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Bishydrazide Derivatives of Isoindoline as Simple Anion Receptors

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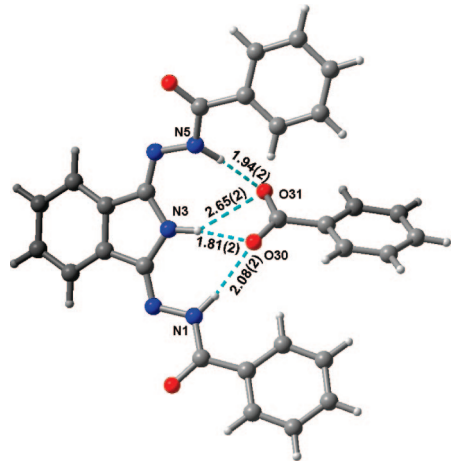
Received October 11, 2008



Isoindoline has been investigated as a scaffold for the construction of anion receptors. A family of bishydrazide derivatives of isoindoline has been synthesized, and the anion-binding properties of these receptors were investigated both in solution and in the solid state. Enhanced affinity toward halides has been observed for isoindoline-based ligands compared to analogous pyrroledicarboxyamides. However, in the case of highly basic anions, the anion binding is accompanied by partial deprotonation of the receptors, which also leads to the color changes of ligands' solutions.

Introduction

Anions are of crucial importance in a range of biological, chemical, medical, and environmental processes.[1] Due to this fact, anion complexation is an intensively explored area of supramolecular chemistry.[2] Binding of negatively charged species can be achieved by utilization of electrostatic attraction[3] or by weaker, but more directional, interactions − Lewis acid−base,[4] hydrophobic,[5] anion−π,[6] and hydrogen bonds.[7] Hydrogen bonds are most commonly used for the construction of neutral receptors, as their accessibility, directional character, and distance-dependent character enable assembly of binding sites that are adjusted for specific anions, thus leading to selective and efficient receptors.[7]

Among frequently used hydrogen bond donors − amides, sulfonoamides, ureas, hydrazides, hydrazones − the pyrrole moiety is an exceptional one. Contrary to the other groups,[8] pyrrole can act only as a donor; therefore, a risk of formation

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(1) Sessler, J. L.; Gale, P. A.; Cho, W. S. *Anion Receptor Chemistry*; The Royal Society of Chemistry: Cambridge, U.K., 2006.

(2) Gale, P. A.; Garcia-Garrido, S. E.; Garric, J. *Chem. Soc. Rev.* **2008**, *37*, 151–190. Katayev, E. A.; Ustynyuk, Sessler, J. L. *Coord. Chem. Rev.* **2006**, *250*, 3004–3037. Gale, P. A.; Quesada, R. *Coord. Chem. Rev.* **2006**, *250*, 3219–3244. Bowman-James, K. *Acc. Chem. Res.* **2005**, *38*, 671–678. Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 191–221. Gale, P. A. *Coord. Chem. Rev.* **2001**, *213*, 79–128. Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486–516.

(3) Worm, K.; Schmidtchen, F. P.; Schier, A.; Schäfer, A.; Hesse, M. *Angew. Chem., Int. Ed.* **1994**, *33*, 327–329. Schmidtchen, F. P. *Angew. Chem., Int. Ed.* **1977**, *16*, 720–722.

(4) Katz, H. E. *J. Am. Chem. Soc.* **1985**, *107*, 1420–1421. Katz, H. E. *J. Org. Chem.* **1985**, *50*, 5027–5032.

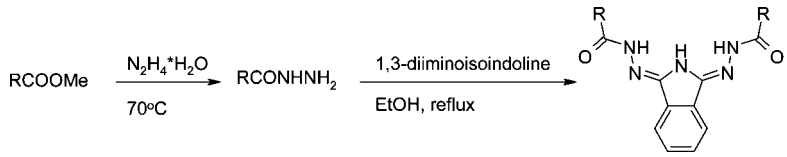
(5) Inoue, Y.; Hakushi, T.; Liu, Y.; Tong, L.-H.; Shen, B.-J.; Jin, D.-S. *J. Am. Chem. Soc.* **1993**, *115*, 475–481. Steed, J. W.; Juneja, R. K.; Atwood, J. L. *Angew. Chem., Int. Ed.* **1994**, *33*, 2456–2457.

(6) Schottel, B. L.; Chifotides, H. T.; Dunbar, K. R. *Chem. Soc. Rev.* **2008**, *37*, 68–83. Mascal, M.; Yakovlev, I.; Nikitin, E. B.; Fettinger, J. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 8782–8784.

(7) Kang, S. O.; Hossain, M. A.; Bowman-James, K. *Coord. Chem. Rev.* **2006**, *250*, 3038–3052. Kang, S. O.; Begum, R. A.; Bowman-James, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7882–7894. Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465–475. Bondy, C. R.; Loeb, S. J. *Coord. Chem. Rev.* **2003**, *240*, 77–99.

10.1021/jo802288u CCC: $40.75
Published on Web 01/27/2009

SCHEME 1. Synthesis of Ligands 2



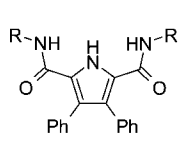
3a: R = n-C_5H_{11}
3b: R = Ph
3c: R = 2-Pyridine
3d: R = 2-Pyrrole

4a: R = n-C_5H_{11}, 93%
4b: R = Ph, 85%
4c: R = 2-Pyridine, 85%
4d: R = 2-Pyrrole, 92%

2a: R = n-C_5H_{11}, 54%
2b: R = Ph, 87%
2c: R = 2-Pyridine, 64%
2d: R = 2-Pyrrole, 95%

of unfavorable intermolecular hydrogen bonds is diminished. Due to this feature, the pyrrole ring has been extensively used for the construction of anion receptors.[9]

Incorporation of two additional amide sidearms to the pyrrole ring leads to the important building block **1**, with the enhanced affinity toward anions, as reported by Gale and co-workers.[10] Inspired by this structural motif, we decided to study a novel building block **2** that offers a similar binding cleft but is equipped with more acidic NHs, so enhanced anion binding may be expected. Moreover, the isoindoline moiety is well-known as a building block for high-performance pigments.[11] Thus the ligands of type **2** represent an attractive combination of an anchoring site with a signaling subunit and potentially can be used for preparation of optical sensors for anions. In this communication, we will present our studies on simple bishydrazides derived from 1,3-diiminoisoindoline as a building block for anion receptors.



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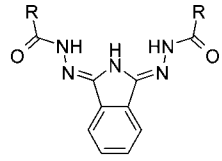

2

Results and Discussion

In order to perform extensive studies of anion-binding properties of the type **2** ligands, we decided to vary significantly the side groups, R, and obtained the derivatives of various acids: caproic, benzoic, picolinic, and 2-pyrrolecarboxylic acid. Aliphatic derivative, **2a**, should have the least acidic NH protons, thus being the weakest binder in the series. **2b** and **2c** represent common aromatic scaffolds, whereas **2d** possesses two additional anchoring points and its enhanced affinity toward anions can be expected.

The first advantage of our systems is a short and simple synthesis, which is a great asset to the future introduction of this building block into more sophisticated systems. All ligands (**2a**−**2d**) were synthesized in two steps from easily obtainable esters,[12] and commercially available 1,3-diiminoisoindoline (Scheme 1) in satisfactory overall yields (50−87%).

Having prepared the model ligands, we started to determine their anion-binding properties. As mentioned above, due to the optical properties of the built-in isoindoline chromophore, we hoped that our systems could signal the presence of specific anionic guests by changes of color. It turned out that interactions with anions, even in a competitive medium such as DMSO, can be confirmed by simple naked-eye observation of the solutions of these receptors (Figure 1). In some cases, this observation allows to distinguish between the types of anions used. For all ligands **2a**−**2d**, the most spectacular color changes were detected for highly basic anions (i.e., fluoride). Having observed such effects, we carried out the UV/vis titration experiments to determine quantitatively the receptors' affinities toward anions.

The changes in the UV/vis spectra allowed us to calculate the values of the binding constants (Table 1), and all the data gave a satisfactory fit with the 1:1 model for all anions. However, careful examination of the UV spectra during the titrations revealed that no clear isosbestic point could be observed upon addition of $H_2PO_4^-$ to the solutions of ligands **2a**, **2b**, and **2d** (Figure S2, Supporting Information), which suggested that other processes occurred than simple 1:1 binding. Thus, we also fitted experimental data using a 1:2 model, and indeed, we obtained a better fit for the interaction of ligands **2a**, **2b**, and **2d** with $H_2PO_4^-$ (see Figure S1). Interestingly, titration of ligand **2c** with $H_2PO_4^-$ gave an isosbestic point, and the data were best fitted to the 1:1 model. The stoichiometry of the complexes was also examined using Job plots analysis, showing 1:1 binding mode even in the case of $H_2PO_4^-$ (Figure S4), which confirms predomination of the 1:1 complexes in the range of concentrations used during the experiments (see the species distribution diagram, Figure S3). The observed selectivity of receptors **2** toward anions followed a common trend of oxoanions over halides: $AcO^- > PhCOO^- > H_2PO_4^- \gg Cl^-$, with unusual preference for carboxylates over phosphate.

In view of the fact that the optical response was more pronounced for more basic anions, it is likely that the color changes on which we based our calculations were mainly an effect of ligand deprotonation, rather than the anion complexation.[13,14] To check this hypothesis, we performed experiments

(8) Imidazolium group also acts only as a hydrogen bond donor; however, it is positively charged and forms electrostatic interactions with anions. Thus, we excluded the group from the list. For the review on imidazolium-based receptors see: Yoon, J.; Kim, S. K.; Singhb, N. J.; Kim, K. S. *Chem. Soc. Rev.* **2006**, *35*, 355–360.

(9) Sessler, J. L.; Seidel, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 5134–5175. Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17–55. Gale, P. A.; Anzenbacher, P., Jr.; Sessler, J. L. *Coord. Chem. Rev.* **2001**, *222*, 57–102.

(10) 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*, 7849–7853.

(11) Herbst, W.; Hunger, K. *Industrial Organic Pigments: Production, Properties, Applications*, 3rd ed.; Wiley-VCH: Weinheim, Germany, 2004. Smith, H. M. *High Performance Pigments*; Wiley-VCH: Weinheim, Germany, 2003.

(12) **3a**−**3c** are commercially available, **3d** was obtained according to: Barker, P.; Gendler, P.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 4849–4855.

(13) Gunnlaugsson, T.; Kruger, P. E.; Jensen, P.; Pfeffer, F. M.; Hussey, G. M. *Tetrahedron Lett.* **2003**, *44*, 8909–8913. Gunnlaugsson, T.; Glynn, M.; Tocci (née Hussey), G. M.; Kruger, P. E.; Pfeffer, F. M. *Coord. Chem. Rev.* **2006**, *250*, 3094–3117.

(14) Amendola, V.; Esteban-Gomez, D.; Fabbrizzi, L.; Licchelli, M. *Acc. Chem. Res.* **2006**, *39*, 343–353. Esteban-Gomez, D.; Fabbrizzi, L.; Liechelli, M. *J. Org. Chem.* **2005**, *70*, 5717–5720. Boiocchi, M.; Del Boca, L.; Esteban-Gomez, D.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *Chem.−Eur. J.* **2005**, *11*, 3097–3104.

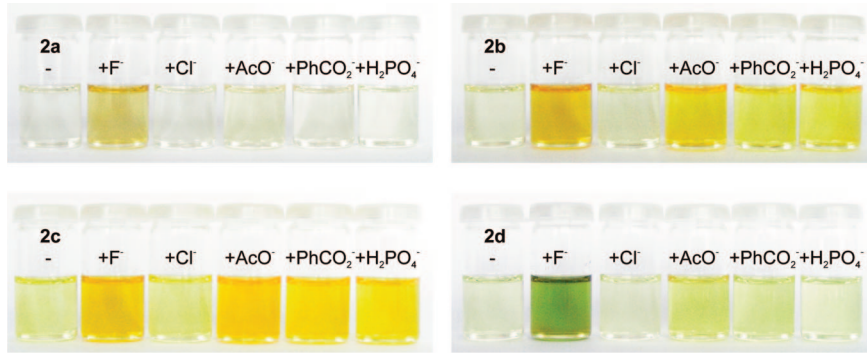

FIGURE 1. Changes of color of ligands **2a**−**2d** in DMSO (C = 4 x 10^{-4} M) in the presence of 3 equiv of anions as TBA salts.

TABLE 1. Binding Constants (log K_a) for the Formation of 1:1 Complexes of Model Ligands with Various Anions in DMSO + 0.5% H_2O at 298 K[a]

anions	2a	2b	2c	2d
Cl^-	<2.6[b]	<2.6[b]	<2.6[b]	<3[b]
$PhCOO^-$	4.4	4.5	>6	4.3
AcO^-	5.7	5.9	>7	5.3
$H_2PO_4^-$	3.8	4.1	5.2	3.8
$H_2PO_4^-$ log β_1[c]	4.3	4.6		4.6
$H_2PO_4^-$ log β_2[c]	7.2	8.4		8.3

[a] Determined by UV/vis titration. Errors estimated to be <15%. TBA salts were used as a source of anions. [b] Interaction too weak to be precisely measured. [c] Values of binding constants (logβ_1 and logβ_2) for the formation 1:2 complexes (ligand:anion).

similar to those reported by Fabbrizzi[14] and compared UV/vis spectra of ligands upon addition of TBA salts and TBA hydroxide.

The trends of spectral changes induced by increasing concentration of highly basic anions (e.g., $PhCOO^-$) and hydroxide anions are quite similar (Figure 2), so the assumption of deprotonation was partially proven, especially by the development of a new band in the region of 390−445 nm. Nevertheless, there were no such observations for less basic anions (e.g., Cl^-; Figure 2), thus we assumed that in these cases complexation was not accompanied by deprotonation of the receptor. However, the binding constants for those anions were too low to be precisely determined by UV/vis technique. They can be roughly estimated between 100 and 1000 [M^{-1}].

In the case of the ligands possessing an acidic hydrogen bond donor, like receptors **2a**−**2d**, anion recognition is often accompanied by a significant degree of deprotonation.[15] This process is favorable in highly diluted receptor solutions since the ratio of hydrogen-bonded and deprotonated forms of ligands is proportional to the total receptor concentration. Therefore, the UV/vis titration technique is much more sensitive to the accompanying process of deprotonation than the ^{1}H NMR technique, for which operating concentration is higher by more than 2 orders of magnitude. Thus, the UV/vis determined binding constants may be more distorted and; consequently, there would be no agreement between the values obtained from both these techniques.

Therefore, we decided to use ^{1}H NMR titration technique as a parallel method of determining the binding constants for the anion complexes. In the course of ^{1}H NMR experiments in DMSO-d_6 + 0.5% H_2O (v/v), we monitored the downfield shifts of hydrazide−NH and isoindoline−NH signals that indicated complex formation reversible on the NMR time scale. For the chloride and bromide anions, we observed sharp proton signals over the whole titration and performed data fitting for the 1:1 model (see Figures S8 and 3). Thus, the deprotonation by less basic anions was excluded, again. Moreover, the binding constant values from both titration techniques were in satisfying agreement for the weak basic anions; therefore, the anion binding was the sole process in the solution. The values of the binding constants are given in Table 2.

We also made the ^{1}H NMR titration experiments with more basic anions (i.e., $PhCOO^-$ and $H_2PO_4^-$). It turned out that upon addition of TBA salts, the signal of hydrazide−NH resonance broadened and eventually disappeared in the baseline (after addition of about 2.5 equiv of anions). For the isoindoline−NH, the same effect was triggered by the addition of the very first portion of anions (ca. 0.2 equiv). Thus, the deprotonation by highly acidic anions was confirmed. Fitting the changes in the chemical shift of the hydrazide−NH resonance to 1:1 isotherm led to values equal to about 5000 and 2000 [M^{-1}] for receptor **2b** with $PhCOO^-$ and $H_2PO_4^-$, respectively (see Figure S7). A comparison of these findings with the UV/vis results (ca. 3 x 10^4 and 4 x 10^4 [M^{-1}] for $PhCOO^-$ and $H_2PO_4^-$, respectively) demonstrates the influence of ligand concentration on the estimated values of the binding constant and confirms the hypothesis of ligand deprotonation.

The differences of the binding constants calculated on the basis of the UV/vis and ^{1}H NMR experiments could also arise from the intermolecular interactions, which are more pronounced in more concentrated solutions. In order to verify this hypothesis, we performed dilution experiments. We verified that compounds **2** obey the Lambert−Beer law (Figure S5), as well that the ^{1}H NMR spectra of ligands **2** do not change upon dilution. Thus, we excluded the possibility of self-aggregation of ligands within the wide range of concentration from about 10^{-6} to 10^{-1} M.

We could not use ^{1}H NMR technique for the ligand **2c** due to its low solubility in DMSO. However, it solubilized readily after addition of TBA−chloride, proving its interaction with anions.

Furthermore, we encountered a more intriguing problem with compound **2a** that exists in three rotameric forms in the DMSO solution. They were observable by the NMR spectroscopy at room temperature (Figure S9a). Elevation of the temperature to 343 K led to a rotation reversible on the NMR time scale and the signals coalesced (Figure S9b). We managed to monitor, independently, the changes of chemical shifts upon addition of TBA−chloride for all three rotamers (Figure 3). We fit the data to a 1:1 model,[16] obtaining three values (about 1000, 100, and 50 [M^{-1}]) assigned to three rotameric forms of ligand **2a**. Similar

(15) Pérez-Casas, C.; Yatsimirsky, A. K. *J. Org. Chem.* **2008**, *73*, 2275–2284.

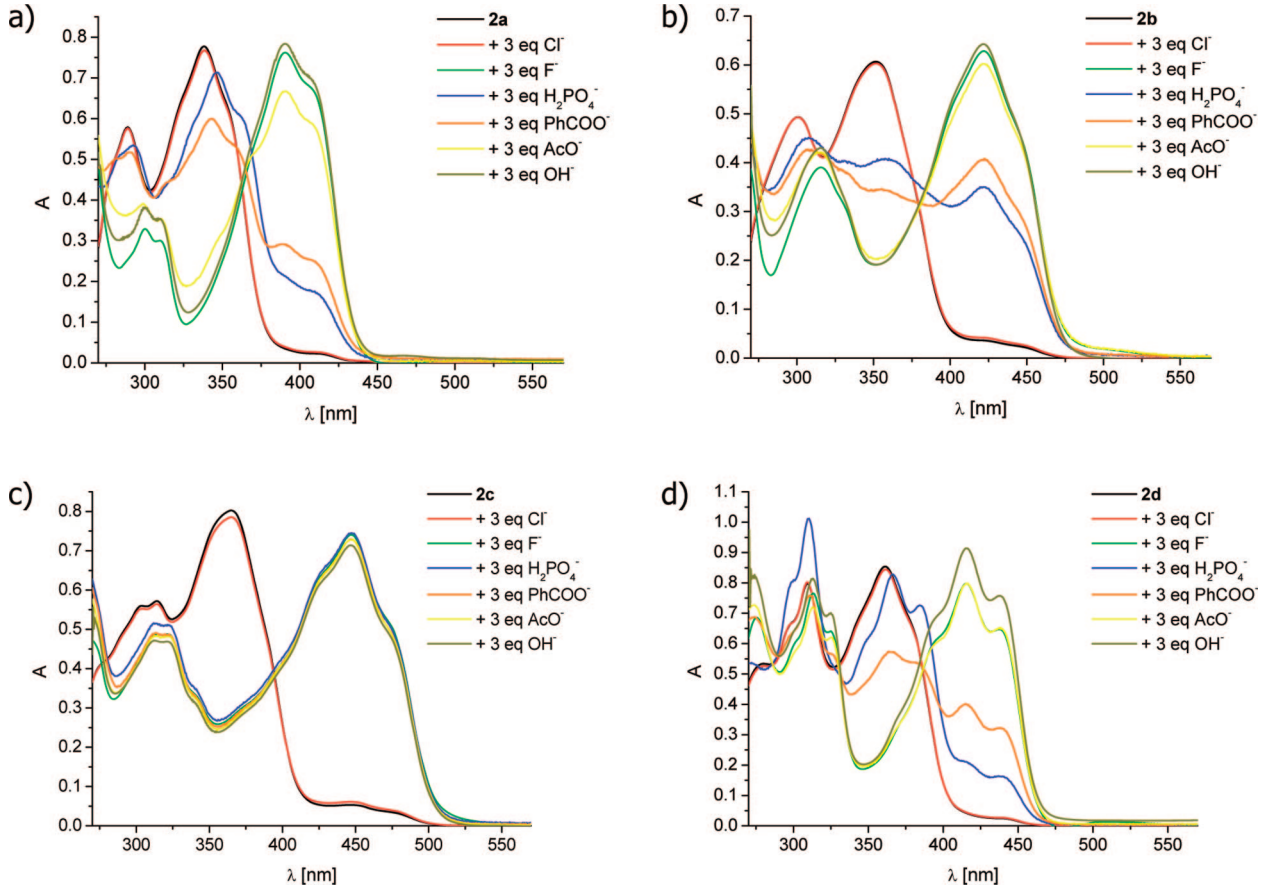

FIGURE 2. UV/vis spectra in DMSO + 0.5% H_2O of free ligand and after addition 3 equiv of anions: (a) ligand **2a**, (b) ligand **2b**, (c) ligand **2c**, and d) ligand **2d**.

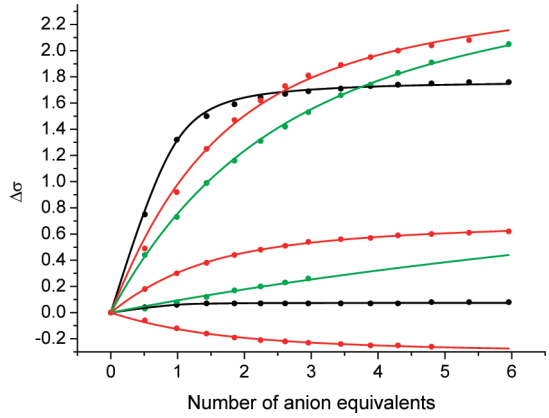

FIGURE 3. ^{1}H NMR titration curves for NH protons in compound **2a** upon addition of TBA−Cl. Black, red, and green colors indicate curves for which K_a values are about 1000, 100, and 50, respectively.

observation was made during titration experiments with TBA−bromide. In this case, we succeeded in fitting a 1:1 isotherm for one rotamer only, while the rest interacted with the bromide anion too weakly. The binding constant was established to be about 50 [M^{-1}] and was attributed to the best pre-organized rotamer of receptor **2a**. We cannot rationalize why such rotamers were observed only for the ligand **2a** and not for all remaining hydrazides **2b**−**2d**.

(16) We assumed that the ratio of distinct forms of a complex is equal to that of free forms of ligand − the more similar values of the binding constants, the more appropriate the assumption.

TABLE 2. Binding Constants [M^{-1}] for the Formation of 1:1 Complexes of Model Ligands with Cl^- and Br^- Anions in DMSO-d_6 + 0.5% H_2O at 298 K[a]

anions	2a[b]	2b[c]	2c[d]	2d[c]
Cl^-	1000	140		500
	100	110	−	200
	50			
Br^-	50	<2		<2
	−[e]		−	
	−[e]			

[a] Determined by ^{1}H NMR titration. Errors estimated to be <10%. TBA salts were used as a source of anions. [b] The values for three rotamers (see text for details). [c] The values for isoindoline−NH and hydrazide−NH signals, respectively. [d] Poorly soluble in DMSO. [e] Interaction too weak to be measured.

The determined binding constants for the ligands **2a**−**2d** are collected in Table 2. Anion binding of the new isoindoline receptors **2a**−**2d** compares favorably with that of ligands of type **1**. The values of the binding constants for complexes of the new ligands **2a**−**2d** are over ten times larger than for the parent receptors (for the receptors of type **1**, the values are <11 [M^{-1}] for Cl^-, and not measurable at all for Br^-).[10,17] Introduction of two additional anchoring points into **2d** results in doubled binding constants compared with that of **2b**. Such a result shows that, in this case, the strong preference of *anti* conformation of pyrrolecarboxamides[17,18] is overcome by the formation of a hydrogen bond between pyrrolic−NH and the anion.

(17) Zieliński, T.; Jurczak, J. *Tetrahedron* **2005**, *61*, 4081–4089.
(18) Zieliński, T.; Dydio, P.; Jurczak, J. *Tetrahedron* **2008**, *64*, 568–574.

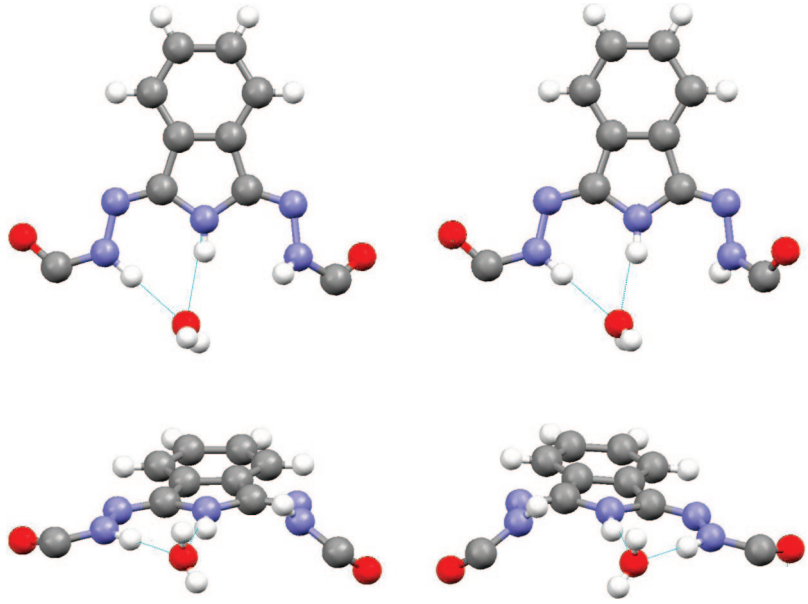

FIGURE 4. Different views (top, bottom) of crystal structure of two forms (left, right) of the ligand **2a**·H_2O (the pentyl groups are omitted for clarity).

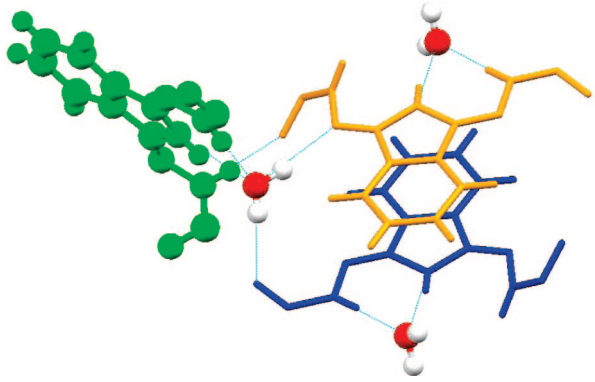

FIGURE 5. Crystal structure of **2a** showing water molecules engaged in hydrogen bonds (the pentyl groups are omitted for clarity).

Although we observed that increasing the acidity of hydrogen bond donors of ligands **2** compared to **1** can increase affinity toward anions (i.e., Cl^-). It can also lead to deprotonation of ligands and change the complexation phenomena into an acid−base reaction. Such behavior was reported previously,[19] and it seemed to hamper further increasing the receptors efficiency by tuning their electronic properties.

For the purpose of the structural analysis, we obtained a diffraction-grade single crystal of the ligand **2a** by slow diffusion of water into its solution in DMSO. The independent part consists of two pairs of ligand and water molecules, the structures of which are similar, and both of them have disorder in their pentyl side chains (Figure S10). Both ligands adopt conformations in which NH groups point almost convergently to the binding cleft (Figure 4). Two of them, the hydrazide and the isoindoline−NHs, are engaged in the binding of water molecules (the N−O distances are about 2.9 Å), which are positioned in such a manner that the oxygen is in the isoindoline plane and the hydrogens are almost perpendicular to the ring (Figure 5). These hydrogen atoms form hydrogen bonds with the carbonyl group and the imine group of adjoining ligands (the N−O and O−O distances are about 2.85 Å). The second hydrazide group is deviated from the plane (the torsion angles are 35°) and forms hydrogen bonds with equivalent groups of next ligand molecules (the N−O distances are about 2.8 Å).

We also succeeded in preparing a diffraction-grade single crystal of the complex of ligand **2b** with tetrabutylammonium benzoate (TBA−PhCOO). This structure undoubtedly confirms the process of anion complexation that takes place beside deprotonation of the receptor in the solution. The ligand adopts almost a symmetrical conformation with its side arms twisted in such a manner that the hydrazide−NHs point below the ring plane (Figure 6). The benzoate anion lies under the plane of the isoindoline moiety and is positioned asymmetrically. One of the oxygen atoms is located near the center of binding cleft, almost in the mean plane, accepting a pair of strong hydrogen bonds from both the central and one arm NHs (the N−O distances are 2.75 and 2.96 Å, respectively). The second oxygen atom is significantly deviated from the plane, is tilted toward the other arm, and is bound also by two hydrogen bonds (the N−O distances are 2.89 and 3.28 Å, respectively).

This complex structure may suggest that the cleft is still slightly too small for the carboxylate anion. In the crystal structure, the hydrazide ligand, **2b**, binds benzoate with four hydrogen bonds, while the parent receptor **1**, reported by Gale,[20] is able to create only three hydrogen bonds (in the range of 2.77−2.86 Å), but the manner of positioning of the benzoate anion remains very similar. One of the oxygen atoms is again located almost in the center of binding cleft, in the pyrrole plane, accepting a pair of hydrogen bonds from the pyrrole and amide−NHs. The second oxygen atom is deviated from the plane and is tilted toward the other amide−NH accommodating a third hydrogen bond. Moreover, the phenyl ring is twisted and deviated from the main plane in the same fashion in both complex structures.

We could not directly compare our ligands with another, simple and efficient pyrrole-based system as published by

(19) Camiolo, S.; Gale, P. A.; Hursthouse, M. B.; Light, M. E.; Shi, A. J. *Chem. Commun.* **2002**, 758–759.

(20) Camiolo, S.; Gale, P. A.; Hursthouse, M. B.; Light, M. E. *Tetrahedron Lett.* **2002**, *43*, 6995–6996.

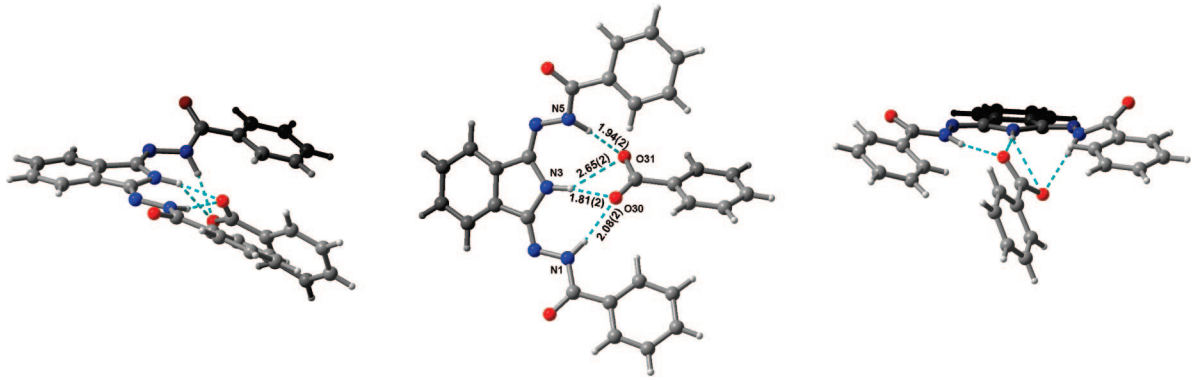

FIGURE 6. Different views of the X-ray crystal structure of the benzoate complex of ligand **2b** (the countercation is omitted for clarity).

Maeda,[21] due to the lack of appropriate crystal structures. However, DFT calculations show that Maeda's dipyrrolyldiketone also binds oxoanions with four hydrogen bonds, but the complex has a completely flat structure. At the same time, unlike the hydrate of ligand **2a**, Maeda's receptor, even upon complexation of chloride anion, does not form a convergent binding site in the solid state.

It is worth emphasizing that the geometry of the anchoring site in the complex of **2b** with benzoate is almost the same as that in the free ligand **2a**. The distance between nitrogen atoms N1−N5 is 5.29 Å and the cleft angle N1−N3−N5 is 142 ° in the anion complex, whereas, in case of the free receptor (fragment **b**), the distance is 5.20 Å and the angle is about 140°. Measurement of the geometric parameters of the binding cleft (the distance between hydrazide donor NHs and the angle N−N−N as described in ref. 22) shows that the binding site of **2** has novel structural properties and can be classified between derivatives of the pyrrole-2,5-dicarboxylic acid and the azulene-1,3-dicarboxylic acid.[22]

Conclusions

We investigated the anion-binding properties of the new derivatives of isoindoline both in the solution and the solid state. Due to the higher acidicity of the donors groups, receptors **2** bound halides more strongly than their parent compounds, pyrroledicarboxamides **1**. Unfortunately, in case of more basic anions, the complexation process was accompanied by the partial deprotonation of the ligands. This process triggered spectacular color changes of the receptor's solution. However, in the solid state, we observed solely the anion binding with no ligand deprotonation. Structural analysis showed that **2** has a geometry of its binding site different from other bidentate building blocks, thus **2** extends the pool of available structural subunits for the design of anion receptors.

Experimental Section

General Procedure for Preparation of the Hydrazides 4a-d. To a 25 mL round-bottomed flask equipped with a magnetic stirrer, $N_2H_4 \cdot H_2O$ (80% in water, 12 mL) and an appropriate ester (3 g) were added. Then the temperature of the mixture was elevated to 70 °C for 45 min and the mixture was cooled to room temperature.

Hexanoic Acid Hydrazide 4a. The above general procedure was followed using hexanoic acid and methyl ester (3.0 g, 23 mmol). The reaction mixture was extracted with ethyl acetate, the extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*. The solid residue was purified by flash chromatography over silica gel using ethyl acetate and MeOH [95:5] as eluents. The product was recrystallized from hot ethyl acetate yielding 2.8 g (93%) of the hydrazide **4a** as colorless crystals, mp 64−67 °C.

^{1}H NMR (200 MHz, DMSO) δ = 8.90 (bs, 1H, NH), 4.13 (s, 2H, NH_2), 1.99 (t, 2H, J_1 = 7.4 Hz), 1.48 (p, 2H, J_1 = 7.4 Hz), 1.23 (m, 4H), 0.85 (t, 3H, J_1 = 6.7 Hz); ^{13}C NMR (50 MHz, DMSO) δ = 172.1, 33.9, 31.4, 25.4, 22.3, 14.3; HR EI calcd for $C_6H_{14}N_2O$−M^+ 130.11061, found 130.11093; Anal. calcd for $C_6H_{14}N_2O$ C 55.35, H 10.84, N 21.52, found C 55.32, H 10.93, N 21.38.

Hydrazides 4b−4d. Detailed procedures and characterizations are described in Supporting Information.

General Procedure for Preparation of the Ligands 2a−2d. In a 100 mL round-bottomed flask equipped with a magnetic stirrer, under an argon atmosphere, 1,3-diiminoisoindoline (435 mg, 2.5 mmol) and the appropriate hydrazide (7.5 mmol) were dissolved in EtOH (30 mL). The mixture was then refluxed over a week.

1,3-Bis(hexanoyl-hydrazone)isoindoline 2a. The above general procedure was followed using the hydrazide **4a** (1.0 g). The created suspension was filtered and washed with Et_2O, and the crude product was recrystallized from hot 1,2-dichloroethane (after cooling down to room temperature, it was placed in a refrigerator). Yield 0.50 g (54%) of the ligand **2a** as yellow crystals, mp 193−195 °C.

^{1}H NMR (500 MHz, DMSO) δ = 10. 07 (bm, 3H, CONH + NH), 7.77 (m, 2H), 7.60 (t, 2H, J_1 = 1.6 Hz), 2.64 (q, 2H, J_1 = 4.2 Hz), 2.25 (m, 2H), 1.61 (m, 4H), 1.33 (m, 8H), 0.88 (m, 6H); ^{13}C NMR (50 MHz, DMSO) δ = 174.5, 174.2, 168.6, 168.4, 145.9, 144.4, 140.1, 139.4, 132.9, 132.5, 130.9, 130.6, 121.4, 120.8, 34.2, 31.5, 31.0, 24.8, 23.8, 21.9, 13.9; HR ESI calcd for $C_{20}H_{29}N_5O_2Na$−M^+ 394.22135, found 394.21965; Anal. calcd for $C_{20}H_{29}N_5O_2$ C 64.67, H 7.87, N 18.85, found C 64.47, H 7.95, N 18.95.

Ligands 2b−2d. Detailed procedures and characterizations are described in Supporting Information.

Acknowledgment. The x-ray measurements were undertaken in the Crystallographic Unit of the Physical Chemistry Laboratory in the Chemistry Department of the University of Warsaw.

Supporting Information Available: General remarks, all experimental procedures and characterization data for compounds **2a−2d** and **4a−4d**, ORTEP plots, ^{1}H, ^{13}C NMR spectra, details concerning the determination of binding constants, titration curves, changes of UV/vis spectra, and Job plots; crystallographic data, also in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802288U

(21) Fujimoto, C.; Kusunose, Y.; Maeda, H. *J. Org. Chem.* **2006**, *71*, 2389–2394. Maeda, H.; Ito, Y. *Inorg. Chem.* **2006**, *45*, 8205–8210.

(22) Zieliński, T.; Kedziorek, M.; Jurczak, J. *Chem.−Eur. J.* **2008**, *14*, 838–846. Zieliński, T.; Kedziorek, M.; Jurczak, J. *Tetrahedron* **2005**, *46*, 6231–6234.