(*cis*)-5,10,15,20-Tetrakis[2-(arylurea)phenyl]porphyrins: novel neutral ligands for remarkably selective and exceptionally strong chloride anion complexation in $(CD_3)_2SO$

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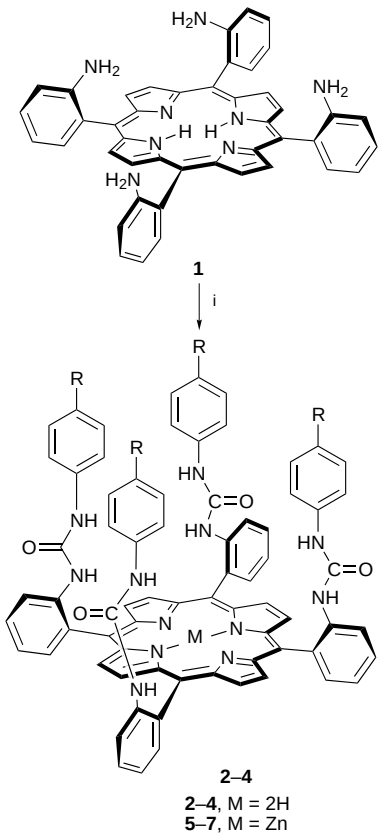
Urea appended free-base porphyrins 2–4 bind strongly (K > 10^5 dm^3 mol^{-1}) to spherical Cl^- in $(CD_3)_2SO$ and exhibit significant binding selectivity since they complex with Cl^- to a much greater extent (10^3–10^2 : 1) than with the trigonal NO_3^- and tetrahedral $H_2PO_4^-$ anions.

The importance of anion binding and transport in chemical and biochemical processes has been the impetus for the design and fabrication of supramolecular anion receptors.[1] We have begun a project to prepare neutral anion receptors that exhibit selective anion binding, ultimately for the development of sensors and transport mimics that function in an aqueous environment. Here, we report the synthesis (Scheme 1) of our initial receptors **2**–**7**, superstructured porphyrins functionalized with urea moieties. Owing to the different pocket size and orientation of urea groups on the porphyrin scaffolding, it was anticipated that **2**–**4** would exhibit different aptitudes and selectivities for anion complexation than those seen with the previously prepared urea appended receptors.[2–6] Furthermore, the addition of electronegative substituents (Cl, F) to the *para* position of the phenyl rings of **3** and **4**, as well as the porphyrin's ability to bind metals in its core, allow for the moderation of the strength and selectivity of anion binding for the supramolecule.



Scheme 1: *Reagents and conditions*: i, *p*-RC_6H_4NCO, $CHCl_3$, room temp.; R = H (**2**, **5**, **8**), Cl (**3, 6, 9**) or F (**4**, **7**, **10**)

These receptors are the first example of a class of neutral, free-base porphyrins† able to act as very selective anion receptors, with **2**–**4** binding Cl^- greater than 1000 : 1 compared to NO_3^- or 280 : 1 compared to $H_2PO_4^-$ (*vide infra*) (Cl^- receptors are biologically relevant, for Cl^- ion channels are involved in the facilitated exchange of Cl^- for HCO_3^- anions in erythrocytes, and, when not functioning properly, have been implicated in the genetic disease cystic fibrosis[7]). For comparison, the expanded porphyrin receptors can bind anions only when protonated, and thus exhibit modest anion selectivity due to nondirectional coulombic interactions[3] (for example, sapphyrin binds $H_2PO_4^-$ and F^- ions with similar binding constants in methanol[1f]). Cobaltocene and ferrocene appended porphyrins have recently been reported.[8] The former is another example of a positively charged anion receptor, whereas the neutral ferrocene appended porphyrins do not bind anions unless metallated; both systems show little anion selectivity (no better than 4 : 1 binding selectivity between halides, nitrate and sulfate ions).

Porphyrins **2**–**4** were synthesized (Scheme 1) by the addition of 4 equiv. of the requisite isocyanate (**8**–**10**) to the *cis* isomer of H_2TAPP[9,10] **1** in $CHCl_3$ at room temp. and were obtained in yields of 70–85% after purification by silica-gel column chromatography and subsequent recrystallization from CH_2Cl_2–C_6H_{14}. The Zn complexes **5**–**7** were synthesized by stirring the free-base ligands with excess $Zn(OAc)_2{\cdot}2H_2O$ in CH_2Cl_2–MeOH (2 : 1, v/v) and were obtained in 90–95% yield. The model tetraphenylporphyrin was prepared using standard literature procedure.[11] The ^{1}H NMR spectra of **2**–**4** recorded in $(CD_3)_2SO$ at ambient temperature revealed a singlet resonance for the β-pyrrole protons, indicative of the *cis* conformation of the molecules. In all cases, the urea NH protons were observed as two broad singlets, the one at high field presumably due to those in close proximity to the porphyrin ring, resulting from the shielding effect of the macrocycle. The proposed structures **2**–**4** were corroborated by HRFABMS.

UV–VIS spectral anion titration revealed anion binding through perturbation of the Soret and visible bands of **2**–**4** when the anions Cl^-, NO_3^- and $H_2PO_4^-$ were added as their NBu_4^+ salts. Addition of NO_3^- and Cl^- anions produced a hypsochromic shift with concomitant decrease in intensity of the Soret band after the addition of 1 equiv. of anion. Further addition of anion resulted in an increase in intensity (Fig. 1). Titration of porphyrins **2**–**4** with $H_2PO_4^-$ produced a hypsochromic shift of the Soret band followed by a bathochromic shift and an increase in absorbance with the addition of >1 equiv. of anion. Furthermore, with porphyrins **3** and **4**, a broadened Soret band with the appearance of a shoulder was observed (Fig. 1). Changes in the Soret band combined with shifts of the porphyrin NH protons (*vide infra*) upon titration with the anions strongly suggests that the anions were bound within the porphyrin–urea pocket.

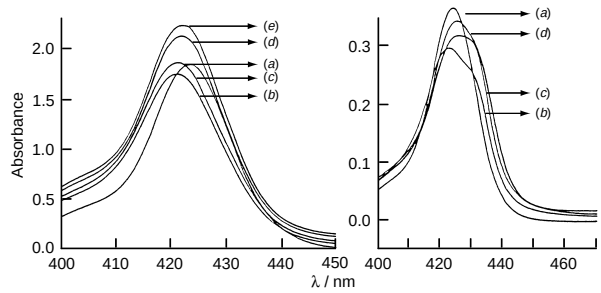


Fig. 1 UV–VIS spectra of porphyrins **3** and **4** demonstrating the change in the Soret bands upon titration with anions in CH_2Cl_2. (Left) porphyrin **4** titrated with NBu_4Cl in mol equiv.: (*a*) 0, (*b*) 1, (*c*) 2, (*d*) 5, (*e*) 10. (Right) porphyrin **3** titrated with $NBu_4H_2PO_4$ in mol equiv.: (*a*) 0, (*b*) 1, (*c*) 2, (*d*) 10.

Quantification of the association constants of neutral hosts **2**–**4** was accomplished by following the titrations of the anions by ^{1}H NMR in the strongly solvating solvent $(CD_3)_2SO$. In all cases, proton shifts were observed for the receptor porphyrin-phenyl, β-pyrrole, porphyrin NH, and urea-phenyl protons. Larger shifts were observed for the urea NH protons, with the downfield urea proton the most perturbed. The larger shift of the urea NH proton was indicative of its essential role in the anion recognition process.[2,4] The association constants of **2**–**4** in $(CD_3)_2SO$ determined from their binding curves (Fig. 2) for the complexation of Cl^- ion were calculated[12] to be $> 10^5$ dm^3 mol^{-1} (Table 1),[13] so it was impossible to judge any selectivity in binding that might be occurring for these anions between the different porphyrins. However, binding constants for $Cl^- > 10^5$ dm^3 mol^{-1} are significantly larger than those that have been previously reported for urea functionalized anion receptors.[1–6] The very strong binding of Cl^- ion allowed the mole ratio method[14] to be used in the determination of the binding stoichiometry, which was found to be 1 : 1 for the three porphyrins.

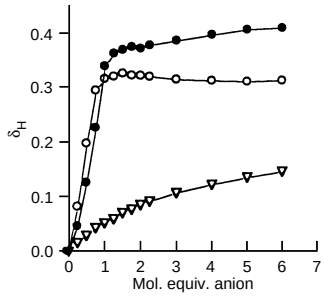


Fig. 2 Binding curves for porphyrin **4** and Cl^- (○), $H_2PO_4^-$ (●) and NO_3^- (▽) ions in $(CD_3)_2SO$

The association constants of **2**–**4** in $(CD_3)_2SO$ for the binding of $H_2PO_4^-$ ion were 400, 300, and 1400 dm^3 mol^{-1} (Table 1), respectively. Thus, there seemed to be some small selectivity between the *p*-fluorophenylurea porphyrin **4** and the other two porphyrins in their affinity for $H_2PO_4^-$. Presumably, the very electronegative *p*-F substituent produced a large enough increase in the acidity of the urea protons to strengthen their hydrogen bonding with the anion electrostatic field. Both Job's method of continuous variations[14] and the mole ratio method,[14] determined by UV–VIS spectrophotometry, showed the stoichiometry of binding was 1 : 1. The binding affinity of **2**–**4** for NO_3^- was even weaker (Table 1).‡ The noteworthy selectivity in the binding of Cl^- with **2**–**4** was presumably due to a less complementary fit of the trigonal NO_3^- or tetrahedral $H_2PO_4^-$ than that of spherical Cl^- within the urea binding pocket of the free-base porphyrins. Under analogous titration conditions, tetraphenylporphyrin exhibited negligible perturbation in its ^{1}H NMR and UV–VIS spectra, indicating the changes observed with ligands **2**–**4** were truly caused by anion binding.

Table 1 Binding constants (K/dm^3 mol^{-1}) for porphyrins **2**–**4** and Cl^-, NO_3^- and $H_2PO_4^-$ anions in $(CD_3)_2SO$

Porphyrin	Cl^-	NO_3^-	$H_2PO_4^-$
2	$> 10^5$	90	400
3	$> 10^5$	60	300
4	$> 10^5$	55	1400

Future investigations will examine solvent systems where the association constants of **2**–**4** for the complexation of Cl^- and other spherical anions are of the proper magnitude (*i.e.* $< 10^5$)[13] to allow for an accurate determination of their binding constants, and therefore the determination of possible selectivity trends with the different porphyrins. Future experiments will also examine if metallated receptors **5**–**7** will bind anions with the same selectivity trends as those observed with the free-base porphyrins.

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Footnotes and References

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† Neutral *meso*-octaethylporphyrinogens have been shown to bind selectively to F^- in CD_2Cl_2.[1a] However, the lack of macrocyclic aromaticity (*i.e.*, little useful UV–VIS, fluorescence, or electrochemical information) makes this system less attractive for sensor development.

‡ Although the complexation stoichiometries for porphyrins **2**–**4** and NO_3^- have yet to determined by Job's method,[14] the calculated errors for the binding constants were small only when a 1 : 1 binding isotherm was utilized.

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