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New porphyrin derivatives for phosphate anion sensing in both organic and aqueous media†‡

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New porphyrin-based anion receptors have been prepared from *meso*-tetrakis(pentafluorophenyl)porphyrin (TPPF$_{20}$) and diamine derivatives. These receptors (compounds 1–3) interact preferentially with phosphate anions both in organic solutions and in basic aqueous media when coated on gold piezoelectric quartz crystals. A single crystal X-ray structure of the bis-HF complex of a imine derivative of 1 was obtained; it serves to highlight the main interactions between the anion and cation receptors in the solid state.

Anions play crucial roles in a number of chemical, biological and environmental processes.[1] For instance, perturbations in anion fluxes across cell membranes are recognized as the underlying cause of a number of diseases, including osteoporosis, Alzheimer's, and cystic fibrosis.[2,3] The well-known threat caused by several anions, such as arsenate and cyanide, when present in the environment underscores the need for systems capable of controlling and monitoring these and related species.[1,2] More broadly, the ubiquity and importance of anions accounts for the current high interest in the design of effective synthetic anion receptors.

Amines and polyamines have long been used to create anion receptors.[4] Apart from this, polypyrrolic macrocycles, such as calixpyrroles,[5] subphthalocyanines,[6] corroles,[7] *N*-confused porphyrins,[8]

porphyrins,[9] protonated sapphyrins[10] and porphyrins[11] (collectively "Pors"), have been reported as successful anion sensors. In most cases involving Pors, anion recognition involves the NH groups of the pyrrole units. However, with adequately substituted Pors, recognition can take place outside the macrocycle, particularly when the inner NH groups are less effective hydrogen bond donors than those present on the substituents. For instance, several Pors bearing NH groups at the *ortho*-positions of *meso*-aryl substituents have been demonstrated as being effective anion sensors.[9] In this communication we show that porphyrins bearing substituents at the *para*-position of the *meso*-aryl groups can also be used for anion recognition. In particular, we show that *meso*-tetrakis(pentafluorophenyl)porphyrin (TPPF$_{20}$) can be used as a platform to build new polyamine anion hosts that are effective receptors for dihydrogen phosphate in organic media. As synthesized, systems 1–3 are hydrophobic. This allows them to be used as recognition elements for coated gold piezoelectric quartz crystals. The resulting electrodes display selectivity for hydrogen phosphate in basic aqueous media.

The polyamine receptors of the present study were obtained from TPPF$_{20}$ *via* nucleophilic aromatic substitution under microwave irradiation (Scheme 1).[12] In this way, compounds 1–3 were obtained from ethylenediamine, *N*-tosylethylenediamine and *N*-isopropylethylenediamine, in 81, 72 and 83% yields, respectively. The assigned structures were supported by ^{1}H, ^{19}F, and ^{13}C NMR spectroscopic and high resolution mass spectrometric (HRMS) analyses (ESI‡). Compound 1 was further characterized in the form of a diprotonated imine derivative by X-ray diffraction analysis (*vide infra*).

The anion affinities of the neutral and amine-protonated forms of Pors 1–3 were determined by means of standard UV-Vis spectroscopic

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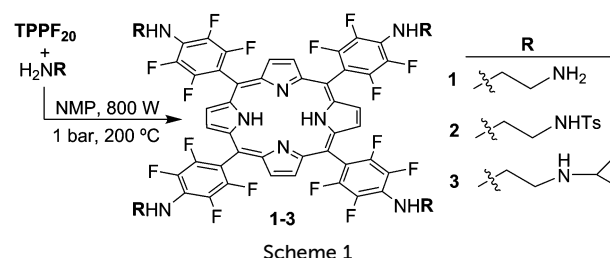
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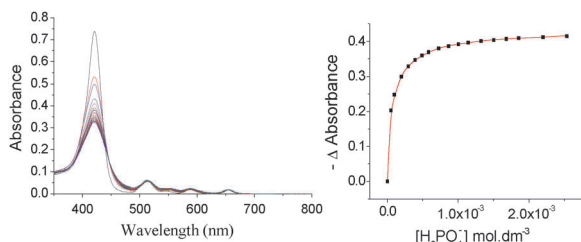[f] Department of Organic Chemistry, Ghent University, B-9000 Gent, Belgium

Scheme 1

Fig. 1 (a) Changes in the absorption spectra of Por **1** (10^{-6} mol dm^{-3}) seen upon addition of H$_2$PO$_4^-$·TBA in CHCl$_3$. (b) Titration data recorded at 422 nm for the protonated form of compound **1** and fit to a non-linear 1:2 binding model.

Table 1 Affinity constants ($K = K_{11} \times K_{12}$) at 22 °C corresponding to the interaction between compounds **1**, **2** and **3** and H$_2$PO$_4$·TBA (see ESI 1.3.1)

Anion	Solvent	K (M^{-2})		
		1	**2**	**3**
H$_2$PO$_4^-$	CHCl$_3$	$1.48 \times 10^{4\,a}$	2.35×10^7	5.46×10^9
	CHCl$_3$[b]	2.95×10^5	6.21×10^5	1.62×10^9

[a] The stoichiometry for this complex is 1:1 (Por:H$_2$PO$_4^-$); therefore, the K units are M^{-1}. [b] Por amino groups protonated with 4 equiv. of TFA.

titrations carried out in chloroform (see ESI‡ for details). In order to obtain the protonated forms, 4 equiv. of TFA were used; under these conditions, the inner pyrrolic nitrogen atoms were not protonated, as inferred from spectroscopic analyses (Fig. S3, ESI‡). Several anions, including fluorides, chlorides, bromides, acetates, nitrates, nitrites and dihydrogen phosphate, all in the form of their respective tetrabutylammonium (TBA) salts, were tested. Upon addition of dihydrogen phosphate, the UV-Vis spectra of the Pors show a clear reduction in the intensity of their Soret bands (Fig. 1a, Fig. S1 and S4, ESI‡). The attenuation and broadening of these bands are ascribed to dihydrogen phosphate-induced formation of dimeric complexes. Fitting the variation of the absorbance at the Soret band as a function of the concentration of the added anion (Fig. S1 and S4, ESI‡) allowed determination of the corresponding affinity constants (K, see ESI‡ and Table 1). In the case of **1**, an improvement in the affinity constant for H$_2$PO$_4^-$ was seen when the external amino groups were protonated (see Fig. S4, ESI‡). Based on the curve fitting, a stoichiometry of 1:2 (Por:anion) was inferred. In the case of **2**, protonation of the amino group leads to a considerable decrease in the affinity constant. This is also true in the case of **3**, albeit to a lesser extent.

Based on these findings, we conclude that all three Pors work as receptors for H$_2$PO$_4^-$, with the further advantage that pre-protonation is not necessary for recognition in the case of compounds **2** and **3**. Upon addition of the fluoride or acetate anions, only a small reduction in the intensity of the Soret band is seen (see Fig. S2 and S5, ESI‡). With the other anions tested (chlorides, bromides, nitrates and nitrites), no appreciable change in the Soret bands could be discerned. We thus conclude that under the conditions of analysis receptors **1**–**3** are selective for H$_2$PO$_4^-$.

In order to gain insights into the host–guest interactions involving **1**–**3** and H$_2$PO$_4^-$, ^{1}H NMR spectroscopic titrations were carried out in CDCl$_3$–DMSO-d_6 (1:1). This solvent mixture was chosen due to the low solubility of Pors in pure CDCl$_3$ at the concentrations needed for

these titrations. Under these conditions, Por **1** gives rise to only a single NH signal at around δ 5.75 ppm, which is ascribed to one of the aromatic amino groups. This signal shifts in the presence of H$_2$PO$_4^-$; however, after the addition of 1 equiv. of TFA this signal disappears (Fig. S6, ESI‡), as would be expected for a hydrogen bond donor interacting with a Lewis base combined with deprotonation. In the case of **2**, deprotonation of the NH-tosyl group protons occurs, as inferred from the disappearance of the peak at δ 7.5 ppm; this occurs even in the presence of very small amounts of H$_2$PO$_4^-$. After deprotonation, the other NH signal, observed at around δ 5.6 ppm (Fig. S7, ESI‡), starts to shift as the H$_2$PO$_4^-$ concentration increases, presumably due to the increased presence of hydrogen bonding interactions. Such findings are in agreement with what has been seen for several other anion receptors, particularly those based on sulphonamide recognition motifs.[13,14] Por **3** shows deprotonation of the NH-isopropyl protons (signal initially at 9.6 ppm) concurrent with a shift of the other NH protons, which resonate at 6.3 ppm (Fig. S8, ESI‡). In contrast, the protonated form of this receptor is characterized by shifts in the NH-isopropyl proton signals to a higher field; these resonances now appear at 9.6 ppm (Fig. S9, ESI‡). Taken together, these NMR spectroscopic results are consistent with the conclusion that receptors **1**–**3** all interact with H$_2$PO$_4^-$, but do so differently in regard to the underlying interactions, including deprotonation. These differences are reflected in the calculated affinity constant values.

In order to test the ability of receptors **1**–**3** to interact with anions in aqueous solutions, piezoelectric quartz crystal gold electrodes coated with each Por were prepared.[15] This coating was made possible by the fact that Pors **1**–**3** are insoluble in water and chemically stable on the laboratory time scale, both in solution and when coated on a gold surface. Tests for anion recognition capability and selectivity were carried out as follows: aqueous solutions of the sodium salts of various anions (10^{-1} to 5×10^{-3} M) at pH 9.7 were injected into a water stream adjusted to the same pH. This stream was then passed through the sensor cell at a rate of 0.8 mL min^{-1} (Fig. S10, ESI‡). Based on the observed response, selectivity coefficients were calculated relative to HPO$_4^{2-}$ (Fig. 2a and Tables S1–S3, ESI‡). From a plot of the data (*cf.* Fig. 2a) it is clear that the sensor based on Por **1** is the most selective for HPO$_4^{2-}$.

The use of high pH for these experiments was deliberate and designed to avoid complications associated with speciation (*e.g.*, the presence of appreciable concentrations of both HPO$_4^{2-}$ and H$_2$PO$_4^-$ in solution). However, the viability of the electrodes as anion
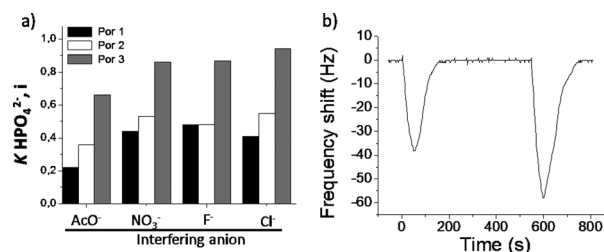

Fig. 2 (a) Selectivity coefficient of the sensors, made with Por **1**–**3**, calculated relative to HPO$_4^{2-}$; (b) frequency shifts seen for a sensor made with Por **2** after exposure to 1.00×10^{-3} and 1.50×10^{-3} M aqueous solutions of Na$_2$HPO$_4$.
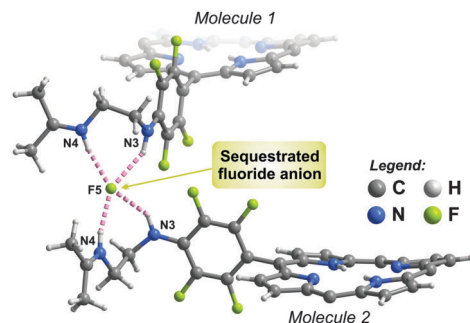
Fig. 3 Schematic representation of the two individual molecules of tetra-imine of **1** that serve to sequester the charge-balancing fluoride anion in a sandwich-like arrangement. A second molecule, not shown, was generated by applying the symmetry operation ($3/4 - x$, $3/4 - y$, z) to the upper one. Hydrogen bonding geometry details (dashed pink lines): for N3–H3···F5, d(D···A) = 2.972(6) Å, <(DHA) = 146(5)°; for N4–H4···F5, d(D···A) = 2.856(5) Å, <(DHA) = 168°.

chemosensors over a range of pH values was demonstrated using F⁻ (Fig. S11, ESI‡). Between pH 6.7 and 9.7 no significant differences were observed. Moreover, the response was rapid and reversible in the case of all three sensors as illustrated in Fig. 2b.

Various attempts were made to obtain diffraction grade single crystals of the above anion complexes. One of these attempts, involving a mixture of Por **1** and F⁻ (TBA salt) in acetone, led to isolation of a new diprotonated Por imine derivative that resulted from the reaction of the amine groups with acetone. Single-crystal X-ray diffraction studies (*cf.* Fig. 3 and Fig. S12, ESI‡) revealed that this diprotonated imine crystallized in a highly symmetric *Fddd* orthorhombic space group ($Z = 8$) in which the molecular unit is subject to an imposed 222 symmetry operation.§ A crystallographically (half-occupied) independent fluoride counter-ion and one CHCl₃ molecule were observed in the lattice (for details see ESI‡ 1.4). The overall structure consists of four "anion clips" that are statistically bound to a total of two fluoride anions (equally distributed with a 50% degree of occupancy), which are further engaged in strong and highly directional N⁺–H···F⁻ charged hydrogen bonds involving the protonated terminal NH⁺=C(CH₃)₂ groups.[16] Although complex, this structure at a minimum provides support for the key assumptions that (i) Por **1** was prepared as claimed and (ii) outside binding of anions is possible as proposed.

Three new Por-based anion receptors, **1–3**, were prepared by a simple and high yielding method starting from the commercially available **TPPF₂₀** and diamines. Hosts **1**, **2** and **3** displayed selectivity for the H₂PO₄⁻ anion in chloroform, which depending on the receptor in question was found to bind in a 1:1 or 2:1 (H₂PO₄⁻:Por) fashion. The highest affinity constants were obtained for Por **3** in both its protonated and neutral forms. The lack of sensitivity of **1**, **2** and **3** towards the fluoride, chloride, bromide, acetate, nitrate or nitrite anions (all anions as their TBA salts) observed by UV-Vis analysis is noteworthy; it could make this set of receptors useful where high selectivity for phosphate-containing substrates is needed. Also, when incorporated into a piezoelectric sensor, Pors **1–3** show high selectivity for HPO₄²⁻ in aqueous media, with lower response levels noted for other test anions. A single-crystal X-ray structure of the tetra-imine:F⁻ complex derived from receptor **1** and acetone was solved. It revealed a complex, sandwich-like structure. This work shows that **TPPF₂₀** can serve as a convenient precursor for the construction of efficient and selective anion receptors that function in both organic and aqueous environments.

Notes and references

§ Synthesis, characterization, details of anion studies, spectral data and crystallographic analyses. Crystal data for the squeezed structure: C₆₆H₅₈Cl₆F₁₈N₁₂, $M = 1573.94$, orthorhombic, space group *Fddd*, $Z = 8$, $a = 14.6651(15)$ Å, $b = 25.318(3)$ Å, $c = 46.706(5)$ Å, $V = 17\,341(3)$ Å³, μ(Mo-K$_\alpha$) = 0.278 mm⁻¹, $D_c = 1.206$ g cm⁻³, purple needles with a crystal size of $0.20 \times 0.16 \times 0.14$ mm³. Of a total of 25 756 reflections collected, 3759 were independent ($R_{int} = 0.0712$). Final $R_1 = 0.0887$ [$I > 2\sigma(I)$] and w$R_2 = 0.2886$ (all data). Data completeness to $\theta = 25.32°$, 94.5%. CCDC 732151.

1 (a) P. A. Gale, C. C. Tong, C. J. E. Haynes, O. Adeosun, D. E. Gross, E. Karnas, E. M. Sedenberg, R. Quesada and J. L. Sessler, *J. Am. Chem. Soc.*, 2010, **132**, 3240; (b) C. H. Lee, H. Miyaji, D. W. Yoon and J. L. Sessler, *Chem. Commun.*, 2008, 24.
2 P. Prados and R. Quesada, *Supramol. Chem.*, 2008, **20**, 201.
3 (a) P. D. Beer and P. A. Gale, *Angew. Chem., Int. Ed.*, 2001, **40**, 486; (b) S. E. Matthews and P. D. Beer, *Supramol. Chem.*, 2005, **17**, 411; (c) J. Rutishauser and P. Kopp, *Eur. J. Endocrinol.*, 1998, **138**, 623.
4 (a) S. Kubik, C. Reyheller and S. Stuwe, *J. Inclusion Phenom. Macrocyclic Chem.*, 2005, **52**, 137; (b) J. L. Sessler, G. H. Sarova and P. S. Gale, *Coord. Chem. Rev.*, 2003, **240**, 17.
5 (a) B. Verdejo, F. Rodríguez-Llansola, B. Escuder, J. F. Miravet and P. Ballester, *Chem. Commun.*, 2011, **47**, 2017; (b) A. S. F. Farinha, A. C. Tomé and J. A. S. Cavaleiro, *Tetrahedron*, 2010, **66**, 7595; (c) G. Gil-Ramírez, M. Chas and P. Ballester, *J. Am. Chem. Soc.*, 2010, **132**, 2520.
6 E. Palomares, M. V. Martínez-Díaz, T. Torres and E. Coronado, *Adv. Funct. Mater.*, 2006, **16**, 1166.
7 C. I. M. Santos, E. Oliveira, J. F. B. Barata, M. A. F. Faustino, J. A. S. Cavaleiro, M. G. P. M. S. Neves and C. Lodeiro, *J. Mater. Chem.*, 2012, **22**, 13811.
8 (a) D. H. Won, M. Toganoh, H. Uno and H. Furuta, *Dalton Trans.*, 2009, 6151; (b) M. Toganoh, H. Miyachi, H. Akimaru, F. Ito, T. Nagamura and H. Furuta, *Org. Biomol. Chem.*, 2009, **7**, 3027.
9 (a) F. D'Sousa, N. K. Subbaiyan, Y. Xie, J. P. Hill, K. Ariga, K. Ohkubo and S. Fukuzumi, *J. Am. Chem. Soc.*, 2009, **131**, 16138; (b) D. P. Cormode, M. G. B. Drew, R. Jagessar and P. D. Beer, *Dalton Trans.*, 2008, 6732; (c) M. Dudic, P. Lhotak, I. Stibor, K. Lang and P. Proskova, *Org. Lett.*, 2003, **2**, 150; (d) P. D. Beer, D. P. Cormode and J. J. Davis, *Chem. Commun.*, 2004, 414.
10 (a) A. E. V. Gorden, J. Davis, J. L. Sessler, V. Kral, D. W. Keogh and N. L. Schroeder, *Supramol. Chem.*, 2004, **16**, 91; (b) J. L. Sessler, J. M. Davis, V. Král, T. Kimbrough and V. Lynch, *Org. Biomol. Chem.*, 2003, **1**, 4113.
11 (a) M. M. Kruk, A. S. Starukhina, N. Zh. Mamardashvilib, G. M. Mamardashvilib, Y. B. Ivanovab and O. V. Maltsevab, *J. Porphyrins Phthalocyanines*, 2009, **13**, 1148; (b) V. B. Sheinin, E. L. Ratkovab and N. Zh. Mamardashvilia, *J. Porphyrins Phthalocyanines*, 2008, **12**, 1211.
12 D. Samaroo, C. E. Soll, L. J. Tadaro and C. M. Drain, *Org. Lett.*, 2006, **8**(22), 4985.
13 L. S. Evans, P. A. Gale, M. E. Light and R. Quesada, *Chem. Commun.*, 2006, 965.
14 S. V. Bhosale, S. V. Bhosale, M. B. Kalyankar and S. J. Langford, *Org. Lett.*, 2009, **11**, 5418.
15 N. I. P. Valente, P. V. Muteto, A. S. F. Farinha, A. C. Tome, J. A. B. P. Oliveira and M. T. S. R. Gomes, *Sens. Actuators, B*, 2011, **157**, 594.
16 J. Bernstein, R. E. Davis, L. Shimoni and N. L. Chang, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1555.