Halogen- and hydrogen-bonding triazole-functionalised porphyrin-based receptors for anion recognition†

Lydia C. Gilday, Nicholas G. White and Paul D. Beer*

Iodotriazole and triazole anion recognition groups have been integrated into a picket-fence zinc(II)-metalloporphyrin scaffold to produce receptors for anion recognition and sensing applications. 1H NMR and UV/visible spectroscopic investigations reveal both host systems exhibit strong anion binding affinities in a range of solvent media. Importantly, the halogen-bonding iodotriazole-containing porphyrin-based host displays halide binding affinities substantially larger than the protic-functionalised analogue concomitant with a reduced strength of oxoanion complexation.

Introduction

Anions are fundamentally important in many biological processes and medical diseases. Moreover, nitrates and phosphates are well-known for their detrimental impact in the aquatic environment. Consequently, the need to selectively complex and detect specific negatively charged species is acute and the field of anion supramolecular chemistry has expanded enormously in recent decades.1 Through the imaginative manipulation of a variety of complementary non-covalent interactions such as electrostatics, hydrogen bonding, Lewis acid–base and anion–π interactions, a plethora of efficient anion receptors have been developed. Constructing receptors which possess anion recognition strengths comparable to that of natural systems, however, is a goal yet to be attained. Halogen bonding (XB), the attractive and highly directional intermolecular interaction between electron-deficient halogen atoms and Lewis bases,2 is beginning to show real promise in solution phase applications such as catalysis, medicinal chemistry and molecular recognition processes.3 Given XB’s complementary analogy to ubiquitous hydrogen bonding (HB), it is surprising that there are so few examples of efficient XB anion receptors reported to date.4,5

The porphyrin macrocycle is endowed with inherent optical and redox properties that can be exploited for signalling anion recognition via a measurable physical response.6 Indeed, we7 and others8 have reported several porphyrin-based host systems with a variety of integrated hydrogen-bond-donating anion recognition groups, which are able to sense anions through spectroscopic and electrochemical means. To the best of our knowledge, however, porphyrin molecules with pendant XB-donor groups for anion recognition applications are unprecedented. Herein, we describe the synthesis of a XB iodotriazole picket-fence porphyrin receptor which is demonstrated to exhibit superior halide anion binding affinities compared with a protic triazole-functionalised analogue.
Results and discussion

Syntheses

The target iodo-triazole- and triazole-containing Zn(II)-metalloporphyrin receptors 5 and 6 were prepared using a copper(I)-catalysed azide–alkyne cycloaddition (CuAAC) reaction9 between a tetra-meso-substituted azide-functionalised Zn(II)-metalloporphyrin and a suitable alkyne species. The required tetra-azide Zn(II)-metalloporphyrin species 3 was prepared as outlined in Scheme 1.

H₂TAPP was prepared by known literature procedures10 and the proportion of the desired α,α,α,α-isomer was increased using the Lindsey method11 to give α,α,α,α-H₂TAPP which was used immediately in the next step. α,α,α,α-Tetrakis(2-(chloroacetamidophenyl))porphyrin was synthesised according to the procedure reported by Collman et al.12 The condensation of α,α,α,α-H₂TAPP with five equivalents of chloroacetyl chloride in the presence of base gave porphyrin 1 in 72% isolated yield. A nucleophilic substitution reaction between compound 1 and sodium azide in dimethyl sulfoxide afforded the tetra-azide porphyrin 2 in 61% yield. Metallation with zinc, to give 3 was achieved by stirring porphyrin 2 with a ten-fold excess of zinc(II) acetate dihydrate in dichloromethane–methanol (9:1, v/v).

The target iodo-triazole-containing Zn(II)-metalloporphyrin 5 was prepared in 46% yield by a copper(I)-catalysed cycloaddition reaction between porphyrin 3 and 4.5 eq. of iodoalkyne 4 (prepared from 4-tert-butyphenylacetylene and N-iodosuccinimide)13 in the presence of copper(I) iodide and triethylamine in anhydrous THF (Scheme 2).

An analogous reaction between tetra-azide porphyrin 3 and 4.5 eq. of 4-tert-butylphenylacetylene, tetrakis(acetonitrile)-copper(I) hexafluorophosphate as the copper(I) catalyst, TBTA and N,N′-disopropylethylamine in anhydrous dichloromethane afforded tetrakis-triazole zinc(II)-porphyrin anion receptor 6 in 80% isolated yield (Scheme 2).

Both receptors were characterised by ¹H NMR spectroscopy, high-resolution electrospray mass spectrometry, and ¹³C NMR spectroscopy and UV/visible spectroscopy (see Experimental section and ESI†).

X-ray crystallography

Crystals of iodo-triazole-porphyrin 5 of suitable quality for single crystal X-ray structural determination were grown by slow diffusion of diethyl ether into a tetrahydrofuran solution. The structure (Fig. 1, top) reveals a picket-fence porphyrin molecule with all amide and iodo-triazole anion recognition motifs on the same side with respect to the porphyrin motif.

Scheme 2 Synthesis of iodo-triazole- and triazole-functionalised porphyrins 5 and 6.

Fig. 1 Structure of compound 5 (top); and diagram showing formation of dimers in the solid state. Halogen bonding interactions are shown as black dotted lines. Hydrogen atoms, except those on coordinated water and amide moieties are omitted for clarity, as are both (top) or one (bottom) of the crystallographically independent THF solvates. Key: grey = C, white = H, blue = N, red = O, violet = Zn, purple = I.
Intermolecular XB interactions are present between an iodo-triazole iodine atom of the receptor and a symmetry-related amide carbonyl group of the adjacent molecule (Fig. 1, bottom). Another iodine atom forms a halogen bond to a THF solvate. In both cases the interactions are close to linear, and the iodine⋯oxygen distance is significantly shorter than the sum of the van der Waals radii [C–I⋯Oamide = 2.920(5) Å, 83% of sum of vdW radii, \( \angle \text{C–I⋯Oamide} = 171.2(2)^\circ \); C–I⋯O_{THF} = 2.961(10) Å, 85% of sum of vdW radii, \( \angle \text{C–I⋯O}_{\text{amide}} = 167.7(3)^\circ \)].

Anion binding studies

A preliminary \(^1\text{H}\) NMR anion binding investigation of 5 and TBA·Cl was undertaken initially in CDCl\(_3\) (Fig. 2). Upon addition of one equivalent of chloride, downfield shifts of meso-phenyl proton \( h \), methylene proton \( g \), and phenyl proton \( f \) were observed, which indicate the chloride anion is binding within the pocket formed by the four arms of the picket-fence architecture in the vicinity of the iodo-triazole groups by four C–I⋯Cl halogen bonds (Fig. 2).

An analogous \(^1\text{H}\) NMR spectroscopic titration experiment with HB triazole receptor 6 revealed the addition of chloride induced downfield shifts in the receptor’s triazole \( h \), methylene \( g \) and phenyl \( i \) protons together with relatively smaller perturbations of the amide proton signal \( f \), which suggests the halide anion is being bound in the vicinity of the triazole groups through C–H⋯anion hydrogen bonds.

The absence of a triazole proton in iodo-triazole zinc(II)-metalloporphyrin 5, and relatively modest anion-binding-induced shifts of other protons prevented quantitative assessment of the anion binding properties of XB receptor 5 from Anion binding studies

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**Fig. 2** Partial \(^1\text{H}\) NMR spectra of (a) receptor 5 and (b) receptor 5 and one equivalent of TBA-Cl (500 MHz, CDCl\(_3\), 293 K).

**Fig. 3** Partial \(^1\text{H}\) NMR spectra of receptor 6 upon addition of equivalents of TBA-Cl (500 MHz, 293 K, CDCl\(_3\)).
being undertaken using $^1$H NMR spectroscopy. Anion association constant data was determined, however, with HB receptor 6 by monitoring the chemical shift of triazole proton $h$ with increasing concentration of anion (Fig. 3).

The observed chemical shift perturbations of the triazole proton $h$ with ten equivalents of anion (Table 1) reveal dihydrogen phosphate causes the largest magnitude of perturbation and the shifts are in general larger for oxoanions than less basic halides. Moreover, no evidence of complex formation was observed with hexafluorophosphate, an anion which typically associates weakly with traditional anion receptors and which is often used as a non-competitive counteranion with positively charged receptors. Monitoring the shift of the porphyrin’s triazole proton $h$ as a function of the concentration of anion gave the titration curves reported in Fig. 4. WinEQNMRR analysis of this titration data gave the 1 : 1 stoichiometric association constants for anion complexation shown in Table 1.

Table 1  Association constants, $K_a$ (M$^{-1}$), for 1 : 1 complexes of porphyrin host 6 with various anions

<table>
<thead>
<tr>
<th>Anion</th>
<th>$\Delta\delta$ (ppm)</th>
<th>$K_a$ (M$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl$^-$</td>
<td>0.37</td>
<td>2226 (183)</td>
</tr>
<tr>
<td>Br$^-$</td>
<td>0.30</td>
<td>662 (23)</td>
</tr>
<tr>
<td>I$^-$</td>
<td>0.23</td>
<td>224 (23)</td>
</tr>
<tr>
<td>AcO$^-$</td>
<td>0.45</td>
<td>$&gt;10^5$</td>
</tr>
<tr>
<td>H$_2$PO$_4^-$</td>
<td>0.65</td>
<td>b</td>
</tr>
<tr>
<td>PF$_6^-$</td>
<td>c</td>
<td></td>
</tr>
</tbody>
</table>

*a* All anions added as their TBA salt. Association constants were determined by monitoring the downfield shift of the triazole proton $h$. Estimated standard errors are given in parentheses. CDCl$_3$, 293 K. Overlapping peaks in the NMR spectra prevented quantitative binding data to be obtained. Chemical shifts changes too small to allow an accurate association constant to be determined.

Sulfate is bound strongly by both XB and HB porphyrin receptors, no doubt as a consequence of its higher charge. Of the singly charged anions, a general preference for oxoanions over halides is observed, with both receptors displaying relatively low binding affinities for larger, more diffuse bromide and iodide. It is interesting to note that there is almost an

Table 2  Association constants, $K_a$ (M$^{-1}$), for 1 : 1 complexes of porphyrin hosts 5 and 6 with various anions

<table>
<thead>
<tr>
<th>Anion</th>
<th>Iodotriazole 5 $K_a$ (M$^{-1}$)</th>
<th>Triazole 6 $K_a$ (M$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl$^-$</td>
<td>3592 (31)</td>
<td>2587 (128)</td>
</tr>
<tr>
<td>Br$^-$</td>
<td>1132 (11)</td>
<td>685 (16)</td>
</tr>
<tr>
<td>I$^-$</td>
<td>305 (23)</td>
<td>150 (5)</td>
</tr>
<tr>
<td>AcO$^-$</td>
<td>258 642 (7578)</td>
<td>335 660 (7383)</td>
</tr>
<tr>
<td>H$_2$PO$_4^-$</td>
<td>$&gt;10^6$</td>
<td>$&gt;10^6$</td>
</tr>
<tr>
<td>SO$_4^{2-}$</td>
<td>$&gt;10^6$</td>
<td>$&gt;10^6$</td>
</tr>
<tr>
<td>PF$_6^-$</td>
<td>b</td>
<td>b</td>
</tr>
</tbody>
</table>

*a* All anions added as their TBA salt. Association constants were determined by monitoring the perturbations of the Soret band. Estimated standard errors are given in parentheses. CHCl$_3$, 293 K. b No evidence of binding.
order of magnitude preference for dihydrogen phosphate over acetate, despite acetate being the more basic anion, which suggests the receptors prefer to bind anions of tetrahedral rather than trigonal geometry.

There are some significant differences between the anion binding affinities of the XB and HB receptors. It is noteworthy that the halogen-bonding iodotriazole host 5 has a greater affinity for chloride and bromide—with the strength of bromide association almost double in magnitude that of the protic species \( K_a = 1132 \text{ M}^{-1} \) versus \( 685 \text{ M}^{-1} \). There is also a reduction in the acetate binding strength with the XB receptor. Enhanced halide anion recognition together with reduced oxoanion binding affinity is consistent with anion binding trends noted with other XB anion receptors.\(^5\)

**Effect of solvent on anion recognition**

The anion binding behaviour of XB receptors in different solvents has not as yet been widely studied. The anion binding properties of XB and HB porphyrin-based receptors 5 and 6, in addition to chloroform, were determined in acetone and acetonitrile to give an insight into solvent effects on anion binding in general, and halogen versus hydrogen bonding in particular. UV/visible spectroscopic titrations were undertaken monitoring the Soret band with increasing anion concentration, producing titration curves (see ESI\(^\dagger\)) from which Specfit\® analysis determined quantitative data shown in Table 3.

As expected there are significant differences in the magnitude of the association constant values obtained in the three solvents. It is important to note, however, that the selectivity trends in anion binding strength remain the same in all cases, where in general, oxoanions are bound more strongly than halides, with sulfate and dihydrogen phosphate displaying the largest association constant values, presumably on account of their tetrahedral shape.

Anion binding strength is maximised by receptors 5 and 6 in acetone, followed by acetonitrile and chloroform. This anion binding behaviour does not correlate with bulk solvent properties such as relative permittivity (\( \varepsilon \)) or dipole moment (\( \mu \)). There is however, a correlation between Gutmann’s acceptor number (AN) of the solvent,\(^16\) which gives a measure of the hydrogen-bond-donor ability of a solvent.

As the hydrogen-bond-donor strength of the solvent increases (larger AN), anion binding affinity of the respective receptor decreases: competing anion–solvent interactions are strongest in chloroform, and weakest in acetone.\(^17\)

One final observation to note is the magnitude of enhancement of chloride and bromide halide anion recognition that occurs upon changing the solvent from chloroform to acetonitrile is more pronounced with the halogen-bonding receptor 5 than the hydrogen-bonding receptor 6. Indeed chloride anion binding affinity increases 75-fold with XB porphyrin 5 but only 13-fold for HB receptor 6. Future, in-depth thermodynamic investigations will be required to help rationalise these observations, through the determination of entropic and enthalpic contributions of XB anion recognition in a range of solvent media.

**Conclusions**

The anion binding properties of a XB iodotriazole- and HB triazole-functionalised zinc(u)-metalloporphyrin receptors have been investigated using \(^1\)H NMR and UV/visible techniques. Both receptors exhibit strong anion binding affinities forming 1 : 1 stoichiometric complexes with a range of halide and oxoanions in chloroform, acetone and acetonitrile solution. It is noteworthy that the XB porphyrin-based anion receptor 5 displays enhanced halide anion recognition and reduced acetate oxoanion binding affinities in comparison with the protic-triazole-functionalised analogue 6. The effect of solvent variation on anion binding efficacy reveals the strength of anion recognition correlates with the hydrogen-bond-donor ability of the solvent as measured by the Gutmann acceptor number: the superior halide anion binding affinities of the XB receptor is more pronounced in acetonitrile (AN = 18.9) than chloroform (AN = 23.1).

**Table 3** Association constants, \( K_a (\text{M}^{-1}) \), for 1 : 1 complexes of porphyrin host 5 and 6 with anions in various solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>( K_a (\text{M}^{-1}) )</th>
<th>( \varepsilon )</th>
<th>( \mu )</th>
<th>AN</th>
<th>( \varepsilon )</th>
<th>( \mu )</th>
<th>AN</th>
<th>( \varepsilon )</th>
<th>( \mu )</th>
<th>AN</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHCl(_3)</td>
<td>5 3592 (31)</td>
<td>4.81</td>
<td>1.15</td>
<td>23.1</td>
<td>6 2587 (128)</td>
<td>37.5</td>
<td>3.45</td>
<td>18.9</td>
<td>5 272 144 (2613)</td>
<td>20.7</td>
</tr>
<tr>
<td>MeCN</td>
<td>5 272 144 (2613)</td>
<td>13 589 (91)</td>
<td>3 462 (184)</td>
<td>6 34 626 (184)</td>
<td>4494 (369)</td>
<td>3 462 (184)</td>
<td>4494 (369)</td>
<td>3 462 (184)</td>
<td>4494 (369)</td>
<td>3 462 (184)</td>
</tr>
<tr>
<td>Acetone</td>
<td>5 &gt;10(^6)</td>
<td>&gt;10(^6)</td>
<td>&gt;10(^6)</td>
<td>&gt;10(^6)</td>
<td>&gt;10(^6)</td>
<td>&gt;10(^6)</td>
<td>&gt;10(^6)</td>
<td>&gt;10(^6)</td>
<td>&gt;10(^6)</td>
<td>&gt;10(^6)</td>
</tr>
</tbody>
</table>

\(^a\)All anions added as their TBA salt. Association constants were determined by monitoring the perturbations of the Soret band. Estimated standard errors are given in parentheses. 293 K. \(^b\)Fitted better to a \( 1:2 \) host:guest model. \( \varepsilon \) = dielectric constants, \( \mu \) = relative permittivity, AN = Gutmann’s acceptor number.
Experimental

General remarks

Unless otherwise stated, commercially available solvents (HPLC grade) and reagents were used without further purification. Triethylamine was distilled from KOH and stored over 3 Å molecular sieves. Pyrrole was distilled over CaH₂, under reduced pressure and stored at −25 °C under N₂. TBA₂SO₄ was azetroped with toluene and stored in a dessicator containing P₂O₅. TBA salts of Cl⁻ and CH₃OH were generally visible in the diaphragm. Hydrogen atoms were used, they were degassed with N₂, and dried by passing through an MBraun MSPS-800 column.

¹H, ³¹C, ¹³C, ¹⁹F, ³¹P NMR spectra were recorded on a Varian Mercury-VX 300, a Varian Unity Plus 500 or a Bruker AVIII500 with cryoprope at 293 K. Mass spectra were obtained using a micromass LCT (ESMS) instrument. Electronic absorption spectra were recorded on a PG instruments T60U spectrometer. Column chromatography was performed on silica gel (particle size: 40–63 μm), preparative TLC was performed on 20 × 20 cm plates, with a silica layer of thickness 1 mm.

Spectral data are uncorrected.

Single crystal X-ray diffraction data were collected at 150(2) K using graphite monochromated Cu Kα radiation (λ = 1.54184 Å). Cell parameters and intensity data (including inter-frame scaling) were processed using Crysalis Pro.¹⁸ The structures were solved by charge-flipping methods using SUPERFLIP¹⁹ and refined using full-matrix least-squares on F² within the CRYSTALS suite.²⁰ All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were generally visible in the difference map, and their positions and displacement parameters were refined using restraints prior to their inclusion in the model using riding constraints.²¹

α,α,α,α-Tetrakis(2-chloroacetamidophenyl)porphyrin 1.

H₂TAPP (603 mg, 0.90 mmol) and Et₃N (0.75 mL, 5.37 mmol) were dissolved in anhydrous THF and cooled to 0 °C in an ice bath to which a solution of chloroacetyl chloride (0.36 mL, 4.47 mmol) in anhydrous THF was added dropwise. The reaction mixture was stirred under N₂ for 3 h and the solvent was then removed _in vacuo_. The crude mixture was purified by column chromatography (SiO₂, 95:5 CH₂Cl₂–MeOH) to give compound 1 as purple powder (0.63 g, 0.65 mmol, 72%). λ_max(CHCl₃)/nm: 418 (ε/dm³ mol⁻¹ cm⁻¹ 491 860), 514 (25 580), 546 (5220), 588 (7664), 643 (1634), δH (500 MHz; CDCl₃) 8.80 (8 H, s, β-pyrole-H), 8.73 (4 H, d, J = 8.0 Hz, meso-phenyl-H), 8.08 (4 H, d, J = 8.0 Hz, meso-phenyl-H, 7.99 (4 H, s, amide-NH), 7.89 (4 H, t, J = 8.0 Hz, meso-phenyl-H), 7.61 (4 H, t, J = 8.0 Hz, meso-phenyl-H), 3.39 (8 H, s, CH₂), −2.66 (2 H, br s, pyrrole-NH); m/z (ES): 1003.2 [(M + Na)⁺, C₅₂H₄₈Cl₄N₄NaO₄ requires 1003.2].

α,α,α,α-Tetrakis(2-azidoacetamidophenyl)porphyrin 2. Compound 1 (500 mg, 0.51 mmol) was dissolved in a 0.5 s solution of NaN₃ in DMSO (10 mL) and the solution was stirred for 16 h. The reaction was cooled in an ice bath to 0 °C and quenched with H₂O (45 mL). The aqueous layer was extracted with CHCl₃ (3 × 50 mL). The combined organic extracts were washed with H₂O (2 × 100 mL) and sat. NaCl(aq) (1 × 100 mL), dried over anhydrous MgSO₄, filtered and the solvent removed _in vacuo_ to give 2 as a purple powder (313 mg, 0.31 mmol, 61%). λ_max(CHCl₃)/nm: 420 (ε/dm³ mol⁻¹ cm⁻¹ 408 000), 515 (24 240), 547 (6180), 589 (8008), 645 (2500); δH (300 MHz; CDCl₃) 8.82 (8 H, s, β-pyrole-H), 8.59 (4 H, d, J = 8.0 Hz, meso-phenyl-H), 7.96 (4 H, d, J = 8.0 Hz, meso-phenyl-H), 7.87 (4 H, t, J = 8.0 Hz, meso-phenyl-H), 7.79 (4 H, s, amide-NH) 7.56 (4 H, t, J = 8.0 Hz, meso-phenyl-H), 3.31 (8 H, s, CH₂), −2.58 (2 H, br s, pyrrole-NH); δC (75.5 MHz; CDCl₃) 164.1, 137.4, 134.9, 131.4, 130.0, 123.8, 121.1, 114.6, 52.5, 40.9; m/z (ES): 1029.3277 [(M + Na)⁺, C₅₂H₄₈N₂₀NaO₄ requires 1029.3301].
(e/dm³ mol⁻¹ cm⁻¹ 449 000), 559 (13 500), 595 (3530); δH (300 MHz; CDCl3) 8.75 [8 H, s, β-pyrrrole-H], 8.21 [4 H, d, J = 8.5 Hz, meso-phenyl-H], 8.18 [4 H, d, J = 8.5 Hz, meso-phenyl-H], 8.10 [4 H, s, amide-NH]. 7.85 (4 H, t, J = 7.5 Hz, meso-phenyl-H), 7.63 [4 H, t, J = 7.5 Hz, meso-phenyl-H], 7.16 (16 H, s, phenyl-H), 3.99 (8 H, s, CH2Cl), 1.25 (16 H, s, CH3); δC (125.5 MHz; CDCl3) 163.1, 151.6, 150.3, 149.2, 137.6, 135.6, 134.8, 132.6, 131.7, 128.9, 128.7, 126.3, 125.5, 125.4, 125.3, 124.3, 114.8, 52.7, 34.6, 31.2; m/z (ES): 1725.6824 ([M + Na]+), C₁₁₀H₄₈N₂₀NaO₄Zn requires 1725.6853.

Acknowledgements

We thank the EPSRC (L.C.G.), Trinity College and the Clarendon Fund (N.G.W.) for funding, and Prof. S. Faulkner for use of UV/visible equipment.

Notes and references


15 Specfit v. 2.02 ed, Spectrum Software Associates, Chapel Hill, NC, USA.