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Bisamides Derived from Azulene-1,3- and -5,7-dicarboxylic Acids as New Building Blocks for Anion Receptors

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Dedicated to Professor Marek Chmielewski on the occasion of his 65th birthday

Abstract: Bisamides based on the azulene moiety were investigated as building blocks for anion receptors. In the course of these studies, derivatives of azulene-1,3- and -5,7-dicarboxylic acid were synthesized and thoroughly characterized. The anion affinities of the derivatives based on functionalization in the five-membered ring and in the seven-membered ring were determined by ^{1}H NMR titration. The structural analysis of these building blocks was performed by X-ray diffractometry, molecular modelling and 2D NMR spectroscopy. The five-membered ring derivatives are easy to obtain, offer a binding site preorganized in the *syn*–*syn* conformation and bind anions with a strength similar to those of pyrrole-based analogues. There is also strong evidence for aromatic CH···anion interactions. The ligands substituted at the 5- and 7-positions offer a binding cleft with an uncommon geometry that originates from the seven-membered ring and seems to be complementary to the chloride anion.

Keywords: amides · anion recognition · azulene · ligand design · thioamides

Introduction

Immense progress in anion coordination chemistry has been achieved during the last twenty years.[1] The importance of anions in biological systems, the environment and medicine is the main driving force for research in this area of supramolecular chemistry.[2] Artificial neutral receptors became attractive targets of studies because of their analogy to natural systems[3] and because their selectivities were higher than in the case of charged ligands. In neutral hosts, anion binding is usually accomplished through hydrogen bonds.[4,5] As a single hydrogen bond is typically weak, strong binding can only be achieved by multiple interactions of this type. In order to achieve perfect complementarity with a target guest, it is necessary to arrange the hydrogen bond donors in a very precise manner within the host structure.[6] However, our knowledge of structure/affinity relationships is still limited[7] and there are many examples of how small changes in ligand constitution can drastically alter the binding properties.[8,9] For this reason, it is important to have a large pool of structural subunits—building blocks—that can help in fine-tuning the host–guest interactions.

Amide groups are one of the most popular hydrogen bond donors used in anion recognition[5] and are often incorporated into ligand structures in the form of aromatic bisamides: namely isophthalamides (type **1**),[10] dipicolinic bisamides (type **2**)[11] and pyrrole derivatives (type **3**)[12] (Scheme 1). Not only do these building blocks introduce the binding sites into a ligand, but they can also be used as organizing elements that determine the shape of a host.[8,13]

We decided to extend the family of known aromatic building blocks to derivatives of azulene, with its seven-membered ring geometry. We thus prepared and studied the bisamide and bisthioamide of azulene-5,7-dicarboxylic acid (**5**, **6**) as reported in our previous paper.[14] Azulene is an interesting subunit for the construction of anion receptors,[15] not only because of the uncommon geometry of its seven-membered ring. Azulene is a strong chromophore and can be regarded as a combination of a cyclopentadienyl anion and a tropylium cation, which results in its large dipole moment of 0.8 D.[16] Azulene-based bisamides therefore rep-

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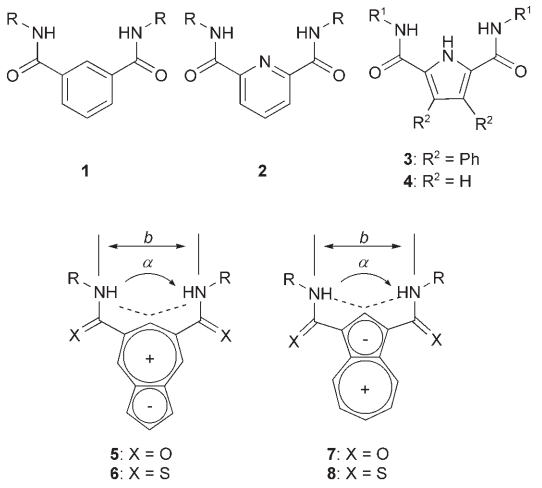


Scheme 1. Aromatic building blocks for anion receptors.

resent the attractive fusion of binding site with signalling subunit. Moreover, we expected an enhancement of anion binding, owing to interaction of the anionic guest with the azulene dipole or through the formation of an additional hydrogen bond with 6-C*H*. However, our preliminary results showed limitations of these advantageous interactions between anions and azulene skeleton.[14] To check how the different geometries and electronic structures of the five- and seven-membered rings would influence the anion binding, we performed a comparison of azulene derivatives based on functionalization in the seven-membered and in the five-membered rings. Here we present our studies on azulene-1,3- and -5,7-dicarboxylic acid bisamides (types **5** and **7**) as building blocks for anion receptors. In order to help readers to distinguish between the two isomers, we will use the terms "five-membered" and "seven-membered" derivative/compound etc. as abbreviations for statements such as "derivative of azulene-1,3-dicarboxylic acid", as we do not report any macrocyclic structures in this work; we hope that such descriptions will not be misleading.

Results and Discussion

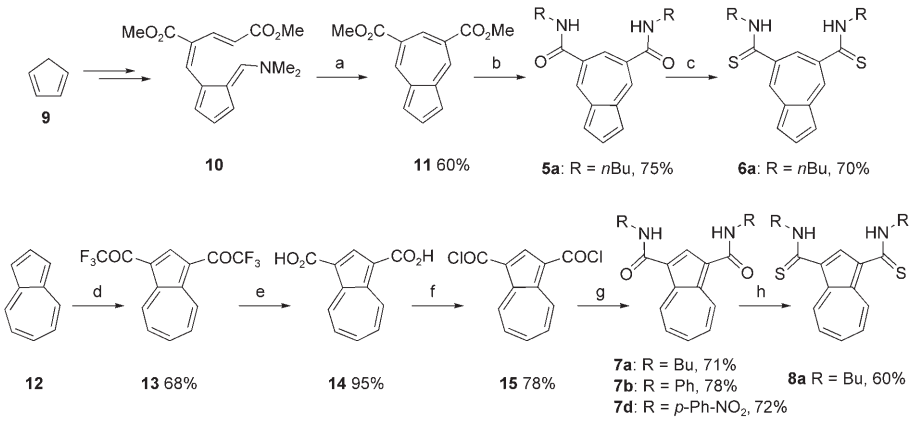
The azulene substituted with carboxyl groups in the seven-membered ring was obtained by skeleton synthesis according to literature procedures (Scheme 2).[17] The availability of the diester **11** was very promising, as one of the most convenient methods for macrocyclization involved aminolysis of diesters with α,ω-diamines. Unfortunately though, the ester **11** was unreactive under standard conditions, and we succeeded in preparation of the desired amide **5a** only by performing the reaction in neat butylamine. Because of the lower nucleophilicity of aniline, we were unable to prepare the aromatic amide (**5b**, R = Ph) in the same manner. To solve this problem, we hydrolysed the ester **11** into the diacid and tried methods known from peptide bond chemistry. Neither the mixed-anhydride method nor the carbodiimide method led to the phenyl amide **5b**, however (in both cases we observed only formation of the activated intermediate).

It seems that the chemistry of 5,7-dicarboxylic acid derivatives of azulene might hamper the introduction of this building block into more sophisticated systems. Only aliphatic amides can be easily prepared, which constrains the potential ligand structures; moreover, the popular method of macrocyclization—aminolysis of esters—cannot be used for the preparation of seven-membered ring derivatives.

The five-membered ring dicarboxylic acid derivatives were prepared by direct acylation of azulene (**12**) with trifluoroacetic acid anhydride, followed by hydrolysis to afford the acid **14** (Scheme 2).[18] The acid **14** was converted into the acid dichloride **15** and subjected to treatment with amines, yielding the amides **7**. The availability of the acid dichloride **15** is a great asset for the five-membered derivatives, since it offers a convenient synthetic route to more elaborate ligands.

From our previous experience with thioamide-based ligands,[19] we knew that thioamide groups "sensitize" receptors to the presence of anions. In order to obtain optical sensors, we decided to convert the butylamides **5a** and **7a** into their thioamide analogues **6a** and **8a**, respectively, using Lawesson's reagent.[20] This transformation was performed in boiling THF and gave the thioamides in good yields.

Having prepared the model ligands, we set out to determine their anion-binding properties. All azulene derivatives are colourful, so it was interesting to see whether the azulene-based bisamides would change their optical properties upon anion complexation. Unfortunately though, interaction of receptors **5a** and **7a** with anions does not lead to signifi-



Scheme 2. Conditions: a) quinoline, 100 °C; b) $BuNH_2$, neat, 60 °C; c) Lawesson's reagent, THF, reflux; d) $(CF_3CO)_2O$, neat, 0 °C→RT; e) 1) KOH, EtOH, H_2O, 60 °C; 2) HCl; f) $SOCl_2$, CH_2Cl_2, reflux; g) RNH_2, CH_2Cl_2, RT; h) Lawesson's reagent, THF, reflux.

cant colour changes, even in noncompetitive solvent such as CH_2Cl_2. Introduction of an additional chromophore—the nitro group in **7d**—also failed to trigger spectacular colour changes. However, the hues of CH_2Cl_2 solutions of the thioamide-based ligands **6a** and **8a** are slightly modified by the presence of anions (Figure 1).

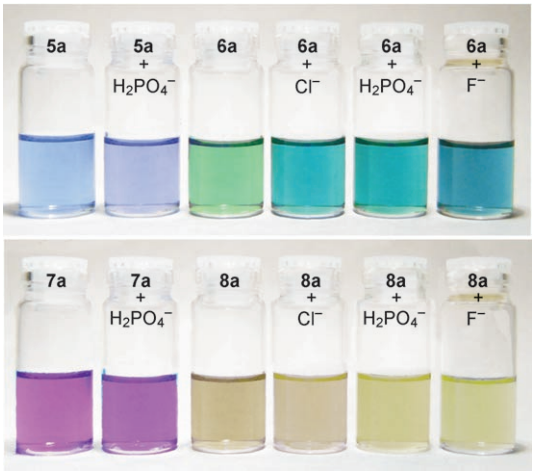


Figure 1. Colour changes of ligands in CH_2Cl_2 in the presence of anions (3 equiv of TBA salts).

In view of the facts that no such colour changes were observable in more demanding media such as DMSO and that the optical response was the most pronounced for the highly basic fluoride anion, it was likely that we were observing an effect of deprotonation of thioamide groups rather than complexation. To check this assumption we performed experiments similar to those reported by Fabbrizzi[21] for urea-/thiourea-based systems, comparing UV/Vis spectra of ligands upon addition of TBA salts and TBA hydroxide (see Figure S1, Supporting Information). However, these UV/Vis measurements did not give the final answer for our ligands. Unlike in the case of urea-based receptors,[21] the presence of the TBA hydroxide did not drastically change the ligands' spectra, and no new band was developed. Since the spectra of the free ligands and those after addition of TBA salts and TBA hydroxide are quite similar, it is impossible to identify the deprotonated forms of ligands and to distinguish unequivocally between complexation and deprotonation. However, keeping in mind the facts that i) more acidic thioamides respond better than amides, ii) the effect takes place for basic anions in noncompetitive, nonpolar CH_2Cl_2, and iii) the spectral changes are moderate, it may be assumed that anion complexation is accompanied by a small degree of deprotonation, which is responsible for the observed colour changes. Nevertheless, these results show that simple acyclic bisamides based on azulene cannot act as optical sensors for anions.

We then embarked on quantitative determination of the receptors' affinities towards anions. As our studies of binding properties were intended as a reference for further generations of azulene-based receptors, we decided to determine the binding constants by ^{1}H NMR titration in DMSO+0.5% H_2O. We were aware that our simple ligands would interact weakly with anions in this very competitive solvent. However, the recently published anion receptors bind anionic guests efficiently in such demanding media as DMSO, methanol or even water,[22] so we chose DMSO to allow further comparison with more elaborate systems.

Upon titration with anions, the signals assigned to amide or thioamide NH protons underwent downfield shifts indicating complex formation that was reversible on the NMR timescale. The lack of disappearance or broadening of NH signals excluded deprotonation, so the main process that takes place in solution is complexation. The changes in chemical shift allowed us to calculate the values of the binding constants (Table 1), and the data gave consistent fit with a 1:1 model, as was confirmed by Job plots (see Figure S2, Supporting Information).

Table 1. Binding constants [M^{-1}] for the formation of 1:1 complexes of model ligands with various anions in [D_6]DMSO+0.5% H_2O or acetone at 298 K.[a]

Anion	Solv.	**4a**[b]	**4b**[b]	**5a**	**6a**	**7a**	**7b**	**7d**	**8a**
Cl^-	D	1.7	3.8	6.1	13	1.2	9.3	17	2.0
Br^-	D	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]
$PhCO_2^-$	D	49	80	13	46	27	105	550	17
$H_2PO_4^-$	D	150	203	27	104	73	496	1400	82
Cl^-	A			500	46500	240	1080	–[d]	1620
Br^-	A			230	1480	185	900	–[d]	520

[a] Determined by ^{1}H NMR titration. Errors estimated to be <10%. TBA salts were used as the source of anions. Solvent: D = [D_6]DMSO+0.5% H_2O, A = acetone. [b] Ref. [19] [c] Interaction too weak to be measured. [d] Insoluble in acetone.

During titration, we also observed the downfield shift of the signal of the "middle" C*H* proton (6-C*H* for the seven-membered derivatives **5** and **6** or 2-C*H* for the five-membered derivatives **7** and **8**). This might in some cases indicate the presence of an advantageous CH···anion interaction helping to bind the anionic guest,[23,24] although in the case of the seven-membered derivatives (**5a** and **6a**) this hypothesis should be dismissed. The obtained values of $\Delta\delta_{max}$ for 6-C*H* are small (about 0.2 ppm) and comparable to those for the 4,8-C*H* protons, which are unlikely to participate in the anion binding. In contrast, the formation of a hydrogen bond between 2-C*H* and anion in the five-membered derivatives (**7** and **8**) is highly likely. The values of $\Delta\delta_{max}$ for 2-C*H* signal are about 1 ppm and much higher than those observed for the other protons (see Table S2, Supporting Information).

The determined binding constants are listed in Table 1; for comparison we also present values obtained for the pyr-

role-based bisamides **4a** ($R^1 = n$Bu, $R^2 = H$) and **4b** ($R^1 =$ Ph, $R^2 = H$),[19] which possess an additional hydrogen bond donor—pyrrole N*H*—but are poorly preorganized in the unfavourable *anti–anti* conformation. The 3,4-diphenylpyrrole derivatives **3** reported by Gale[12] interact with anions more strongly than the unsubstituted ligands **4**; as this fact cannot be clearly explained at this moment, we chose ligands **4** for comparison, as they are structurally more similar to compounds **5**–**8**. The azulene-based ligands show a typical preference for oxo anions over halides, and the interaction with bromide anion was too weak to be measured in all the cases studied. The amide **5a** substituted in the seven-membered ring binds the benzoate only twice as strongly as the chloride anion, so a change in relative selectivity is observed. This may indicate that the geometry of its binding site is better suited for the chloride anion than those based on a five-membered ring as in **4** or **7**.

The neighbourhood of the formal cyclopentadienyl anion in the five-membered derivatives **7** does not obstruct interaction with anions. In contrast, the amide **7a** binds oxo anions more strongly than its seven-membered analogue **5a**. The five-membered phenyl amide **7b** is an even better receptor than the pyrrole-based ligand **4b** ($R^1 =$ Ph, $R^2 = H$), even though the latter compound possesses an additional hydrogen bond donor in the form of the pyrrole NH, though it has to be mentioned that, in the case of butylamides **7a** and **4a** ($R^1 = n$Bu, $R^2 = H$), the pyrrole-based ligand **4a** binds the anion more strongly than the azulene-based **7a**. These results support the thesis of the presence of the advantageous 2-C*H*···anion interaction in the five-membered derivatives. As expected, the amide **7d** derived from *p*-nitroaniline is the best receptor studied, due to the higher acidity of its N*H* protons.

Conversion of amides into thioamides is expected to boost anion binding[25] as a result of the more acidic character of the latter compound class.[26] However, this beneficial effect can be counterbalanced by undesirable structural preferences of the thioamide groups.[19] In the case of the azulene-based ligands studied here, transformation of the amide groups into the thioamide groups has an ambiguous character (Table 1). Replacement of the carbonyl group with a thiocarbonyl moiety increased the values of the binding constants for the seven-membered ligand **6a**, whereas it did not significantly influence the interactions with oxo anions in the case of **8a**.

Although the values of K_a obtained for interaction with chloride anion in DSMO are small, they are reliable and reproducible, and since they were measured in the same conditions, they can be used for comparison. However, the low values of K_a mean that under typical conditions (concentrations about 10^{-2} M) dissociation predominates over complexation. We thus decided to measure the affinity towards halides in a less demanding solvent, acetone, that is structurally similar to DMSO and still a more competitive medium than acetonitrile or CH_2Cl_2. Using acetone as the solvent, we were able to determine binding constants for both bromide and chloride (Table 1). We observed similar trends in the values of K_a in acetone and DMSO. Because of the lower charge density of bromide anion, the complexes with this anion are less stable than those with chloride. The seven-membered ligands **5a** and **6a** bind chloride more strongly than their five-membered ring analogues (**7a**, **8a**), which is in agreement with the results obtained in DMSO. The conversion of amide groups into thioamides increases affinity towards both halides, but the selectivity for chloride over bromide is improved. The binding constant for complexation of chloride with **6a** in acetone is remarkably high, but we cannot explain why the interaction of the ligand **6a** with chloride is so efficiently enhanced in this medium. The behaviour of the aromatic protons in positions 2 and 6 was similar in both solvents, while the values of K_a and $\Delta\delta_{max}$ for 2-C*H* in **7** and **8** are comparable with those for NH signals, so the possibility of CH···anion interaction is also quite high in acetone.

In advanced receptors, guest binding is achieved through multiple interactions that originate from various binding sites incorporated into the host structure. The observed selectivity and binding strength cannot be ascribed as addition or multiplication of binding constants determined for the building blocks used for the ligand construction. However, the geometrical parameters and conformational preferences of the structural subunits determine the host structure and arrangement of its binding sites. As a result, the structural properties of building blocks are crucial for rational receptor design and more important than their binding properties. For this reason, we performed a comprehensive structural analysis of azulene-based building blocks using different methods of structural analysis.

We succeeded in preparing diffraction-grade crystals of the three amide-based ligands **5a**, **7a** and **7b**; the structure of the seven-membered ligand **5a** had been described previously[14] and is very similar to that of its five-membered analogue **7a** (Figure 2a, b; for colour versions of all enclosed figures see the Supporting Information file). In both cases, the ligand molecules adopt a *syn–syn* conformation, and the carbonyl groups deviate from the plane of the azulene and point in opposite directions (the torsion angles are between 21 and 36°). To describe amide groups' orientations we use *syn* and *anti* descriptors: the *syn* orientation denotes a conformation in which the carbonyl oxygen is close to the aromatic backbone and the amide NH is directed "outside", while in the *anti* conformation the positions of nitrogen and oxygen are reversed (in other words, in a *syn-syn* conformation, the amide hydrogens point in the same direction as the "middle" C*H* (6-C*H* in **5** or 2-C*H* in **7**)). The structures of **5a** and **7a** showed the amide groups engaged in hydrogen bonds with neighbouring molecules in such a manner that two lines of hydrogen bonds are formed (the N–O distances are about 2.9 Å; Figure 2).

The crystal structure of the phenyl amide **7b** also resembles those described above (Figure 2c). The amide groups are in the *syn–syn* orientation, thus they are tilted and point in opposite directions so that the carbonyl groups are located on the different sides of the azulene ring. Two lines of

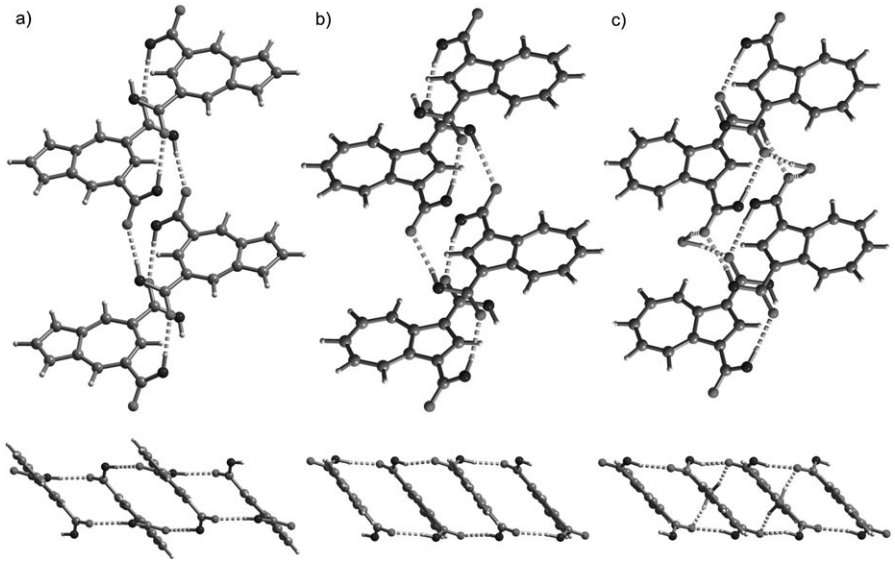


Figure 2. Different views (top, bottom) of crystal structures of model ligands showing the arrangements of molecules engaged in hydrogen bond networks (the butyl and phenyl groups are omitted for clarity). a) **5a**, b) **7a**, c) **7b**.

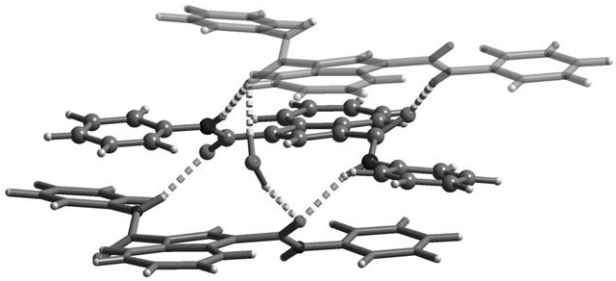


Figure 3. Crystal structure of **7b** showing water molecule engaged in hydrogen bonds.

hydrogen bonds are formed, linking adjoining molecules (the N–O distance is 2.9 Å). The main difference in this structure is the presence of water in the independent part. The water molecule is positioned in such a manner that the oxygen is in the azulene plane and the hydrogens are almost perpendicular to the ring (Figure 3). These hydrogen atoms form hydrogen bonds with the carbonyl groups, bridging every third molecule of the ligand (the O–O distances are about 2.9 Å). Although the three aromatic C*H*s (*o*-C*H* in phenyl arms and 2-C*H* of azulene) point towards the water oxygen atoms, the C–O distances are longer than 3.9 Å, which dismisses any possibility of CH–anion interactions.

It is worth emphasizing that all three structures are very similar. Firstly, the azulene subunits of neighbouring molecules are alternately placed, probably to compensate their dipole moments. Secondly, two lines of hydrogen bonds are formed between the amide groups. Finally, the amide groups are in the *syn-syn* orientation. The last feature is important from the point of view of anion binding.

To bind anions with convergent hydrogen bonds, the aromatic bisamides must adopt the *syn-syn* conformation. A preference for such a conformation is a great asset in a building block, as its binding site is already preorganized for interaction with an anionic guest. To determine the ligand structure in solution, we measured the 2D NOSY spectra of compounds **5a** and **7a** in DMSO (see Figure S3, Supporting Information). In both cases, the NOE effect indicates that the carbonyl groups adopt both *syn* and *anti* orientations (NOE effects between the amide N*H* and 4-C*H* and 6-C*H* protons for ligand **5a**, and between N*H* and 2-C*H* and 4-C*H* for **7a**). This means that the amide groups are either in the *syn-anti* conformation or, more likely, they can switch in solution between *syn* and *anti* orientations.

A further insight into the conformation preferences of ligands came from molecular modelling. We performed DFT B3LYP calculations for the bismethyl amides (**5c** and **7c**, R = Me) and thioamides (**6c** and **8c**, R = Me) in the gas phase to optimize the conformer structures and the energy distributions (the methyl bisamides were chosen in order to simplify calculations). Since the carbonyl groups deviate from the azulene plane, it is necessary to consider whether they occupy the same or opposite sides of the ring. We denoted the former orientation "++" and the latter "+−". Both orientations have distinct energies. In all cases, the "+−" conformers possess lower energy, probably due to the opposite dipole orientations of the carbonyl groups (Table 2).

For the seven-membered amide **5c**, the *syn–anti* conformations have the lowest energy, followed by the *syn–syn*(+−) and then the *syn–syn*(++), which has an energy value close to those of the *anti–anti* conformations. In the case of its thioamide analogue **6c**, the preferred conformation is also *syn–anti*(+−), but the *syn–syn*(++) conformation (the one with convergent binding sites) has an energy higher than that of the *anti–anti*(+−) form. The five-mem-

Table 2. Relative energies [kJ mol^{-1}] for the conformers of the amides **5c** and **7c** and the thioamides **6c** and **8c**.[a]

	5c	6c	7c	8c
$E_{anti\text{–}anti+-}$	8.3	8.1	22.2	9.2
$E_{anti\text{–}anti++}$	10.4	13.6	24.8	12.7
$E_{syn\text{–}anti+-}$	0	0	6.1	1.5
$E_{syn\text{–}anti++}$	1.5	4.3	6.2	3.9
$E_{syn\text{–}syn+-}$	3.7	3.0	0	0
$E_{syn\text{–}syn++}$	7.7	10.0	0.8	3.3

[a] Calculations in the gas phase with use of DFT B3LYP/6-311+G(3df, 2pd)//B3LYP/6-31+G(d,p) method and basis sets.

bered derivatives—amide **7c** and the thioamide **8c**—prefer the advantageous *syn-syn* conformations and in the case of the amide **7c**, the difference between *syn–syn* and *anti–anti* orientations is greater than 20 kJ mol^{-1}. On the basis of these results, it can be assumed that the stronger anion binding by the five-membered derivatives (type **7**) originates from their better preorganization in the *syn–syn* conformation. However, it has to be remembered that, in solution, we observed both *syn* and *anti* orientations of the amide groups for both isomers.

Analysis of the distributions of formal charges explains why the seven-membered derivatives do not take advantage of the azulene dipole moment. Analysis of Mulliken charges reveals that the introduction of two carbonyl groups into the 5- and 7-positions in compound **5c** induces the formation of a negative charge on 6-C (Table 3). As a result, the charges present on 6-C*H* and 2-C*H* hydrogen atoms are negative for both five- and seven-membered derivatives (**5c** and **7c**, respectively). Moreover, the electron distributions around the binding clefts are almost identical for both isomers (Figure S4). Similar observations can be made by two other approaches: Natural Population Analysis (NPA) and Electrostatic Potential Fit (ESP) Table 3. These results may suggest that the ligands of both types are able to form hydrogen bonds of comparable strength, and that the observed differences in anion affinity are caused by different geometries of binding sites and conformational preferences of the ligands.

Table 3. The formal charges on selected atoms for bisamides **5c**, **7c** and azulene **12** estimated by the different methods.[a]

	Atom	M[b]	NPA	ESP		M	NPA	ESP
5c ss_{+-}	6-C	−0.42	−0.17	0.20	**5c** ss_{++}	−0.48	−0.17	0.07
	6-CH	0.12	0.24	−0.07		0.12	0.24	0.02
	N	−0.31	−0.68	−0.39		−0.32	−0.68	−0.45
	NH	0.30	0.43	0.30		0.29	0.42	0.28
7c ss_{+-}	2-C	−0.24	−0.18	0.03	**7c** ss_{++}	−0.37	−0.18	−0.05
	2-CH	0.12	0.29	0.06		0.12	0.23	0.11
	N	−0.31	−0.67	−0.51		−0.30	−0.67	−0.50
	NH	0.29	0.43	0.34		0.28	0.42	0.31
12	6-C	−0.01	−0.20	−0.06				
	6-CH	0.13	0.25	0.11				
	2-C	−0.14	−0.21	0.12				
	2-CH	0.13	0.25	0.10				

[a] DFT B3LYP/6-31+G(d,p) calculations in gas phase; ss_{+-} and ss_{++} denote the conformations *syn-syn*$_{+-}$ and *syn–syn*$_{++}$, respectively. [b] M: Mulliken charges.

To throw some light on the binding pattern, we also performed molecular modelling of the ligands' complexes with chloride anion. For all model ligands **5c**–**8c**, we obtained the structures in which the chloride is bound by two hydrogen bonds formed by amide/thioamide N*H*s and the anion is positioned above the azulene plane (Figure 4, Figure S5). Deviations from coplanarity and distances between the anion and the central carbonyl atom (6-C for **5c**, **6c** or 2-C for **7c**, **8c**) are smaller in the case of the five-membered derivatives (**7c**, **8c**) (Table 4). The values of these parameters for ligand **7c**—3.4 Å, 164°—are in the CH hydrogen bond range; moreover, the C–Cl distance corresponds to the bonds formed by arenes with electron-withdrawing substituents,[23] which may suggest the presence of the CH···anion interaction for the ligands of type **7**. These results correlate with those of the ^{1}H NMR titration experiments: the 2-C*H* proton signals of **7a** and **8a** were shifted more strongly downfield than the 6-C*H* of the seven-membered analogues **5a** and **6a**. At the same time, the calculated lengths of the NH hydrogen bonds to chloride are smaller for the seven-membered **5c** and **6c** than for **7c** and **8c** (Table 4). There is also a parallel to the titration experiments, as this anion was bound more strongly by the seven-membered derivatives than by the five-membered ones (cf. Tables 1 and 4).

We obtained crystal structure of the complex of ligand **7b** with tetrapropylammonium chloride (TPA-Cl). Unfortunately, the crystals are twined by pseudomerohedry. A possible twinning element is the composition plane (010), and twin obliquity (the angle between the [010]* and [010] directions) is equal to 2.96°. Because of the low symmetry of the crystals (triclinic system) and the differently overlapping reflections it was not possible to apply procedures for the twin crystals during the structure refinement. Therefore the final discrepancy factors are quite large.

The independent part consists of two ligand complexes, the structures of which are similar, though one ligand has disorder in one of its phenyl side chains (Figure 5a). The ligand molecules are in the *syn-syn* conformations, and bind chlorides through the amide groups (N–Cl distances are about 3.5 Å). In both complexes the carbonyl groups deviate from the azulene planes (the torsion angles are 7.5 and 17° in one ligand, and 11 and 14° in the other), so the chloride anion is located above the ligand plane (Figure 5b). Although the amide groups are twisted with different angles, the chloride is positioned symmetrically with respect to the azulene. The crystal structure of **7b**·TPA-Cl is in very good agreement with the results of molecular modelling for the complex of **7c** and Cl^- (cf. Figure 4b and 5b). The arrangements of ligands and chloride anion in the two complexes are very similar, while the dis-

Table 4. The calculated distances between hydrogen bond donors and chloride anion, and the angle between anion and azulene plane for model ligands' complexes.[a]

	$d_{N\text{–}Cl}$ [Å]	$d_{C\text{–}Cl}$ [Å][b]	$\alpha_{C\text{-}H\text{-}Cl}$[b] [°]
amide **5c**	3.19	3.66	136
amide **7c**	3.49	3.38	164
thioamide **6c**	3.16	3.59	114
thioamide **8c**	3.29	3.34	118

[a] Calculations in gas phase by the DFT B3LYP/6-31+G(d,p) method. [b] The carbon (C) refers to 6-C for **5c** and **6c** or 2-C for **7c** and **8c**

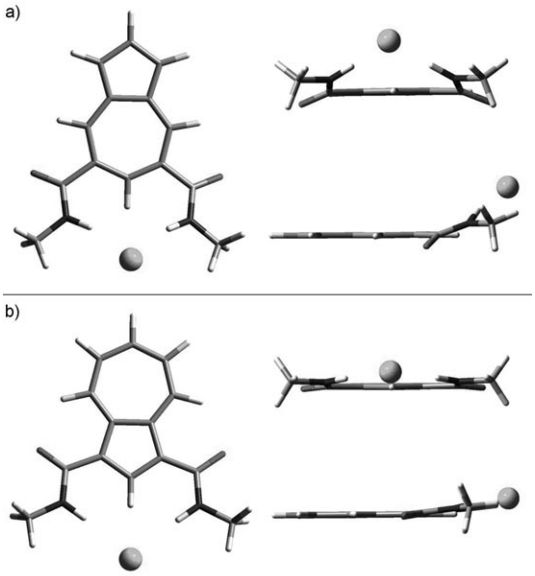


Figure 4. Calculated structures of chloride anion complexes with ligands by the DFT B3LYP/6-31+G(d,p) method. a) **5c** b) **7c**.

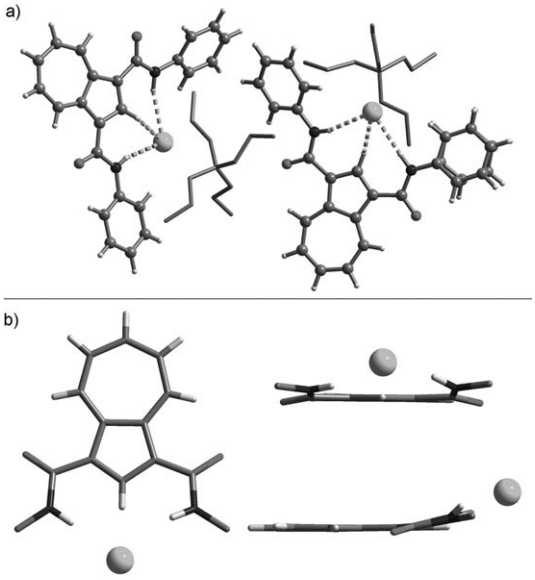


Figure 5. Crystal structure of **7b**·TPA-Cl. a) Independent part (the disorder in the TPA cation removed for clarity); b) different views of one of the complexes, with the phenyl groups omitted.

tances between 2-CH, amide groups and chloride anion in the solid state also match the calculated values (distances both in the modelled structure and in the solid state are about 3.4 and 3.5 Å, respectively). The main difference in the crystal structure is that the carbonyl groups are twisted with a larger angle, and as result the anion is located "higher" above the ligand plane (the C-H-Cl angles for the two ligands in the independent part are 156 and 150°).

The crystal structure of **7b**·TPA-Cl also supports the thesis that 2-C*H* is involved in hydrogen bond with anions; moreover, there is also a close contact between *m*-C*H* of the phenyl side chains and the anion, which may indicate the presence of additional aromatic CH···anion interactions and explain the efficiency of the receptor **7b**.

To describe the sizes and geometries of the binding clefts of the azulene-based building blocks, we defined two parameters: the angle "α" assigned to the angle between the amide/thioamide groups and the middle atom of a ligand, and the distance "*b*" between the hydrogen bond donors (Scheme 1). Since the amide groups are not coplanar in the *syn–syn* conformations, here we report the values obtained from different measurements: that based on X-ray analysis, and three others based on molecular modelling, for the *syn–syn*(++) and *syn–syn*(+−) conformations and for the complexes with chloride anions (Table 5).

Table 5. Geometric parameters of the binding clefts of the azulene-based building blocks.[a]

Data		5	6	7	8
X-ray structure[b]	*b* (α)	4.0 (117°)	5.6 (145°)		
conf. *syn–syn*$_{+-}$[c]	*b* (α)	4.9 (116°)	5.00 (122°)	5.6 (142°)	5.5 (145°)
conf. *syn–syn*$_{++}$[c]	*b* (α)	4.7 (110°)	4.73 (111°)	5.5 (138°)	5.4 (135°)
Cl^- complex	*b* (α)[c]	4.8 (111°)	4.6 (109°)	5.3 (135°)	5.1 (127°)

[a] Parameter *b* [Å]: the distance between (thio)amide Ns, α [°]: angle N-C-N; see Scheme 1. [b] X-ray measurements at 100 K, for butyl bisamides **5a** and **7a**. [c] DFT B3LYP/6-311+G(d,p) calculations for methyl bisamides **5c**–**8c**.

The parameters obtained for the complexes with chloride anions seem to be the most relevant because they describe the geometry of a binding site that is involved in the host–guest interaction. At the same time, the calculated values of *b* and α for the **7c**·Cl complex are similar to those found in the crystal structure of **7b**·TPA-Cl ($b = 5.3$ Å, $\alpha = 134°$). On the basis of the collected parameters, it is apparent that the five-membered ring derivatives have binding clefts much wider than those of their seven-membered analogues. Such differences in geometry can lead to dramatic changes in selectivity and binding affinity, as has been shown for hybrid systems containing different building blocks.[8,9]

Conclusion

Bisamides based on azulene are attractive building blocks for anion receptors and they extend the pool of available structural subunits for ligand design. The five-membered ring azulene-1,3-dicarboxylic derivatives offer binding clefts with geometries similar to those of the pyrrole-based bisamides. This building block prefers the *syn–syn* conformation of its amide groups; this feature should lead to well preorganized hosts containing azulene subunits. The aromatic amides of azulene-1,3-dicarboxylic acid are especially promising, as the model ligand **7b** binds anions even more strongly than the corresponding pyrrole-based ligand **4b**. There is also some evidence that the efficiency of these ligands is improved by the CH···anion interactions. Moreover, because of the ready accessibility of azulene-1,3-dicarboxylic acid di-

chloride (**15**), the synthesis of the five-membered ring azulene derivatives should be simple and convenient.

The azulene-5,7-dicarboxylic acid derivatives possess narrow binding sites, the geometries of which originate from the uncommon seven-membered ring. Such an arrangement of the amide groups seems to be quite complementary to the chloride anion. However, the preparation of receptors containing 5,7-substituted azulene units is more challenging, which might obstruct possible application of this building block in the more elaborate systems.

Interaction of the ligands with anions does not significantly affect the azulene chromophore. At this moment, it is uncertain whether this lack of optical response is caused by weak anion binding by these simple model ligands or whether the charge perturbation in the amide groups upon hydrogen bond formation is unable to trigger the colour changes in the chromophore.

Our comprehensive studies of azulene-based bisamides, particularly their structural properties, should help in preparation of advanced and efficient receptors for anions.

Experimental Section

Details concerning the determination of binding constants are provided in the Supporting Information, together with structural data. The syntheses of the amide **5a** and the thioamide **6a** have already been published.[14] Azulene-1,3-dicarboxylic acid (**14**) was prepared by the literature procedure.[18]

CCDC-267792, -267793, -633021, 633022 and -642743 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Azulene-1,3-dicarboxylic acid bis-butylamide (7a): Azulene-1,3-dicarboxylic acid (**14**, 2 g, 9.2 mmol) was suspended in dry CH_2Cl_2 (80 mL), and thionyl chloride (5.5 mL, 74 mmol) was then added, followed by two drops of DMF, and the reaction mixture was heated under reflux under argon for 12 h. Additional thionyl chloride (2 mL) was added, and heating was continued for the next 4 h. The solvent and unreacted $SOCl_2$ were removed in vacuo. The crude dichloride **15** was recrystallized from hot CH_2Cl_2, yielding red crystals (1.8 g, 78%) that were used without further purification.

A suspension of the dichloride **15** (0.33 g, 1.3 mmol) in dry CH_2Cl_2 was cooled to 0°C under argon, a butylamine solution (0.8 mL, 8 mmol) in CH_2Cl_2 (1 mL) was added dropwise, and the reaction mixture was stirred overnight. The solvent was removed in vacuo, and the solid residue was purified by column chromatography on silica gel (30 g) with use of a gradient of CH_2Cl_2 and MeOH [100:1 (100 mL), 100:2 (100 mL), 100:3 (50 mL), 100:4 (100 mL)]. The amide **7a** was recrystallized from hot dichloroethane, yielding 0.3 g (71%) of amide **7a** in the form of violet crystals. M.p. 150–151°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=9.32 (d, J_1=9.8 Hz, 2H; 4,8-C*H*), 8.00 (s, 1H; 2-C*H*), 7.72 (t, J_1=9.7 Hz, 1H; 6-C*H*), 7.37 (dd, J_1=J_1=9.8 Hz, 2H; 5,7-C*H*), 6.70 (t, J_1=5.5 Hz, 2H; N*H*), 3.40 (dt, J_1=6.0 Hz, J_2=6.4 Hz, 4H; CH_2N*H*), 1.57 (m, 4H; CH_2), 1.40 (m, 4H; CH_2), 0.94 ppm (t, J_1=7.1 Hz, 6H; CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ=166.0, 140.9, 140.2, 138.8, 134.0, 128.1, 120.0, 39.5, 31.9, 20.25, 13.81 ppm; HR ESI: *m*/*z*: calcd for $C_{20}H_{27}N_2O_2$: 327.2067; found: 327.2088 [*M*+H]$^+$; elemental analysis (%) calcd for $C_{20}H_{26}N_2O_2$: C 73.59, H 8.03, N 8.58; found: C 73.67, H 8.04, N 8.66.

Azulene-1,3-dicarboxylic acid bis-phenylamide (7b): Dichloride **15**, prepared as described above, was suspended in dry CH_2Cl_2 (0.8 g, 3.1 mmol in 60 mL), aniline was added dropwise (1.7 mL, 18.6 mmol), and the mixture was stirred overnight. The precipitate was filtered off and thoroughly washed with HCl (2M). The remaining solid was added to the CH_2Cl_2 phase and dissolved in ethyl acetate (200 mL), washed with HCl (2M, 2×30 mL) and water (30 mL) and dried over $MgSO_4$. The solvent was removed in vacuo, and the crude product was recrystallized from hot dichloroethane with a small amount of pentane, yielding the amide **7b** (0.7 g, 78%) as violet crystals. M.p. 215–216°C; ^{1}H NMR (200 MHz, DMSO): δ=10.29 (s, 2H; N*H*), 9.71 (d, J_1=9.8 Hz, 2H; 4,8-C*H*), 9.10 (s, 1H; 2-C*H*), 8.12 (t, J_1=9.6 Hz, 1H; 6-C*H*), 7.89–7.77 (m, 6H; *o*-C*H*+5,7-C*H*), 7.38 (dd, J_1=J_1=7.8 Hz, 4H; *m*-C*H*), 7.13 ppm (t, J_1=7.5 Hz, 2H; *p*-C*H*); ^{13}C NMR (50 MHz, DMSO): δ=164.3, 142.1, 142.0, 140.1, 139.5, 138.4, 129.8, 129.1, 123.7, 120.4, 120.2 ppm; HR ESI: *m*/*z*: calcd for $C_{24}H_{19}N_2O_2$: 367.1441; found: 367.1442 [*M*+H]$^+$; elemental analysis (%) calcd for $2C_{24}H_{18}N_2O_2{\cdot}H_2O$: C 76.78, H 5.10, N 7.46; found: C 76.62, H 5.48, N 7.53.

Azulene-1,3-dicarboxylic acid bis(4-nitrophenyl)amide (7d): A suspension of the acid dichloride **15** (1 g, 4 mmol) and *p*-nitroaniline (3.2 g, 23 mmol) in dry CH_2Cl_2 (60 mL) was heated at reflux under argon for 24 h. The solid was filtered off and thoroughly washed with HCl (2M), CH_2Cl_2 and MeOH. The remaining solid was flash chromatographed over silica gel with THF as the eluent. Removal of the solvent gave amide **7d** (1.3 g, 72%) as dark red crystals. M.p. t.t. >340°C; ^{1}H NMR (200 MHz, DMSO): δ=10.88 (s, 2H; N*H*), 9.73 (d, J_1=10 Hz, 2H; 4,8-C*H*), 9.19 (s, 1H; 2-C*H*), 8.30 (d, J_1=9.2 Hz, 4H; *o*-C*H*), 8.21 (t, J_1=9.7 Hz, 1H; 6-C*H*), 8.13 (d, J_1=9.2 Hz, 4H; *m*-C*H*), 7.93 ppm (dd, J_1=J_2=9.9 Hz, 2H; 5,7-C*H*); ^{13}C NMR (50 MHz, DMSO): δ=164.6, 146.4, 142.9, 142.6, 139.8, 139.1, 131.2, 125.5, 119.8, 119.3 ppm; elemental analysis (%) calcd for $C_{24}H_{18}N_2O_2$: C 63.16, H 3.53, N 12.28; found: C 63.04, H 3.47, N 12.10.

Azulene-1,3-dicarbothioic acid bis-butylamide (8a): Amide **7a** (0.4 g, 1.2 mmol) and Lawesson's reagent (1.3 g, 3.2 mmol) were suspended in dry THF (60 mL) and the mixture was heated at reflux under argon overnight. The solvent was evaporated in vacuo, and the solid residue was purified by column chromatography on silica gel (60 g) with CH_2Cl_2 (1.7 L) and CH_2Cl_2/MeOH 100:1 (0.5 L) as eluents. The product was recrystallized from a hexane/ethyl acetate mixture 7:3 (20 mL), yielding the thioamide **8a** (0.26 g, 60%) as brown-green crystals: m.p. 146–147°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=9.24 (d, J_1=9.8 Hz, 2H; 4,8-C*H*), 8.01 (t, J_1=5.1 Hz, 2H; N*H*), 7.81 (s, 1H; 2-C*H*), 7.74 (t, J_1=9.7 Hz, 1H; 6-C*H*), 7.36 (dd, J_1=J_1=9.8 Hz, 2H; 5,7-C*H*), 3.76 (dt, J_1=7.2 Hz, J_2=5.6 Hz, 4H; CH_2N*H*), 1.77 (m, 4H; CH_2), 1.47 (m, 4H; CH_2), 1.02 ppm (t, J_1=7.3 Hz, 6H; CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ=192.3, 140.8, 139.7, 138.5, 133.0, 128.0, 127.6, 45.9, 30.3, 20.4, 13.8 ppm; HR EI: *m*/*z*: calcd for. $C_{26}H_{26}N_2S_2$: 358.15374; found: 358.15324 [*M*]$^+$; elemental analysis (%) calcd for $C_{20}H_{26}N_2S_2$: C 66.99, H 7.31, N 7.81, S 17.89; found: C 66.97, H 7.25, N 7.72, S 17.69.

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