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Quinoxaline-oligopyrroles: Improved pyrrole-based anion receptors†

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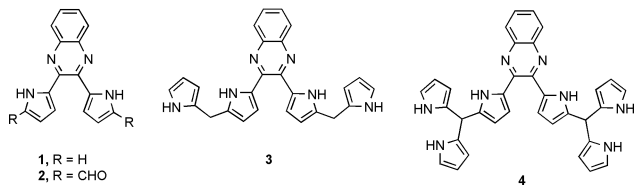
Received (in Cambridge, UK) 2nd January 2002, Accepted 6th March 2002
First published as an Advance Article on the web 21st March 2002

Novel quinoxaline derivatives bearing dipyrromethane or tripyrromethane substituents act as improved anion receptors as compared to the unsubstituted dipyrrolylquinoxaline core from which they are derived.

Simple chemical systems capable of recognizing, sensing, and transporting anions are of interest not only within the realm of supramolecular chemistry but also in terms of potential clinical applications.[1] As a consequence of this interest, considerable efforts have been devoted to the development of new anion receptors. One strategy being pursued in this context involves the use of pyrrolic subunits as the key anion recognizing motif, an approach that has led to the successful use of protonated sapphyrins,[2] neutral calixpyrroles,[3] and several other pyrrole-containing entities[4] as useful anion receptors.

One of the key concepts underscored by this work is that preorganization and cooperative effects play a critical role in mediating anion binding.[5] For instance, derivatives of calix[4]pyrrole bearing a sulfonamide or thiourea group were found to bind anions such as fluoride, chloride, dihydrogenphosphate well precisely because they provide an additional hydrogen bond donor site that complements that present in the calixpyrrole NH core.[6] Recently we reported that dipyrrolylquinoxaline (DPQ, **1**), which was first synthesized by Oddo and later refined by Behr,[7] is a useful colorimetric anion sensor.[8–11] While not yet established unequivocally, the proposed mechanism of anion recognition is thought to involve the cooperative interaction of both pyrrolic subunits with the bound anion *via* NH···A$^-$ hydrogen bonds. Consistent with this suggestion was the finding that a DPQ derivative wherein one of the nitrogens was substituted by a SEM protecting group displayed anion affinities that were dramatically decreased compared to **1** (by *ca.* 1/100 in the case of fluoride binding).[8] Left unanswered by these studies, however, was the question of whether *increasing* the number of pyrrolic NH donor groups would serve to enhance the inherent anion affinities of DPQ derivatives. In this communication, we report the synthesis and anion binding properties of two novel quinoxaline derivatives bearing dipyrromethane (**3**) and tripyrromethane groups (**4**), respectively. These systems, which contain built-in pyrrole-derived NH 'claws', display anion affinities that are substantially augmented relative to DPQ (**1**).



Quinoxaline derivatives **3** and **4** were synthesized from diformyl-substituted DPQ (**2**)[8] in 33 and 84% yield, respectively, by treating with $NaBH_4$ followed by TFA and pyrrole in the case of **3** and TFA and pyrrole in the case of **4**. Support for the proposed structures of **3** and **4** came from ^{1}H NMR spectroscopic and CIMS analyses. The former revealed that the six pyrrole subunits present in **4** may be classified into two types: those directly attached to a quinoxaline moiety (two) and those attached, in turn, to these pyrroles as part of the 'claw-like' trispyrrolylmethane substructure (four). The same kind of division can be made in the case of **3**. In this instance, however, there are two sets of two pyrroles each that correspond to those bound directly to the quinoxaline and attached *via* a methylene tether, respectively.

Support for this classification and for the structure as a whole came from an X-ray diffraction analysis of derivative **3**.‡ As inspection of the resulting structure reveals (Fig. 1), the two pyrrole rings directly attached to the quinoxaline core have their NH pyrrolic 'heads' oriented out and away from the central molecular axis, in analogy to what is seen in other DPQ derivatives.[11] These pyrrolic rings are also canted by 22.1 and 24.3° relative to the quinoxaline mean plane. A far greater degree of tilting is seen for the outer pyrroles; these subunits adopt a nearly vertical orientation and are twisted relative to their neighboring pyrroles by 88.3 and 85.7°, respectively. Thus, although a proper preorganization for anion binding is not observed in the solid state structure of **3**, a degree of flexibility is inferred that would support the notion that this system and its more complex congener, **4**, would be able to act as anion receptors under appropriate solution phase conditions.

The ability of **3** and **4** to function as possible anion receptors was tested by following the changes in the UV-vis absorption spectra in CH_2Cl_2 that were induced upon the addition of tetrabutylammonium (TBA) salts of fluoride, chloride, and dihydrogenphosphate anions, respectively. The resulting titration plots revealed a distinct saturation curve, with good isosbestic behavior being displayed. The spectral changes were thus assigned to a 1 : 1 binding interaction (*c.f.* Table 1).§ In the specific case of **3**, it was found that adding TBAF to a dilute CH_2Cl_2 solution (2.1×10^{-5} mol dm^{-3}) causes the color to change from yellow to red. These changes correlate with the appearance of a broad shoulder around 500–580 nm and a decrease in the intensity of the band at 426 nm. Standard curve

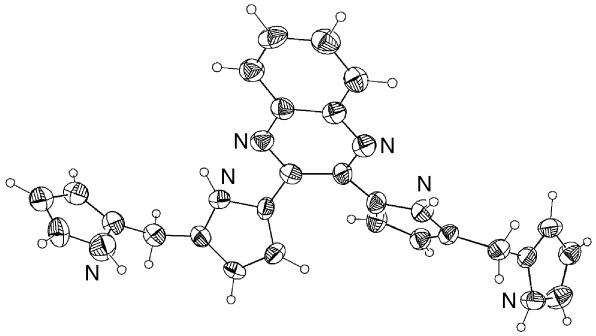


Fig. 1 X-Ray structure of **3** with the nitrogen atoms labeled. The thermal ellipsoids were scaled to the 50% probability level.

† Electronic supplementary information (ESI) available: synthetic details of **3** and **4**, titration studies for anion binding of **3** and **4**, and crystallographic details for **3**. See http://www.rsc.org/suppdata/cc/b1/b111708d/

DOI: 10.1039/b111708d

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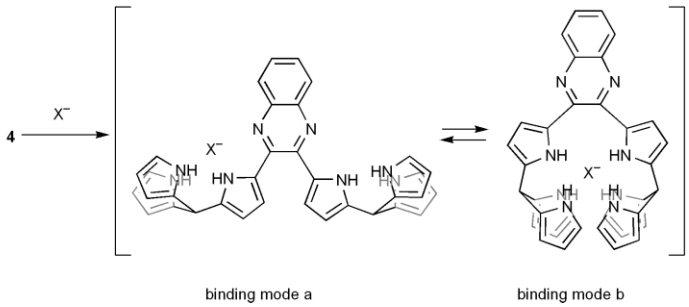
fitting gave an association constant, K_a, for 1:1 binding of (3.2 ± 0.4) × 10^4 mol^{-1} dm^3. While this value is almost a factor of two larger than that determined for DPQ (**1**) itself under analogous conditions (K_a = 1.82 × 10^4 mol^{-1} dm^3),[8] the degree of increase is not appreciable when compared to the *ca.* 100 fold increase in binding affinity seen upon moving from a SEM-protected DPQ, a species with only one NH donor, to DPQ itself. On the other hand, the 1:1 association constant for the complexation of F^- by **4** under similar conditions was estimated to be > 10^6 mol^{-1} dm^3, which represents a 50-fold increase over what is seen for **1**.

As shown in the Table 1, the chloride anion is bound by both **3** (K_a = 550 ± 90 mol^{-1} dm^3) and **4** (K_a = 5800 ± 600 mol^{-1} dm^3),¶ with the latter species again acting as the superior anion complexing agent. These values are now substantially enhanced compared to the unsubstituted control DPQ system **1**. Nonetheless, the extent of augmentation observed in the case of Cl^- is dwarfed by what is observed in the case of $H_2PO_4^-$ binding. Here, 1:1 binding constants of 4300 (± 300) mol^{-1} dm^3 and 3.0 (± 0.6) × 10^5 mol^{-1} dm^3 are calculated in the case of **3** and **4**, respectively.

Table 1 Association constants (mol^{-1} dm^3) for anion binding by the quinoxaline derivatives, **1**, **3**, and **4**, as determined from absorption spectral changes seen in CH_2Cl_2 upon the addition of TBA salts of the anion in question

	1[8]	**3**	**4**
F^-	18200	32000	> 1000000
Cl^-	50	550	5800
$H_2PO_4^-$	60	4300	300000
K_{F^-}/K_{Cl^-}	360	58	> 170
$K_{F^-}/K_{H_2PO_4^-}$	300	7.4	> 3.3

The substantial increase in affinities seen in the case of $H_2PO_4^-$ (K_a ratios for **4**:**3**:**1** of 5000:70:1) is ascribed to the greater number of pyrrole NH donors required to bind the larger dihydrogenphosphate anion as compared to a small spherical substrate such as F^- (K_a ratios of 50:1.7:1 are seen for **4**:**3**:**1**, respectively). That an enhancement is also seen in the case of Cl^- (K_a ratios of 100:10:1 for **4**:**3**:**1**, respectively) is also ascribed to size effects and is thought to reflect the fact that this larger anion[4] is better able to fit into the pyrrolic 'claws' of **3** and **4**. In other words, in the case of Cl^- and $H_2PO_4^-$ binding, it is proposed that these anionic substrates are 'chelated' in accord with *binding mode b* in Scheme 1. Such a conclusion is supported by ^{1}H NMR spectral studies. For instance, in the case of **4**, the resonances ascribable to the two kinds of pyrrole NH signals seen in $CDCl_3$ are observed to move to lower field and do not split (as would be expected were binding in accord with *mode a* of Scheme 1). Interestingly, such ^{1}H NMR spectroscopic behavior was also seen in the case of the smaller anion fluoride and receptor **4**. Here again, downfield shifts without splitting were seen through the addition of 1 equiv. of F^-. That larger shifts were seen for the four outer 'claw-like' pyrrole NH signals of **4** compared to the inner pyrrolic ones (3.80 *vs.* 2.05 ppm, respectively) leads us to suggest that the former NHs may associate F^- more effectively and that within the context of *binding mode b* the binding interactions are not ideal. Furthermore, the fact that the pyrrole NH signals become broadened and, in fact, disappear at higher F^- concentrations means that, in contrast to what is seen with $H_2PO_4^-$ where the NH signals remain sharp even in the excess of anionic guest, other competitive modes, including *binding mode a* and, under the higher concentration conditions of the NMR analyses, 1:2 ligand-to-anion complex formation, may be important in this case. Consistent with this proposal are the specific K_{F^-}/K_{Cl^-} and $K_{F^-}/K_{H_2PO_4^-}$ ratios recorded in the Table 1; these help highlight the fact that adding 'extra' pyrroles to a DPQ core augments Cl^- and $H_2PO_4^-$ binding more effectively than F^- binding.‖



Scheme 1 Proposed anion binding modes for receptor **4**.

In summary, the first examples of quinoxaline derivatives (**3**, **4**) bearing oligopyrrolyl-substituents have been synthesized. These species bind F^-, Cl^-, and $H_2PO_4^-$ anions effectively in CH_2Cl_2 solution as the result of the pyrrole-rich 'claws' they contain. Current work involves testing whether systems **3** and **4** will prove effective in the recognition of more complex anionic substrates and exploring whether these functionalized quinoxaline derivatives can be used as 'building blocks' to prepare various new, preorganized macrocyclic systems.

This work was supported by the National Institutes of Health and the Robert A. Welch Foundation (grants GM58907 and F-1018 to J. L. S.). H.M. thanks Professor Atsuhiro Osuka, Graduate School of Science, Kyoto University for a study leave and the JSPS for a Research Fellowship for Young Scientists.

Notes and references

‡ Crystallographic data for **3**: $C_{26}H_{22}N_6$, M_w = 418.50, monoclinic, $P2_1/c$ (#14), a = 22.2659(12), b = 5.3668(2), c = 17.3911(7) Å, β = 96.131(2)°, V = 2066.29(16) Å^3, D_c = 1.345 g cm^{-3}, Z = 4, R = 0.103, GOF = 1.185 ($I > 2\sigma(I)$), R_w = 0.214 (all data). CCDC 176723. See http://www.rsc.org/suppdata/cc/b1/b111708d/ for electronic files in .cif or other electronic format.

§ A Job plot analysis was also carried out and was consistent with 1:1 binding being the dominant substrate–receptor interaction mode.

¶ At the recommendation of a reviewer, a standard ^{1}H NMR spectroscopic titration was used to confirm the validity of this value; using this latter method, a K_a of 5,900 ± 800 mol^{-1} dm^3 was obtained.

‖ Further support for this conclusion is the observation that in the case of receptor **3** (only) slight deviations from a strict 1:1 binding isotherm, ascribed to the incipient formation of a 1:2 receptor-to-anion complex, become apparent at high F^- concentrations. Such deviations were not seen for either Cl^- and $H_2PO_4^-$ binding or, in the case of **4**, for any of the anions tested at least under the conditions of the UV-vis experiments.

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