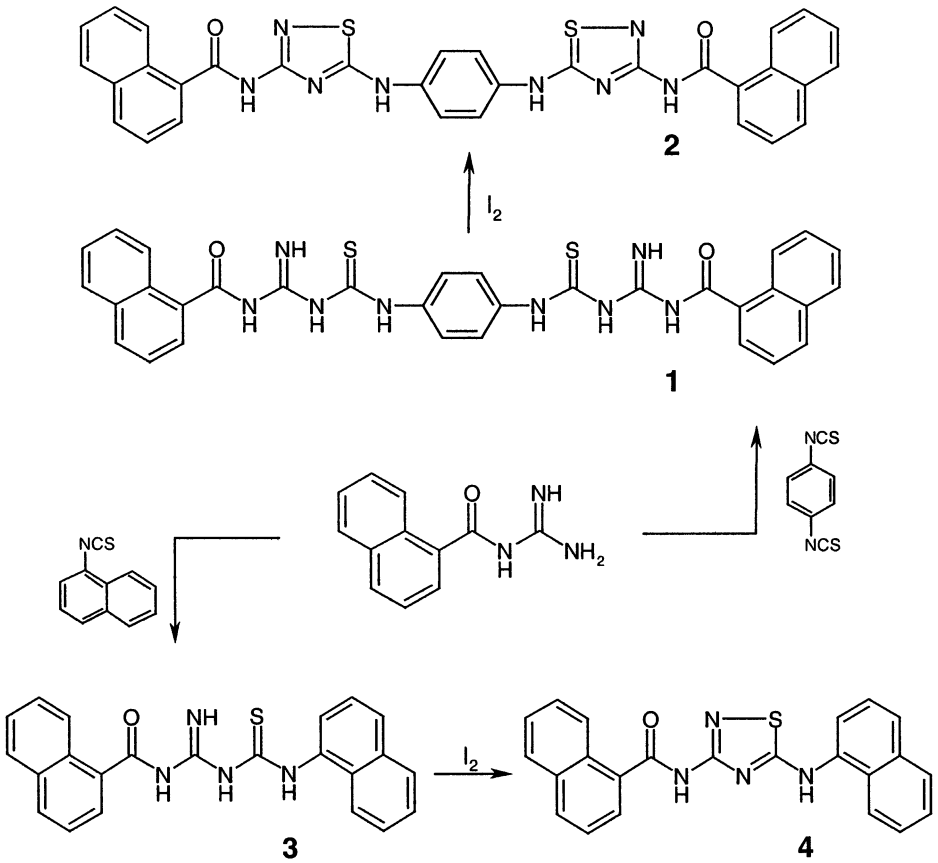

Figure 1. Synthesis of the anion receptors **1** and **3** (reduced forms), and **2** and **4** (oxidized forms).

The fluoroionophore system **1**/**2** consists of two receptor side arms connected via a phenylene group. The reduced form **1** possesses eight potential hydrogen bond donating NH groups. Upon oxidation, the iminoylthiourea unit is converted into 1,2,4-thiadiazole and concurrently, the number of free NH groups lowered to four in compound **2**. To estimate a potential cooperative complexation effect by the two heteroatomic side arms, the simple iminoylthiourea **3** and the respective 1,2,4-thiadiazole derivative **4** were synthesized. All the receptor molecules carry terminal naphthyl substituents as fluorescent reporter groups.

The spectroscopic investigations were performed in methanol as a polar, protic solvent with the anions added as aqueous solutions of their sodium salts. As follows from previous studies on the cation complexation features of similar compounds, the influence of Na^+ on the spectroscopic behavior of **1**, **2**, **3** and **4** can be disregarded.[12] Free **1** and **2** show broad structureless naphthalene-like emission bands with a maximum at 387 and 392 nm, respectively, when excited at 310 nm. The absorption spectra of both compounds between 200 and 400 nm are dominated by the broad naphthalene band with a maximum at 303 nm (**1**) and 304 nm (**2**).

Upon addition of various anions in a 1000-fold excess, no changes in the emission properties of both **1** and **2** could be observed for Cl^-, I^-, Br^-, ClO_4^- and NO_3^-. A strong fluorescence enhancement (FE) is obtained for **1** in the presence of CO_3^{2-} (53-fold) and HCO_3^- (39-fold). However, minor effects are found for HPO_4^{2-} and HSO_4^- with FE-factors of 12 and 4, respectively (Fig. 2). Upon complexation, the emission band is shifted hypsochromically to 373 nm while no remarkable anion binding induced changes in the absorption spectra can be detected. The changes in fluorescence are strongly

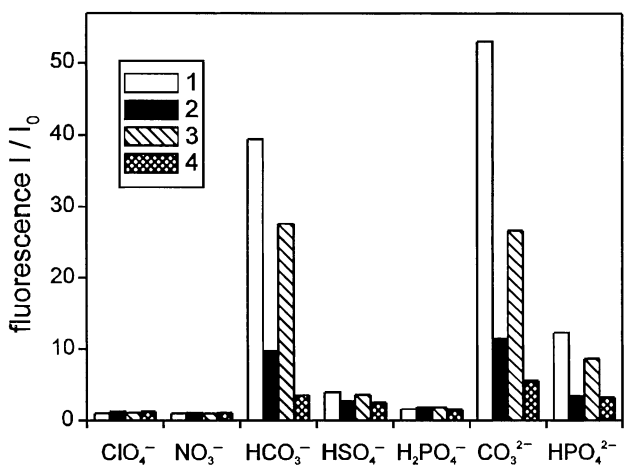

Figure 2. Fluorescence intensity (I_0: uncomplexed, I: complexed) of **1**, **2**, **3** and **4** ($c = 10^{-5}$ mol/L in unbuffered methanol solution, excitation at 310 nm) in the presence of a 1000-fold excess of various anions (Cl^-, Br^- and I^- left out), measurement 120 h after addition.

time dependent, reaching constant signals after approximately 72 hours. In the case of **2**, showing similar spectral effects, the following anion-induced FE-factors are observed: 12 upon addition of CO_3^{2-}, 10 in the presence of HCO_3^-, 4 and 3 with HPO_4^{2-} and HSO_4^-, respectively.

Since the HSO_4^- anion is a relatively strong acid ($pK_a = 1.94$ in aqueous solution), the enhancement of the emission intensity is mainly the consequence of a simple protonation. As no effects occur in the presence of $H_2PO_4^-$, the HPO_4^{2-} induced changes of the emission behavior of **1** and **3** cannot be attributed to the anion's acidity. The same is true for the rather basic HCO_3^- and CO_3^{2-} anions. Also, protonation of all four compounds **1**, **2**, **3** and **4** using perchloric acid immediately leads only to modest fluorescence enhancements with FE-factors of 3 (**1**), 2 (**2**), 4 (**3**) and 3.5 (**4**) for complete protonation. The pK_b values determined by fluorometric pH titration were almost identical with 4.44 for compound **1** and 4.20 for **2** and again very similar with 4.56 for **3** and 4.16 for compound **4**. Hence, the H-donor capacity of the amido-NH is nearly equal for all four receptors molecules. Considering this fact, it is not surprising to find the same tendencies in the anion selectivities as for the reduced forms **1** and **3** using receptors **2** and **4** (oxidized forms).

A similar time dependent fluorescence enhancement has been measured for **3** in the presence of CO_3^{2-} and HCO_3^- (FE-factor 27 for both), for HPO_4^{2-} (FE-factor 9) and HSO_4^- (FE-factor 5). As observed for receptor **2**, a certain preference for the same anions is found using the thiadiazole **4**, likewise, leading only to a modest enhancement in the emission intensity of **4** (CO_3^{2-}: FE-factor 5; HCO_3^- and HPO_4^{2-}: FE-factor 3; HSO_4^-: FE-factor 2). The spectroscopic behavior of **3** and **4**, the shape and the spectral position of the emission and absorption bands before and after anion complexation resemble those described for **1** and **2**. Hence, there is no hint that the naphthyl-NH function in compounds **3** or **4** is participating in the anion coordination.

The time dependence of the fluorescence effects which is absolutely unusual in the formation of hydrogen bonded assemblies led us to consider that a chemical reaction—involving the formation of covalent bonds—between the host molecules and the anionic guests is taking place. For example, in analogy to the addition of potassium carbonate to primary amines, one might think of the formation of carbamates by adding CO_3^{2-} to the iminoylthioureas **1** and **3**.[13] However, under the conditions used this possibility appears even more unlikely in the case of HCO_3^- or HPO_4^{2-} in whose presence a comparably strong, time dependent enhancement of the fluorescence intensity of **1** and **3** is also found. ^1H NMR studies did not show evidence for any such species formed during the titration of **1** and **3** with an aqueous solution of $NaCO_3$. We succeeded recently in following a slow complexation of the Cu(II) cation by a fluoroionophore system very similar to that of **3**/**4** via mass spectroscopy.[14] However, in this case ESI mass spectroscopy did not indicate the formation of a conceivable CO_3^{2-} addition product of **3** which should be reasonably stable to be detected.[15] In order to prove anion complexation by **3** serving as a model compound for the anion receptors studied, the reversibility of the fluorescence effects observed with CO_3^{2-} was investigated. In order to prove the reversibility of a suggested anion complexation by **3** serving as model compound, the following experiment was carried out: To a methanol–water (100:1) solution of **3** (10^{-5} M) and $NaCO_3$ (1000 equivalents) that gave the full extent of fluorescent enhancement after 120 hours (FE-factor 27) as described above, aqueous $HClO_4$ (1500 equivalents) was added and argon gas was bubbled through the solution for 30 minutes. The resulting fivefold increase of the emission intensity, refering to the free iminoylthiourea **3**, is in good agreement with the protonation experiments carried out. Finally, compound **3** was identified by its molecular mass peak (m/z 399) and its fluorescence behavior. This clearly demonstrates the reversibility of the interaction between **3** and CO_3^{2-}.

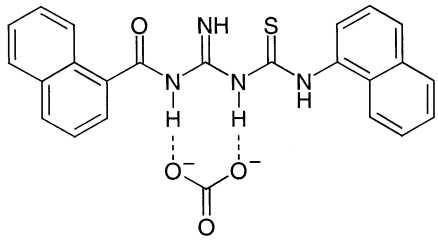

Figure 3. Proposed model structure of the CO_3^{2-}-**3** complex.

In conclusion, we attribute the spectroscopic effects discussed to the slow formation of anion complexes of the receptors used with different coordination modes for each ligand. Hydrogen bond mediated anion coordination most likely takes place at the NH groups of the central guanindyl moiety. A possible structure for the CO_3^{2-}-**3** complex is shown (Fig. 3). In the case of receptor **2**, the same host–guest interaction at the amido-NH group can occur and also a second ion–dipole interaction at the thiadiazole nitrogen is possible. Receptor **2** displays the same trend in anion selectivity as the corresponding iminoylthiourea **1**, however, due to the missing additional H-bond coordination site at the thiadiazole ring, the strength of the anion complexation is drastically lowered. Comparing the results of the complexation studies using **1** and **3**, there is no unequivocal evidence for cooperative anion binding by the two preorganized sidearms in compound **1**. Only the pronounced anion selectivity using compounds **1** and **2** and the magnitude of the anion induced fluorescence enhancement compared to the receptors **3** and **4** points to a cooperative interaction of the two sidearms to a certain extent.

The astonishingly strong enhancement of the fluorescence intensities observed is most likely the result of an increase of the rigidity of the receptor molecules upon anion complexation. As follows from the protonation studies, only minor contributions from a complexation controlled photoinduced electron transfer (PET effect) seem to be involved.[16]

Acknowledgements

We gratefully acknowledge the financial support by the Deutsche Forschungsgemeinschaft (DFG).

References

1. (a) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609; (b) *Supramolecular Chemistry of Anions*; Bianchi, A.; Bowman-James, K.; Garcia-España, E., Eds.; Wiley-VCH: New York, 1997. Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *3*, 486.
2. (a) Luecke, H.; Quioncho, F. A. *Nature* **1990**, *347*, 402; (b) He, J. J.; Quioncho, F. A. *Science* **1991**, *251*, 479.
3. (a) Rudkevich, D. M.; Verboom, W.; Brzozka, Z.; Palys, M. J.; Stauthamer, W. P. R. V.; van Hummel, G. J.; Franken, S. M.; Harkema, S.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, *116*, 4341; (b) Alcazar, V.; Segura, M.; Prados, P.; de Mendoza, J. *Tetrahedron Lett.* **1998**, *39*, 1033; (c) Niikura, K.; Bisson, A. P.; Anslyn, E. V. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1111; (d) Davis, A. P.; Perry, J. J.; Williams, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 1793.
4. (a) Dixon, R. P.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1992**, *114*, 365; (b) Bühlmann, P.; Nishizawa, S.; Xiao, K. P.; Umezawa, Y. *Tetrahedron* **1997**, *53*, 1647.
5. (a) Berger, M.; Schmidtchen, F. P. *J. Am. Chem. Soc.* **1999**, *121*, 9986; (b) Gale, P. A. *Coord. Chem. Rev.* **2000**, *199*, 181.
6. (a) Kavallieratos, K.; Hwang, S.; Crabtree, R. H. *Inorg. Chem.* **1999**, *38*, 5148; (b) Werner, F.; Schneider, H.-J. *Helv. Chim. Acta* **2000**, *83*, 465.
7. (a) Sasaki, S.; Mizuno, M.; Naemura, K.; Tobe, Y. *J. Org. Chem.* **2000**, *65*, 275; (b) Hayashita, T.; Onodera, T.; Kato, R.; Nishizawa, S.; Teramae, N. *Chem. Commun.* **2000**, 755; (c) Lee, K. H.; Hong, J.-I. *Tetrahedron Lett.* **2000**, *41*, 6083.
8. Beer, P. D. *Acc. Chem. Res.* **1998**, *31*, 71.
9. (a) Keefe, M. H.; Benkstein, K. D.; Hupp, J. T. *Coord. Chem. Rev.* **2000**, *205*, 201; (b) Fabbrizzi, L.; Licchelli, M.; Rabaioli, G.; Taglietti, A. *Coord. Chem. Rev.* **2000**, *205*, 85; (c) Czarnik, A. W. *Acc. Chem. Res.* **1998**, *27*, 302.
10. (a) Miyaji, H.; Sato, W.; Sessler, J. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 1777; (b) Kubo, Y.; Tsukahara, M.; Ishihara, S.; Tokita, S. *Chem. Commun.* **2000**, 653; (c) Xie, J. H.; Yang, X.; Wu, S. *New J. Chem.* **1999**, *23*, 1105.
11. Hennrich, G.; Sonnenschein, H.; Resch-Genger, U. *Eur. J. Org. Chem.* **2000**, 539.
12. Hennrich, G.; Sonnenschein, H.; Resch-Genger, U. *J. Am. Chem. Soc.* **1999**, *121*, 5073.
13. Gomez-Parra, V.; Sanchez, F.; Torres, T. *J. Chem. Soc., Perkin Trans. 2* **1987**, 695.
14. Hennrich, G.; Walther, W.; Resch-Genger, U.; Sonnenschein, H. *Inorg. Chem.* **2001**, *4*, 641.
15. Immediately after and 120 hours after addition of CO_3^{2-} (aqueous solution, addition of 1000 equivalents) to a methanolic solution of **3** there was no additional peak occuring in the mass spectrum that could be assigned to a new species with a presumably higher molar mass than the original compound **3** with a mass peak at m/z 399 (molecular ion $[3+H]^+$). The fragmentation pattern and the molecular mass peak of **3** remained unchanged.
16. de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515.