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The azulene moiety as a chromogenic building block for anion receptors

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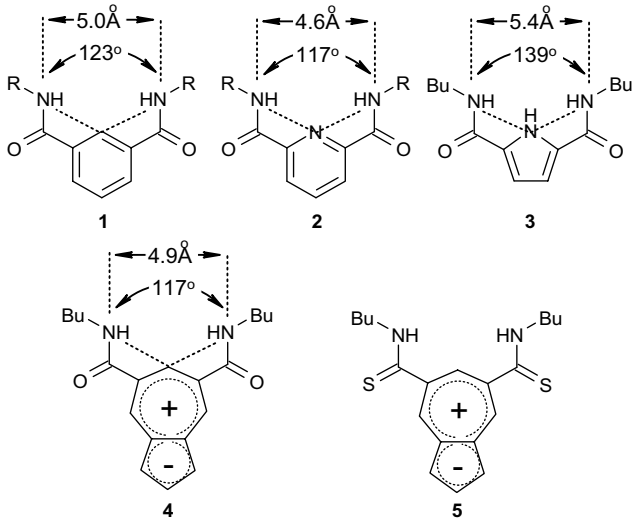
Abstract—The azulene moiety has been investigated as a new building block for optical sensors for anions. In the course of these studies, amide and thioamide derivatives of azulene-5,7-dicarboxylic acid were synthesized. Their affinity towards anions and structural preferences are described. The X-ray analysis of the thioamide revealed the formation of a supramolecular helix.

The development of neutral receptors for recognition of anions has attracted much attention in supramolecular chemistry during recent years.[1] The design and synthesis of fluorescent or colorimetric sensors[2,3] are of vital importance due to their potential applications in medicine and biology or environmental monitoring. The optical sensors consist of an anion binding site and a fluorophore or chromophore subunit and the recognition and reporting processes usually take place in different parts of the receptors.[2]

The ability of amides to form hydrogen bonds is extensively used in the construction of anion receptors.[4] Aromatic scaffolds for amide groups are common motifs in anion receptors (Scheme 1). The effectiveness of such building blocks was shown by Crabtree with isophthalamide[5] (type **1**) and dipicolinic bisamide[6] (type **2**), followed by Gale with pyrrole derivatives[7] (similar to **3**). We decided to extend this family of aromatic building blocks to azulene derivatives. The azulene moiety with its seven-membered ring offers a new geometry for the binding site. Moreover, the azulene moiety can be considered as being a conjunction of a cyclopentadienyl anion and a tropylium cation and has a large dipole moment of 0.8 D.[8] Anion binding might be enhanced by interaction with the dipole and by the formation of a hydrogen bond with 6-C*H*. Azulene is also known as a strong chromophore[9] and has been previously used in signaling systems.[10] Therefore, an azulene-based building block is an interesting fusion of a binding site and a chromophore. For these reasons, we decided to examine the properties of azulene-5,7-dicarboxylic acid bisbutylamide **4** and its thioamide analogue **5** in the context of anion binding (Scheme 1).



Scheme 1. Aromatic bisamides and their geometry in *syn–syn* conformations. See text for references.

We started the synthesis of target bisamide **4** from bismethyl azulene-5,7-dicarboxylate prepared according

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to the literature procedure.[11] The ester was subjected to aminolysis, however, due to its low reactivity, we had to conduct the reaction in neat butylamine. We prepared the butylamide **4** in 75% yield.[12]

We obtained diffraction grade crystals of **4** by slow diffusion of pentane into a 1,2-dichloroethane solution of **4** and performed the X-ray analysis. The independent part consists of one ligand molecule with amide groups in the *syn–syn* relationship necessary for anion binding (Fig. 1). Carbonyl groups deviate from the azulene plane (the torsion angles are 30° and 32°) and occupy different sides of the azulene ring. They are engaged in hydrogen bonds with neighboring molecules (the N–O distances are 2.86 and 2.87 Å), so two lines of hydrogen bonds are formed along the [1 0 0] direction (Fig. 1).

This structure allowed us to study the novel geometry of the binding cleft. The distance between nitrogen atoms is 4.88 Å and the cleft angle is 117°, whereas in the case of isophthalamide **1**, the distance is 5.01 Å and the angle is 123°, in the case of pyridine **2**, 4.64 Å and 117°, and in the case of pyrrole derivative **3**, 5.41 Å and 139°, respectively (Scheme 1).[13] Such differences in geometry can lead to dramatic changes in selectivity and binding affinity as was shown for hybrid systems containing different building blocks.[14,15]

In order to bind anions by convergent hydrogen bonds, bisamides have to adopt a *syn–syn* conformation, therefore, the preference for the *syn–syn* conformation is an important asset of a building block. Furthermore, such a preference can be used to organize the structure of more complex systems,[16] and increase their binding affinity.[15] To check the conformational preferences of azulene derivatives, we performed energy calculations for azulene-5,7-dicarboxylic acid bis-methylamide using the DFT method [B3LYP/6-311+G(3df, 2pd)//B3LYP/6-31+G(d,p)].[17] Indeed, the azulene bismethylamide *syn–syn* conformation has lower energy than the *anti–anti* one by about 4.5 kJ/mol, however, the *syn–anti* conformation possesses the lowest energy ($E_{syn-syn} - E_{syn-anti}$ is 3.7 kJ/mol).

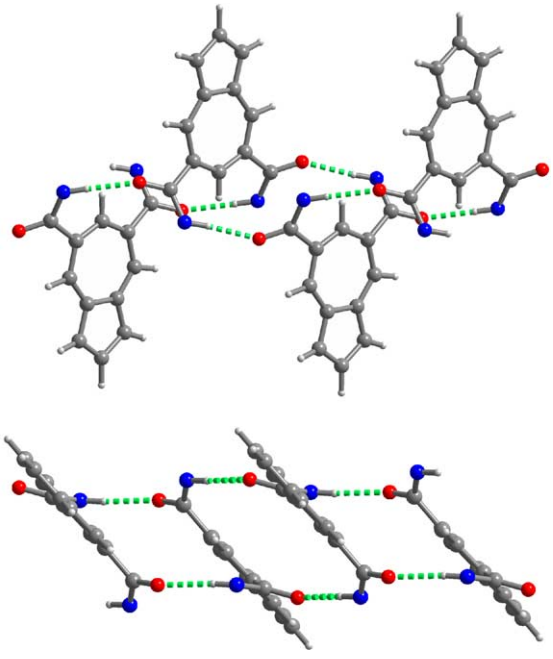

Figure 1. Crystal structure of **4** showing the arrangement of molecules engaged in a hydrogen-bond network (the butyl groups were omitted for clarity).

Table 1. The binding constants (M^{-1}) for the formation of 1:1 complexes of **3**, **4** and **5** with various anions in DMSO-d_6+0.5% H_2O at 298 K[a]

	4	**5**	**3**[b]
$H_2PO_4^-$	27	104	150
$PhCOO^-$	13	46	49
Cl^-	6.1	13.3	1.7
Br^-	—[c]	—[c]	—[c]

[a] Determined by ^{1}H NMR titration. Errors estimated to be <10%. Tetrabutylammonium salts were used as anions sources.
[b] Ref. 18.
[c] Interaction too weak to be measured.

The downfield shift of amide protons in the presence of anions allowed us to determine the binding constants by ^{1}H NMR titration. Inspection of Table 1 proves that even the simple azulene derivative **4** can bind anions in a competitive solvent such as DMSO. The azulene ligand shows typical preference for basic anions over chloride. For basic anions, azulene **4** has smaller association constants than pyrrole **3**.[18] This may indicate that the azulene with its correct dipole orientation cannot compete with the ability of pyrrole to form an additional N*H* hydrogen bond. Comparison of **4** and **3** shows that the azulene derivative has a bigger affinity towards chloride than the pyrrole derivative, which can result from the different ligand geometry. Interaction with a bromide anion was too small to be measured.

The signal of 6-C*H* was shifted downfield during the titrations, however, the 4,8-C*H* signal behaved in the same way and, moreover, $\Delta\delta_{max}$ values for 6-C*H* and 4,8-C*H* were very similar and much lower than that for the amide N*H* ($\Delta\delta_{max}$ is about 0.2 ppm for C*H* and about 1.5 ppm for N*H*, respectively). These results show limitations of the potentially beneficial effect of the heptatrienyl ring in anion complexation.

The blue solution of azulene bisamide **4** in CH_2Cl_2 was treated with various anions, but no significant colour changes were observed (Fig. 2). Therefore, azulene bis-butylamide **4** seems to be too simple a system for naked eye detection. From our previous experience with thioamide ligands[18] we knew that thioamide spectra were shifted in the presence of anions. In order to obtain an optical sensor, we decided to convert compound **4** into thioamide **5** using Lawesson's reagent.[19] We carried out the reaction in boiling THF and obtained thioamide **5** in 70% yield.[20] In contrast to its amide precursor, the colour of the thioamide solution changed upon addition

Figure 2. Color changes of ligands in CH_2Cl_2 in the presence of anions (3 equiv of TBA salts). From the left: **4**; **4**+$H_2PO_4^-$; **5**; **5**+Cl^-; **5**+$H_2PO_4^-$; **5**+F^-.

of anions (Fig. 2 and Supplementary data). We observed a blue shift and deepening of the colour.

Binding constants of azulene thioamide **5** with typical anions were determined by ^{1}H NMR titrations (Table 1). As expected, thioamide **5** bound anions about two times stronger than its amide analogue **4**. At the same time, thioamide **5** showed similar selectivity.

We succeeded in the preparation of diffraction-grade single crystals of thioamide **5** by slow evaporation of its ethanol–water solution. X-ray analysis revealed its extraordinary structure. The independent part consists of five azulene molecules, each molecule stacks with its seven-membered ring above the preceding one and is rotated by an angle of about 72°, thus forming a pseudo five-fold screw axis (Figs. 3 and 4). Ligand molecules are connected by hydrogen bonds between thioamide groups (the N–S distances are between 3.35 and 3.59 Å). These hydrogen bonds define a helix. The thioamide groups are in *anti–anti* conformation and point to opposite directions (the torsion angles are between −130° and −150°). Therefore, two spiral lines of hydrogen bonds are formed, one is climbing the helix whilst the other is descending (Fig. 4).

The azulene rings are close to each other (distances about 3.4 Å) and hence π-stacking is another non-covalent interaction that can organize this helical structure. The seven-membered rings directly overlap and such orientation is usually disfavored due to electrostatic repulsion.[21] However, the heptatrienyl rings are electron deficient, and direct ring stacking is allowed for such systems.[21] Nevertheless, it would appear that the molecules are arranged mainly by hydrogen bonds. Although the thiocarbonyl group is considered to be a weak acceptor of hydrogen bonds,[22] it is engaged in this structure in intermolecular hydrogen bonds, which are strong enough to organize molecules into the supramolecular structure.

To summarize, new bisamide and thioamide derivatives of azulene-5,7-dicarboxylic acid were synthesized and were shown to interact with anions. This is the first application of an azulene moiety in anion recognition. The geometry and conformation preferences of this new building block were investigated, which will pave the way for incorporating this system into more elaborate, amide-based sensors for anions.

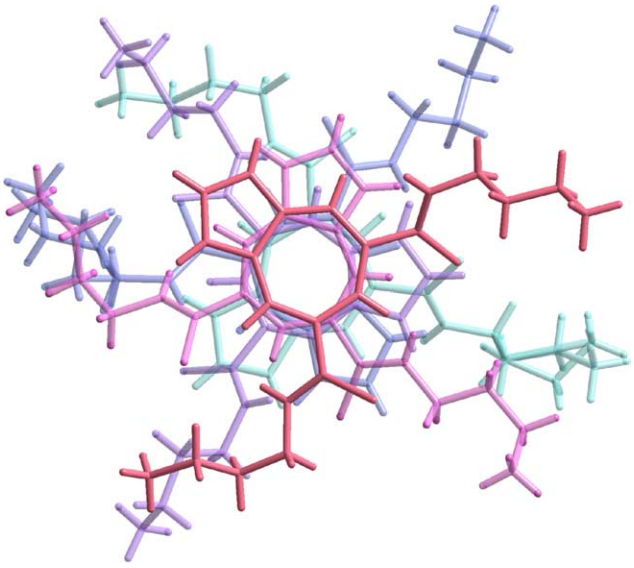

Figure 3. The top view of the crystal structure of **5**. Inequivalent molecules are shown in different colours.

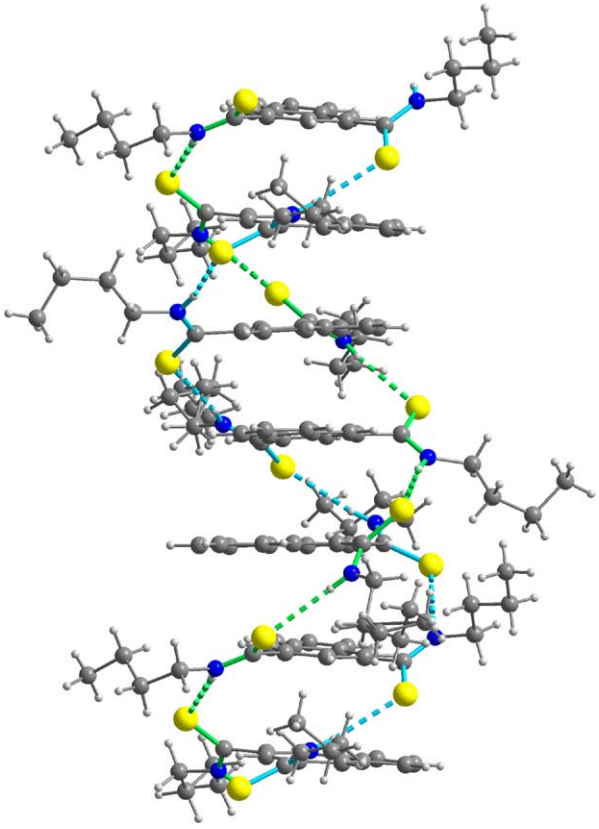

Figure 4. The side view of the crystal structure of **5** (only five molecules are independent).

Supplementary data

Supplementary data are available: synthesis of **4** and **5**, UV/vis spectra, titration experiments and DFT calculations. Crystallographic data for the structures discussed

in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 267792, 227793. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.061.

References and notes

1. Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 191; Gale, P. A. *Coord. Chem. Rev.* **2001**, *213*, 79; Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609.
2. Martinez-Manez, R.; Sancenon, F. *Chem. Rev.* **2003**, *103*, 4419, and references cited therein.
3. Gunnlaugsson, T.; Kruger, P. E.; Lee, T. C.; Parker, R.; Pfeffer, F. M.; Hussey, G. M. *Tetrahedron Lett.* **2003**, *44*, 6575; Wu, J. L.; He, Y. B.; Zeng, Z. Y.; Wie, L. H.; Meng, L. Z.; Yang, T. X. *Tetrahedron* **2004**, *60*, 4309; Vazquez, M.; Fabbrizzi, L.; Taglietti, A.; Pedrido, R. M.; Gonzalez-Noya, A. M.; Bermejo, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1962; Costero, A. M.; Banuls, M. J.; Aurell, M. J.; Ward, M. D.; Argent, S. *Tetrahedron* **2004**, *60*, 9471; Kang, J.; Kim, J. *Tetrahedron Lett.* **2005**, *46*, 1759.
4. Bondy, C.; Loeb, S. *Coord. Chem. Rev.* **2003**, *240*, 77.
5. Kavallieratos, K.; Gala, S. R.; Austin, D. J.; Crabtree, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 2325.
6. Kavallieratos, K.; Bertoo, Ch. M.; Crabtree, R. H. *Org. Chem.* **1999**, *64*, 1675.
7. Gale, P. A.; Camiolo, S.; Chapman, C. P.; Light, M. E.; Hursthouse, M. B. *Tetrahedron Lett.* **2001**, *42*, 5095; Gale, P. A.; Camiolo, S.; Tizzard, G. J.; Chapman, C. P.; Light, M. E.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2001**, *66*, 7849.
8. Tobler, H. J.; Bauder, A.; Günthard, H. H. *J. Mol. Spectrosc.* **1965**, *18*, 239.
9. Liu, R. S. H.; Asato, A. E. *J. Photochem. Photobiol. C* **2003**, *4*, 179.
10. Löhr, H.-G.; Vögtle, F. *Chem. Ber.* **1985**, *118*, 905.
11. Jutz, Ch.; Schweiger, E.; Löbering, H.-G.; Kraatz, A.; Kosbahn, W. *Chem. Ber.* **1974**, *107*, 2956.
12. Compound **4**: Dark blue crystals, mp 216–217 °C; ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 8.70$ (d, 2H, $J_1 = 1.4$ Hz, 4-C*H*), 8.24 (s, 1H, 6-C*H*), 7.93 (t, 1H, $J_1 = 3.8$ Hz, 1-C*H*), 7.54 (d, 2H, $J_1 = 3.8$ Hz, 2-C*H*), 6.77 (t, 2H, $J_1 = 5.4$ Hz, N*H*), 3.47 (dt, 4H, $J_1 = 5.4$ Hz, $J_2 = 7.0$ Hz CH_2NH), 1.65 (m, 4H, CH_2), 1.43 (m, 4H, CH_2), 0.98 (t, 6H, $J_1 = 7.2$ Hz, CH_3); ^{13}C NMR (50 MHz $CDCl_3$) $\delta = 169.9$, 138.6, 137.7, 136.3, 133.4, 127.7, 124.4, 40.6, 31.7, 20.2, 13.8; HR ESI calcd for $C_{20}H_{26}N_2O_2Na$ $[M+Na]^+$: 349.1886 found: 349.1905; Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.55; H, 8.06; N, 8.45. Crystal data for **4**: $C_{20}H_{26}N_2O_2$, $M = 326.43$, monoclinic, $a = 8.9268(7)$, $b = 25.9516(19)$, $c = 8.1564(6)$ Å, $\alpha = 90°$, $\beta = 103.434(7)°$, $\gamma = 90°$, $U = 1837.8(2)$ Å^3, $T = 100$ K, space group $P(1)/c$, $Z = 4$, μ(Mo-Kα) = 0.081 mm^{-1}, 16742 reflections measured, 4437 unique ($R_{int} = 0.0436$) which were used in all calculations. The final R indices are $[I > 2\sigma I]$: $R1 = 0.0476$ $wR2 = 0.1202$, (all data) $R1 = 0.0819$ $wR2 = 0.1343$; CCDC 267793.
13. Based on X-ray crystal data. Structures of compound **3** (CCDC 256442 Ref. 18) and **4** were measured at 100 K. There were no structures of simple analogues of **1** and **2** with *syn–syn* conformation measured at 100 K in the Cambridge Crystallographic Database, so we used the data of a macrocyclic compound (CCDC 250961, see Ref. 15).
14. Sessler, J. L.; An, D.; Cho, W.-S.; Lynch, V.; Yoon, D.-W.; Hong, S.-J.; Lee, C.-H. *J. Org. Chem.* **2005**, *70*, 1511.
15. Chmielewski, M. J.; Jurczak, J. *Tetrahedron Lett.* **2005**, *46*, 3085.
16. Jeong, K.-S.; Cho, Y. L.; Song, J. U.; Chang, H.-Y.; Choi, M.-G. *J. Am. Chem. Soc.* **1998**, *120*, 10982; Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1996**, *118*, 7529; Dolain, Ch.; Maurizot, V.; Huc, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 2738.
17. Gaussian 03, Revision B.05, Gaussian, Inc., Pittsburgh PA, 2003.
18. Zieliński, T.; Jurczak, J. *Tetrahedron* **2005**, *61*, 4081.
19. Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.
20. Compound **5**: Green crystals, mp 187–188 °C; ^{1}H NMR (200 MHz, DMSO-d_6) $\delta = 10.57$ (t, 2H, $J_1 = 5.2$ Hz, N*H*), 8.79 (d, 2H, $J_1 = 1.6$ Hz, 4-C*H*), 8.19 (s, 1H, 6-C*H*), 7.97 (t, 1H, $J_1 = 3.8$ Hz, 1-C*H*), 7.67 (d, 2H, $J_1 = 3.8$ Hz, 2-C*H*), 3.72 (dt, 4H, $J_1 = 5.4$ Hz, $J_2 = 7.0$ Hz CH_2NH), 1.67 (m, 4H, CH_2), 1.42 (m, 4H, CH_2), 0.95 (t, 6H, $J_1 = 7.3$ Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 199.8$, 140.5, 137.6, 136.0, 133.3, 132.7, 125.0, 47.6, 29.8, 20.5, 13.9; HR EI calcd for $C_{20}H_{26}N_2S_2M^+$: 358.1537 found: 358.1525; Anal. Calcd for $C_{20}H_{26}N_2S_2$: C, 66.99; H, 7.31; N, 7.81; S, 17.88. Found: C, 67.23; H, 7.47; N, 7.80; S, 18.00. Crystal data for **5**: $C_{20}H_{26}N_2S_2$, $M = 358.56$, triclinic, $a = 13.4497(6)$, $b = 17.1480(8)$, $c = 21.3179(10)$ Å, $\alpha = 85.692(4)°$, $\beta = 84.311(4)°$, $\gamma = 88.347(4)°$, $U = 4877.5(4)$ Å^3, $T = 100$ K, space group P-1, $Z = 10$, μ(Mo-Kα) = 0.081 mm^{-1}, 88740 reflections measured, 22336 unique ($R_{int} = 0.1090$) which were used in all calculations. The final R indices are $[I > 2\sigma I]$: $R1 = 0.0513$ $wR2 = 0.0785$, (all data) $R1 = 0.1900$ $wR2 = 0.1112$; CCDC 267792.
21. Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525.
22. Lee, H.-J.; Choi, Y.-S.; Lee, K.-B.; Park, J.; Yoon, C.-J. *J. Phys. Chem. A* **2002**, *106*, 7010; Allen, F. H.; Bird, C. M.; Rowland, R. S.; Raithby, P. R. *Acta Cryst. Sect. B* **1997**, *53*, 680.