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Anion receptors based on 7,7′-diamido-2,2′-diindolylmethane†

Paweł Dydio,[ab] Tomasz Zieliński[a] and Janusz Jurczak*[ab]

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7-Aminoindole has been successfully used as a building block for the construction of new anion receptors that have strong a affinity towards anions, especially dihydrogen phosphate, even in very competitive solvents.

An understanding of the host–guest chemistry of anions is important in the fields of catalysis, analytical applications, medicine and industrial processes,[1] and the design and synthesis of receptors for anions is currently an area of extensive exploration.[2] Much effort has been devoted to ligands that exploit hydrogen bonding, since such interactions can potentially lead to highly selective receptors. Due to its unique ability to act only as a hydrogen bond donor, the pyrrole moiety is one of the most attractive building blocks for the construction of binding sites.[3]

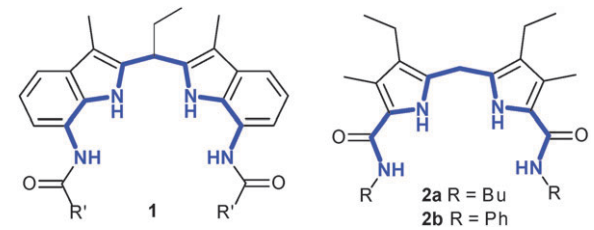
Pyrrole-based anion receptors have been introduced and developed by the Sessler group,[4] while receptors with a combination of pyrrole and amide groups have been contributed by Gale and co-workers.[5] A further, logical extension of the pyrrole-based designs should include benzopyrroles, which also contain only hydrogen bond donors, but are more acidic, usually more stable and offer broader structural diversity than pyrroles. However, only recently have indoles,[6,7] biindoles,[8] carbazoles[9,10] and indolocarbazoles[11] attracted the attention of researchers for applications in anion recognition.[12]

Amides derived from 7-aminoindole have been independently investigated by both the Gale group[13] and us.[14] This structural subunit has two hydrogen bond donors which are situated similarly to 2-amidopyrrole. Inspired by this observation, we decided to prepare amides **1**, the indole-based analogues of 2,2′-bisamidodipyrrolylmethanes **2**, which are efficient anion receptors.[15] (Scheme 1).

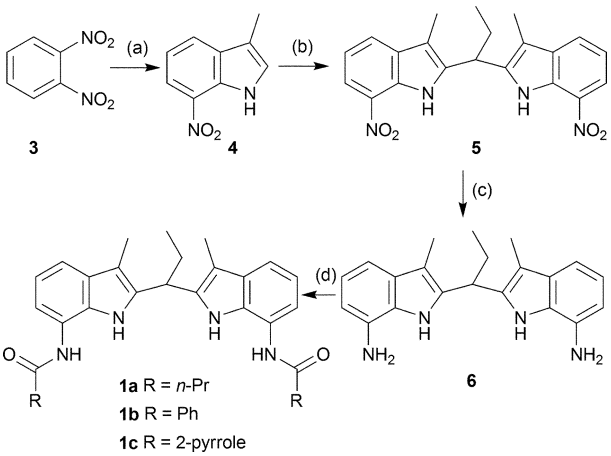
Contrary to the reactivity of pyrroles, direct condensation of indoles and carbonyl compounds leads to 3,3′-diindolylmethanes, which were exploited in the preparation of a colorimetric sensor.[16] To facilitate the synthesis, we had to block the 3-position of indole with a methyl substituent. In our first approach, 7,7′-bisnitro-2,2′-diindolylmethane **5** was obtained in a one-pot synthesis that combined the Fisher indole synthesis and subsequent condensation with propional, in 40% overall yield.[17] We also developed a more general method, that started with the Bartoli type synthesis of 7-amino-3-methylindole **4**, followed by the reaction with an aldehyde in hydrochloric acid. The nitro derivative **5** was then hydrogenated to bisamine **6**, and subsequently reacted with three different acid chlorides leading to the desired ligands **1a–c** in good yields (Scheme 2).

The stability constants of receptors **1a–c** with model anions were determined by ^{1}H NMR titrations (Table 1). The preliminary results showed a remarkable affinity of the new diindolylmethanes **1a–c** towards oxo-anions. They interacted too strongly to be measured in the commonly used solvent: DMSO + 0.5% H_2O. Thus, we had to use an even a more competitive medium and increase the water content up to 5%, which also allowed us to make a direct comparison with the parent compounds **2**.[15]

Ligands **1a–c** had a common preference for more basic oxoanions over halides (Fig. 1), and formed complexes with a 1 : 1 stoichiometry, which was also confirmed by the Job plots. The association constants determined independently using amide and indole NH signals are in good agreement,



Scheme 1



Scheme 2 Synthesis of receptors **1a–c**. (a) $CH_3CH{=}CHMgBr$; (b) C_2H_5CHO, HCl; (c) H_2, Pd/C; (d) RCOCl.

[a] *Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224, Warsaw, Poland. E-mail: jurczak@icho.edu.pl; Fax: +48 22 632 66 81; Tel: +48 22 632 05 78*
[b] *Department of Chemistry, Warsaw University, Pasteura 1, 02-093, Warsaw, Poland*

† Electronic supplementary information (ESI) available: Synthesis of receptors **1a–c**, description of titration experiments, Job plots, crystallographic data. CCDC 707058, 725837 and 707057. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b907164d

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Table 1 Binding constants [M^{-1}] for the formation of 1 : 1 complexes of ligands **1a–c** with various anions in DMSO–H_2O mixtures[a]

			Stability constant (K_a/M^{-1})		
Anion	% water[b]	Signal[c]	**1a**	**1b**	**1c**
Cl^-	0.5	amide	—[d]	30	130
		indole	470	30	80
Br^-	0.5	amide	20	<2	<2
		indole	20	<2	<2
$PhCO_2^-$	0.5	amide	>10 000	2010	1020
		indole	>10 000	2140	1660
$H_2PO_4^-$	0.5	amide	>10 000	3850	—[e]
		indole	>10 000	4460	—[e]
Cl^-	5	amide	—[d]	7	20
		indole	150	7	20
Br^-	5	amide	10	<2	<2
		indole	10	<2	<2
$PhCO_2^-$	5	amide	1880	360	260
		indole	2060	340	300
$H_2PO_4^-$	5	amide	>10 000	980	130
		indole	>10 000	990	400
$PhCO_2^-$	10	amide	540	—[f]	—[f]
		indole	590	—[f]	—[f]
$H_2PO_4^-$	10	amide	5980	—[f]	—[f]
		indole	5640	—[f]	—[f]
$H_2PO_4^-$	25	amide	210	<2	—[f]
		indole	210	<2	—[f]

[a] Values determined by ^1H NMR titration experiments at $T = 298$ K, errors < 10%, tetrabutylammonium (TBA) salts were the source of anions. [b] DMSO-d_6 + H_2O mixture used as the solvent, water content as specified in the column. [c] NH signal used for the calculations. [d] Fitting failed due to too small signal shift. [e] Fitting failed due to signal broadening. [f] Not measured.

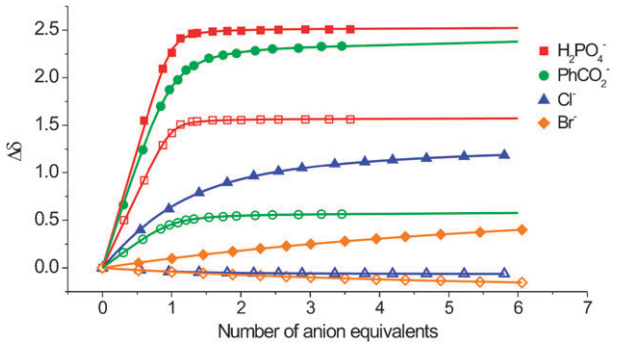

Fig. 1 ^1H NMR titration of ligand **1a** with different anions in DMSO-d_6 + 5% H_2O. Changes of chemical shift of indole NH (solid symbols) and amide NH (void ones).

with slightly higher values for the indole measurements. Aliphatic amide **1a** binds anions the strongest, and has an exceptional affinity towards $H_2PO_4^-$: the exact value of its association constant could only be determined in DMSO containing 10–25% water. The relative selectivity for $H_2PO_4^-$ over $PhCO_2^-$ is not affected by the water content in the medium, and is approximately 10 for **1a** and around 2 for **1b**.

Unexpectedly, the phenyl derivative **1b** is a much weaker receptor than **1a**, despite the higher acidity of its amide NH groups. A similar observation was reported for the carbazole-based bisamides,[9] and at this moment, it can only be rationalised in terms of steric hindrance.

A comparison of the K_a for receptors **1b** and **1c** reveals that the introduction of the additional pyrrole moiety does not improve the affinity towards anions. Smaller values of K_a and $\Delta\delta_{max}$ for the pyrrole NH in **1c** (see ESI†) suggest that this group is too far from the "binding center" of the receptor. Moreover, the structural analysis of **1c** shows an unfavourable pre-organisation.

In order to judge how successful our design was, we compared receptors **1** with parent ligands **2**. The diindolylmethane-based receptor **1a** interacts with anions more strongly than any of the previously reported dipyrrolylmethane-based ligands. Receptor **1b** has an anion affinity that is similar to **2b**, however, **1b** is superior to the *meso*-substituted analogues of **2**. It is worth mentioning that all the compounds **1a–c**, unlike **2**, are stable in the solution even in the presence of anions.

We obtained diffraction-grade crystals of the solvated ligand **1b** and of two complexes: **1a**·$TBAPhCO_2$ and **1c**·TBACl, which allowed us to characterise the geometric properties of these new diindolylmethane-based receptors.‡

The structural analysis of **1b** monohydrate reveals that the ligand adopts a "bent sheet" conformation (the angle between the indolyl planes is 65°) in which all NH groups point convergently to the centre of the binding cleft (Fig. 2a). Both indole NHs form hydrogen bonds with a water molecule (N–O distances of 2.92 and 2.96 Å). The guest water molecule is positioned in such a manner, that its hydrogen atoms are almost perpendicular to the ligand and interact with the carbonyl groups of neighbouring ligands, bridging every third molecule of the receptor (the O–O distances are 2.74 and 2.80 Å). It is also noteworthy that the phenyl rings contribute to the binding of water through CH–O interactions (the CH–O distances are 2.65 and 2.74 Å). Each two ligand molecules form a centrosymmetric dimer stabilized by a pair of hydrogen bonds formed by the amide groups (the N–O distances are 3.06 Å). In this structure, ligand **1b** is better pre-organised than the reported dipyrrolylmethanes, in which the pyrrole rings are almost perpendicular to each other.

The X-ray analysis of **1a**·$TBAPhCO_2$ shows that the independent part of the structure contains two complexes that are very similar in their geometry. In both subunits, the ligands have a bent sheet shape (plane angles are about 63°) and bind benzoate with all four NHs (Fig. 2b). The anion is positioned almost centrally above the receptor with its phenyl ring pointing outwards. Each oxygen forms two hydrogen bonds with indole and amide NHs, however one pair of bonds is shorter than the other one, so the anion is slightly tilted. Such a binding motif is different from the one observed for the diindolylurea-based receptors,[7] in which hydrogen bonds are almost coplanar while the carboxylate group is perpendicular to the ligand plane. Judging by the bonds lengths, indole NHs interact with the anion more strongly than the amide groups (N–O distances are 2.72–2.82 Å for indoles and 2.86–2.91 Å for amides), this observation is in agreement with the results of the titration experiments.

Finally, the crystal structure of the complex **1c**·TBACl consists of two independent fragments, that differ slightly in ligand conformation. The chloride anion is bound by four NH groups of the receptor and lies above the bent sheet shaped ligand molecule (the angles between indole planes are about 66°) (Fig. 2c). The two hydrogen bonds formed by indole NHs

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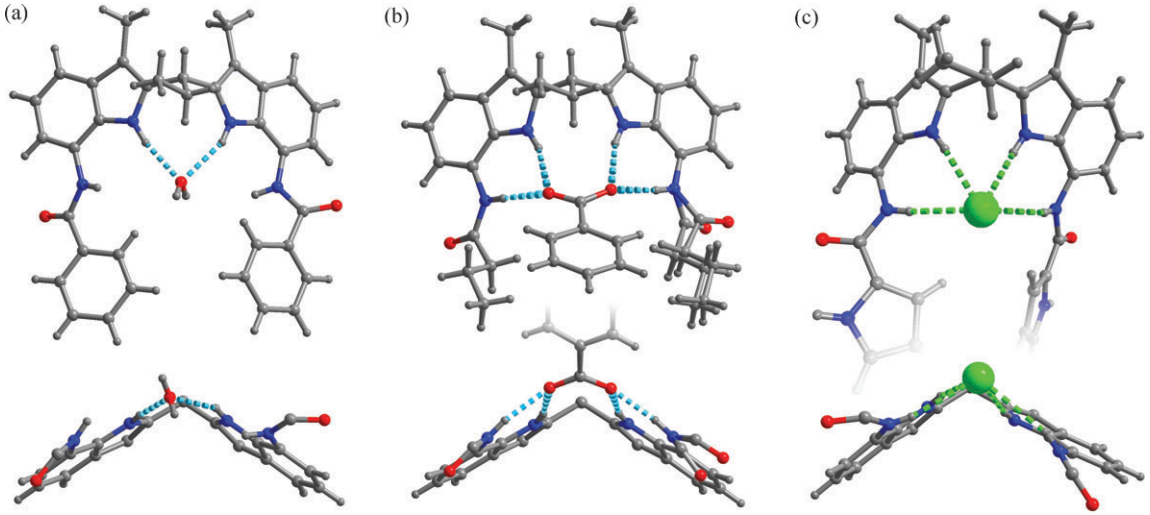

Fig. 2 Different views of the crystal structures of (a) **1b**·H_2O; (b) **1a**·TBAPhCO_2; (c) **1c**·TBACl; some parts are omitted for clarity

are evidently stronger than the ones engaging the amide groups (the N–Cl distances are in the range 3.11–3.27 Å for indole and between 3.40–3.70 Å for amide). The amidopyrrole subunit adopts the *anti* conformation preferred by this building block, which prevents it from interacting with the anion and explains the results of titration experiments. Nevertheless, the pyrrole rings are involved in hydrogen bonds, but with carbonyl groups of adjoining molecules (the N–O distances are about 2.8 Å), which leads to the formation of a supramolecular chain with chloride–ligand complexes linked together.

Remarkably, all three crystal structures of receptors **1a–c** show similar conformations despite the different ligand side chains and different guests present (Fig. 2). This suggests that this geometry is preferred by this building block, and its binding site is readily available for the interactions involving all four hydrogen bond donors.

To summarise, we prepared stable and efficient diindolylmethane-based receptors that show high affinity and selectivity towards dihydrogen phosphate even in a very polar medium. This work confirmed how effective and versatile 7-aminoindole is as a building block for the construction of anion receptors. Moreover, we demonstrated how further progress in anion recognition can be achieved by the modification of known structures by replacing pyrrole-containing subunits with benzopyrroles, maintaining an equivalent array of hydrogen bonds.

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Notes and references

‡ Crystal data for compounds **1b**, **1a**·TBAPhCO_2 and **1c**·TBACl can be found in the ESI† or accessed using the following CCDC numbers: 707058, 725837, 707057.

1 J. L. Sessler, P. A. Gale and W. S. Cho, *Anion Receptor Chemistry*, Royal Society of Chemistry, Cambridge, 2006.

2 C. Caltagirone and P. A. Gale, *Chem. Soc. Rev.*, 2009, **38**, 520–563; P. A. Gale, S. E. Garcia-Garrido and J. Garric, *Chem. Soc. Rev.*, 2008, **37**, 151–190.

3 J. L. Sessler, S. Camiolo and P. A. Gale, *Coord. Chem. Rev.*, 2003, **240**, 17–55; J. L. Sessler and D. Seidel, *Angew. Chem., Int. Ed.*, 2003, **42**, 5134–5175; P. A. Gale, *Chem. Commun.*, 2005, 3761–3772.

4 P. A. Gale, J. L. Sessler, V. Kral and V. Lynch, *J. Am. Chem. Soc.*, 1996, **118**, 5140–5141; A. Andrievsky, F. Ahuis, J. L. Sessler, F. Vogtle, D. Gudat and M. Moini, *J. Am. Chem. Soc.*, 1998, **120**, 9712–9713.

5 P. A. Gale, S. Camiolo, G. J. Tizzard, C. P. Chapman, M. E. Light, S. J. Coles and M. B. Hursthouse, *J. Org. Chem.*, 2001, **66**, 7849–7853; P. A. Gale, S. Camiolo, C. P. Chapman, M. E. Light and M. B. Hursthouse, *Tetrahedron Lett.*, 2001, **42**, 5095–5097.

6 F. M. Pfeffer, K. F. Lim and K. J. Sedgwick, *Org. Biomol. Chem.*, 2007, **5**, 1795–1799; J. O. Yu, C. S. Browning and D. H. Farrar, *Chem. Commun.*, 2008, 1020–1022; G. W. Bates, Triyanti, M. E. Light, M. Albrecht and P. A. Gale, *J. Org. Chem.*, 2007, **72**, 8921–8927.

7 C. Caltagirone, P. A. Gale, J. R. Hiscock, S. J. Brooks, M. B. Hursthouse and M. E. Light, *Chem. Commun.*, 2008, 3007–3009; C. Caltagirone, J. R. Hiscock, M. B. Hursthouse, M. E. Light and P. A. Gale, *Chem.–Eur. J.*, 2008, **14**, 10236–10243.

8 K. J. Chang, B. N. Kang, M. H. Lee and K. S. Jeong, *J. Am. Chem. Soc.*, 2005, **127**, 12214–12215; U. I. Kim, J. M. Suk, V. R. Naidu and K. S. Jeong, *Chem.–Eur. J.*, 2008, **14**, 11406–11414; V. R. Naidu, M. C. Kim, J. M. Suk, H. J. Kim, M. Lee, E. Sim and K. S. Jeong, *Org. Lett.*, 2008, **10**, 5373–5376.

9 M. J. Chmielewski, M. Charon and J. Jurczak, *Org. Lett.*, 2004, **6**, 3501–3504.

10 J. R. Hiscock, C. Caltagirone, M. E. Light, M. B. Hursthousea and P. A. Gale, *Org. Biomol. Chem.*, 2009, **7**, 1781–1783; P. Piątek, V. M. Lynch and J. L. Sessler, *J. Am. Chem. Soc.*, 2004, **126**, 16073–16076.

11 M. J. Chmielewski, L. Y. Zhao, A. Brown, D. Curiel, M. R. Sambrook, A. L. Thompson, S. M. Santos, V. Felix, J. J. Davis and P. D. Beer, *Chem. Commun.*, 2008, 3154–3156; J. M. Suk and K. S. Jeong, *J. Am. Chem. Soc.*, 2008, **130**, 11868–11869; D. Curiel, A. Cowley and P. D. Beer, *Chem.Commun.*, 2005, 236–238.

12 P. A. Gale, *Chem. Commun.*, 2008, 4525–4540.

13 G. W. Bates, P. A. Gale and M. E. Light, *Chem. Commun.*, 2007, 2121–2123.

14 T. Zielinski, P. Dydio and J. Jurczak, *Tetrahedron*, 2008, **64**, 568–574.

15 I. E. Vega, P. A. Gale, M. B. Hursthouse and M. E. Light, *Org. Biomol. Chem.*, 2004, **2**, 2935–2941; I. E. Vega, S. Camiolo, P. A. Gale, M. B. Hursthouse and M. E. Light, *Chem. Commun.*, 2003, 1686–1687.

16 X. M. He, S. Z. Hu, K. Liu, Y. Guo, J. Xu and S. J. Shao, *Org. Lett.*, 2006, **8**, 333–336.

17 H. Bauer and E. Strauss, *Ber. Dtsch. Chem. Ges.*, 1932, **65**, 308–315.

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