Isophthalamides and 2,6-dicarboxamidopyridines with pendant indole groups: a 'twisted' binding mode for selective fluoride recognition†

Gareth W. Bates, Philip A. Gale* and Mark E. Light

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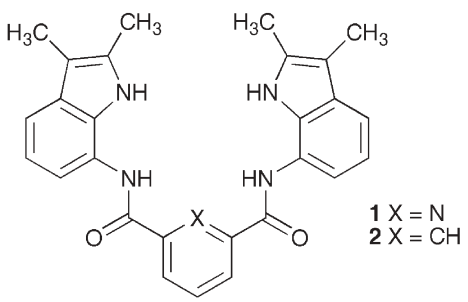
Two cleft-like anion receptors have been synthesised that contain indole hydrogen-bond donors and show fluoride selectively in a DMSO–water solution with crystallographic studies showing a 'twisted' binding mode for fluoride in the solid state.

Twisted structures have long been of particular interest to the supramolecular chemistry community. From early work on metal templated helices[1] through more recent work on foldamers[2] and organic helical structures,[3] these species are not only elegantly designed but can also play roles in molecular recognition and sensing.[4]

Our interest in anion complexation has led us to investigate a new series of compounds containing indole hydrogen bond donors.[5] Indole (or biindole) had been neglected as an anion receptor moiety. However recently, in a series of elegant papers, Jeong and co-workers[6] and Sessler and co-workers[7] have shown that indole or biindole containing receptors exhibit high affinities and selectivities for anions.

Inspired by the independent work of Crabtree[8] and Smith,[9] we have synthesised a series of receptors based upon the isophthalamide and 2,6-dicarboxamidopyridine skeleta.[10] In 2003, we reported the first example of a fluoride-templated double helix which consisted of two 3,5-dinitrophenylisophthalamide ligands, adopting twisted conformations, encapsulating two fluoride anions.[11] Here we report the synthesis and anion binding properties of indole functionalised isophthalamide and 2,6-dicarboxamidopyridine anion receptors. These systems show a high selectivity for fluoride over other putative anion guests with X-ray crystal structure analysis of the complexes showing fluoride bound in a 'twisted' conformation whereas chloride perches on one face of the complex.



School of Chemistry, University of Southampton, Southampton, UK SO17 1BJ. E-mail: philip.gale@soton.ac.uk; Fax: +44 23 8059 3332
† Electronic supplementary information (ESI) available: Synthesis details and binding curves. See DOI: 10.1039/b703905k

The compounds were prepared by reduction of 2,3-dimethyl-7-nitroindole with hydrazine hydrate/10% Pd/C and subsequent reaction with pyridine-2,6-dicarbonylchloride or isophthaloyl chloride to afford compounds **1** and **2** in 63% and 60% respective yields.

Crystals of compound **1** were grown by slow evaporation of a DMSO solution of the receptor.‡ The crystal structure (Fig. 1) shows the receptor binding two equivalents of DMSO in the solid state, one to the two amide NH groups (N···O 2.895(4) and 2.922(4) Å) and the other to the indole NH moieties (N···O 2.839(4) and 2.845(4)Å).

Crystals of the tetabutylammonium fluoride complexes of compounds **1**§ and **2**¶ were grown by slow evaporation of acetonitrile solutions of the receptors in the presence of excess fluoride salt. The structures of both complexes are similar and reveal that the receptors have adopted 'twisted' conformations in which one indole is oriented above the central aromatic ring in the receptor and one below coordinating the fluoride anion *via* four hydrogen bonds (Fig. 2). In the case of the complex of the fluoride complex of receptor **1** the hydrogen bonding interactions (N···F) range from 2.563(5)Å to 2.795(5) Å. However, in the complex with receptor **2** the hydrogen bonds to fluoride were found to be slightly longer and are in the range N···F 2.6102(5) Å to 3.0066(4) Å. Additionally, there is a short interaction between the isophthalamide CH group in the 2-position of the central aromatic ring and the anion (C17···F1 2.9423(5) Å). The space-filling view of this complex (Fig. 3), clearly illustrates the anion encapsulated by the NH hydrogen bond donor groups and the twisted conformation adopted by the receptor. The torsion angles defined by the indole and amide nitrogen atoms were found to be 37.93°(N1,N2,N4,N5)

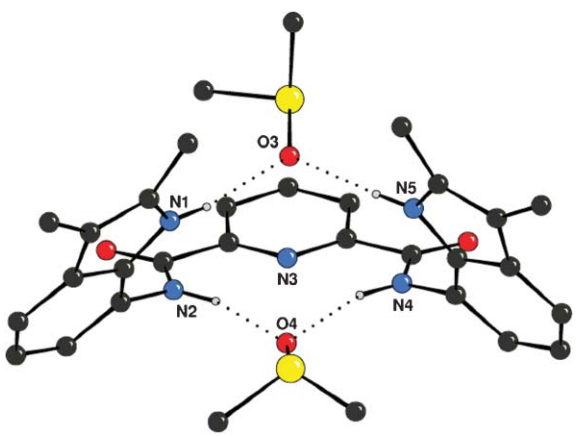


Fig. 1 The X-ray crystal structure of the DMSO solvate of compound **1**.

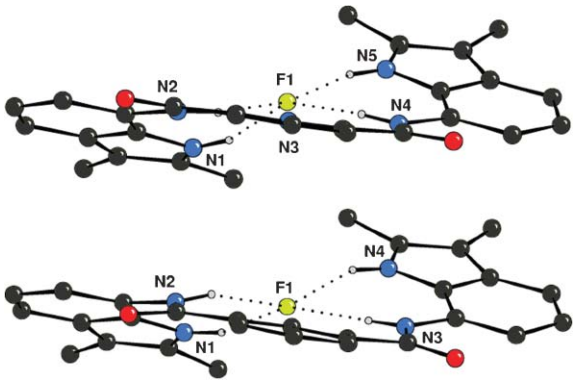


Fig. 2 Side views of the fluoride complex of receptor **1** (top) and receptor **2** (bottom). Tetrabutylammonium counter cations and non-acidic hydrogen atoms have been removed for clarity.

and 37.47°(N1,N2,N3,N4) for the fluoride complexes of compounds **1** and **2** respectively.

Crystals of the chloride complexes of receptors **1**‖ and **2**** were grown by slow evaporation of an acetonitrile solution of each receptor in the presence of excess tetrabutylammonium salt. The structures (Fig. 4) reveal that the larger anion perches over and is bound by the four hydrogen bond donor groups. In the case of the complex with receptor **1** the hydrogen bonding interactions (N···Cl) were found to be in the range 3.1137(17)–3.4108(16) Å and in the complex with receptor **2** they were found to lie in the range 3.1474(19)–3.3690 (19) Å. The torsion angles defined by the indole and amide nitrogen atoms were found to be 13.10°(N1,N2,N4,N5) and 8.36°(N1,N2,N3,N4) for the chloride complexes of compounds **1** and **2** respectively.

A space-filling model of the chloride complex of receptor **2** with chloride is shown in Fig. 5 illustrating that the NH groups hydrogen bonds to a single face of bound anion.

Proton NMR titrations were conducted in both DMSO–0.5% water and DMSO-d_6–5% water solutions with both receptors. The stability constants (calculated using the EQNMR computer program)[12] are shown in Table 1 and reveal that both compounds **1** and **2** have a high selectivity for fluoride over chloride in both DMSO–0.5% water and 5% water solutions with the exception

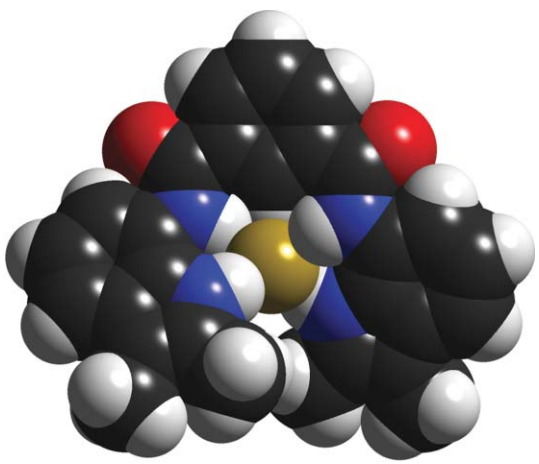


Fig. 3 Space-filling view of the encapsulated fluoride anion in the complex with receptor **2**.

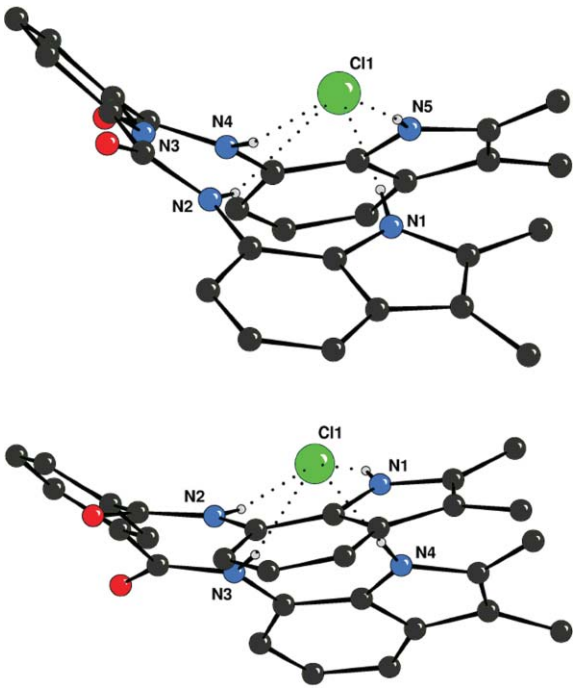


Fig. 4 Side views of the chloride complexes of receptor **1** (top) and receptor **2** (bottom). Tetrabutylammonium counter cations and non-acidic hydrogen atoms have been removed for clarity.

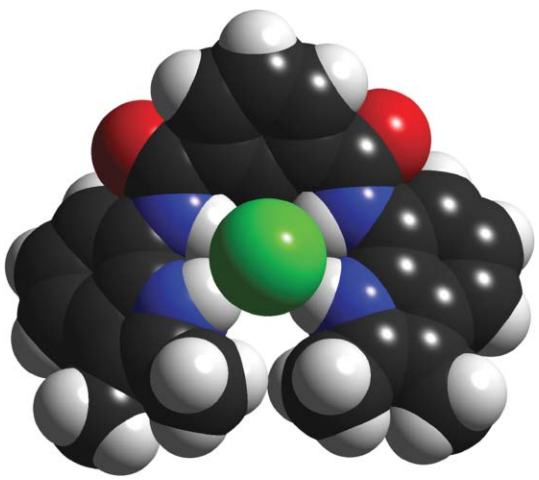


Fig. 5 Space-filling view of the chloride complex of receptor **2**.

that a stability constant for compound **2** with fluoride in DMSO-d_6–0.5% water could not be obtained. This may be due to the absence of preorganization of the cleft[13] (*syn–syn*) conformation of compound **2** so presumably leading to the formation of complexes with a variety of stoichiometries. However, the sharp titration curve obtained (see ESI†) is indicative of strong complex formation. In this case, when moving to a 5% water solution the binding data can be fitted to a 1 : 2 receptor: anion complex model.

The selectivity of these receptors for fluoride in these competitive solvent mixtures is notable. By comparison, under slightly different conditions, namely in dry DMSO solution, *meso*-octamethylcalix[4]pyrrole displays no significant selectivity for fluoride over chloride, in contradistinction to findings in less polar solvent

Table 1 Stability constants (M^{-1}) of compounds **1** and **2** with a variety of putative anionic guests (added as tetrabutylammonium salts) at 298 K. 1 : 1 receptor : anion stoichiometry was observed except where noted

Anion	Compound **1**	Compound **2**
fluoride[a]	$>10^4$	[c]
chloride[a]	<10	17
bromide[a]	no interaction	no interaction
acetate[a]	250	880
dihydrogen phosphate[a]	70	1140
benzoate[a]	17	120
fluoride[b]	1360	K_1 = 940 K_2 = 21
chloride[b]	<10	15
acetate[b]	14	110
dihydrogen phosphate[b]	26	260
benzoate[b]	<10	35

[a] DMSO-d_6–0.5% water. [b] DMSO-d_6–5% water. [c] NMR titration data is consistent with strong binding but could not be successfully fitted to either 1 : 1 or 1 : 2 receptor : anion binding models.

mixtures.[14] In the case of the compounds reported here, this high selectivity may be due to the formation of a twisted conformation in solution, which more effectively isolates the smaller fluoride ion from the solvent mixture than the larger chloride anion. We are continuing to study the anion complexation properties of these and other indole containing receptors. These results will be reported in due course.

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Notes and references

‡ Crystal data for compound **1**·2DMSO $C_{31}H_{37}N_5O_4S_2$, *M*r = 607.78, *T* = 120(2) K, monoclinic space group *C*2/*c*, *a* = 26.9646(10), *b* = 9.8223(3), *c* = 27.2375(10) Å, *β* = 119.586(3)°, *V* = 6273.4(4) Å^3, ρ_{calc} = 1.287 g cm^{-3}, μ = 0.213 mm^{-1}, *Z* = 8, reflections collected: 37226, independent reflections: 7183 (R_{int} = 0.0784), final *R* indices [$I > 2\sigma I$]: *R*1 = 0.0925, w*R*2 = 0.2375, *R* indices (all data): *R*1 = 0.1403, w*R*2 = 0.2748. CCDC 640965. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b703905k

§ Crystal data for **1**·TBAF $C_{43}H_{61}FN_6O_2$, *M*r = 712.98, *T* = 120(2) K, monoclinic space group $P2_1$, *a* = 9.8813(4), *b* = 18.1336(7), *c* = 11.4775(5) Å, *β* = 103.333(2)°, *V* = 2001.15(14) Å^3, ρ_{calc} = 1.183 g cm^{-3}, μ = 0.077 mm^{-1}, *Z* = 2, reflections collected: 17825, independent reflections: 4709 (R_{int} = 0.0580), final *R* indices [$I > 2\sigma I$]: *R*1 = 0.0754, w*R*2 = 0.1329, *R* indices (all data): *R*1 = 0.1058, w*R*2 = 0.1484. CCDC 640964. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b703905k

¶ Crystal data for **2**·TBAF $C_{44}H_{62}FN_5O_2$, *M*r = 711.99, *T* = 120(2) K, monoclinic space group $P2_1$, *a* = 9.7830(4), *b* = 18.6247(5), *c* = 11.3671(5) Å, *β* = 102.697(2)°, *V* = 2020.50(13) Å^3, ρ_{calc} = 1.170 g cm^{-3}, μ = 0.075 mm^{-1}, *Z* = 2, reflections collected: 27652, independent reflections: 4764 (R_{int} = 0.0818), final *R* indices [$I > 2\sigma I$]: *R*1 = 0.0605, w*R*2 = 0.1233, *R* indices (all data): *R*1 = 0.0915, w*R*2 = 0.1339. CCDC 640967. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b703905k

‖ Crystal data for **1**·TBACl $C_{43}H_{61}ClN_6O_2$, *M*r = 729.43, *T* = 120(2) K, monoclinic space group $P2_1/n$, *a* = 16.1573(3), *b* = 15.3680(3), *c* = 17.4031(2) Å, *β* = 109.859(1)°, *V* = 4064.30(12) Å^3, ρ_{calc} = 1.192 g cm^{-3}, μ = 0.137 mm^{-1}, *Z* = 4, reflections collected: 51747, independent reflections: 9289 (R_{int} = 0.0674), final *R* indices [$I > 2\sigma I$]: *R*1 = 0.0491, w*R*2 = 0.1124, *R* indices (all data): *R*1 = 0.0811, w*R*2 = 0.1258. CCDC 640963. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b703905k

** Crystal data for **2**·TBACl $C_{44}H_{62}ClN_5O_2$, *M*r = 728.44, *T* = 120(2) K, triclinic space group $P\bar{1}$, *a* = 11.6862 (3), *b* = 13.0971(3), *c* = 14.2217(3) Å, *α* = 98.8110(1), *β* = 94.723(1), *γ* = 101.283(1)°, *V* = 2095.16(7) Å^3, ρ_{calc} = 1.155 g cm^{-3}, μ = 0.132 mm^{-1}, *Z* = 2, reflections collected: 28340, independent reflections: 9550 (R_{int} = 0.0452), final *R* indices [$I > 2\sigma I$]: *R*1 = 0.0525, w*R*2 = 0.1250, *R* indices (all data): *R*1 = 0.0881, w*R*2 = 0.1413. CCDC 640966. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b703905k

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