Quinoxaline-oligopyrroles: Improved pyrrole-based anion receptors

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Novel quinoxaline derivatives bearing dipyromethane or tripyrromethane substituents act as improved pyrrole-based anion receptors as compared to the unsubstituted dipyrylquinoloxaline 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. 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, neutral calixpyrroles, and several other pyrrole-containing entities 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. 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. Recently we reported that dipyrrolylquinoxaline (DPQ, 1), which was first synthesized by Oddo and later refined by Behr, is a useful colorimetric anion sensor. 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 hydrogen bonds. Consistent with this suggestion was the finding that a DPQ derivative wherein one of the nitrogen atoms was substituted by a SEM protecting group displayed anion affinities that were dramatically decreased compared to the unsubstituted dipyrrolylquinoloxaline core. 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 the unsubstituted dipyrrolylquinoloxaline core. The question of whether the interaction of both pyrrolic subunits with the bound anion via NH hydrogen bonds is mediated in anion binding.

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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 pyrrolic 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. 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 pyroles 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 congeners, 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 CH2Cl2 that were induced upon the addition of 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 CH2Cl2 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

\[ H_2NN\text{H+} + R_2\text{CH} \rightarrow \text{H}_2\text{NNH} \cdot \text{H} \text{R}_2\text{CH} \]

Quinoxaline derivatives 3 and 4 were synthesized from diformyl-substituted DPQ (2) in 33 and 84% yield, respectively, by treating with NaBH₄ 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 1H 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’ tripyrrolylmethane 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.

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Fig. 1 X-Ray structure of 3 with the nitrogen atoms labeled. The thermal ellipsoids were scaled to the 50% probability level.
fitting gave an association constant, $K_a$, for 1:1 binding of (3.2 ± 0.4) $\times 10^4$ mol $^{-1}$ dm$^3$. While this value is almost a factor of two larger than that determined for DPQ (1) itself under analogous conditions ($K_a = 1.82 \times 10^3$ mol $^{-1}$ dm$^3$), 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$^-$/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 ($K_a = 550 \pm 90$ mol $^{-1}$ dm$^3$) and 4 ($K_a = 5800 \pm 600$ 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$_2$PO$_4^-$/ binding. Here, 1:1 binding constants of 4300 (± 300) mol $^{-1}$ dm$^3$ and 3.0 (± 0.6) $\times 10^3$ 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 CDCl$_3$ upon the addition of TBA salts of the anion in question

<table>
<thead>
<tr>
<th>Anion</th>
<th>1</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>F$^-$</td>
<td>18200</td>
<td>3200</td>
<td>&gt;100000</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>50</td>
<td>550</td>
<td>5800</td>
</tr>
<tr>
<td>H$_2$PO$_4^-$</td>
<td>60</td>
<td>4300</td>
<td>300000</td>
</tr>
<tr>
<td>$K_p/K_{CT}$</td>
<td>360</td>
<td>58</td>
<td>&gt;170</td>
</tr>
<tr>
<td>$K_p/K_{H_2PO_4^-}$</td>
<td>300</td>
<td>7.4</td>
<td>&gt;3.3</td>
</tr>
</tbody>
</table>

The substantial increase in affinities seen in the case of H$_2$PO$_4$- ($K_a$ ratios for 4:3:1 of 5000:70:1) is ascribed to the larger 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 is better able to fit into the pyrrolic ‘claws’ of 3 and 4. In other words, in the case of Cl$^-$ and H$_2$PO$_4^-$ 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$_2$PO$_4$- 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 $K_p$/$K_a$ and $K_p/K_{H_2PO_4^-}$ ratios recorded in the Table 1; these help highlight the fact that adding ‘extra’ pyrroles to a DPQ core augments Cl$^-$ and H$_2$PO$_4^-$ binding more effectively than F$^-$ binding. 

In summary, the first examples of quinoxaline derivatives (3, 4) bearing oligopyrrolyl-substituents have been synthesized. These species bind F$^-$, Cl$^-$, and H$_2$PO$_4^-$ anions effectively in CH$_2$Cl$_2$ 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 anions; substrates and exploring whether these functionalized quinoxa-line derivatives can be used as ‘building blocks’ to prepare various new, preorganized macrocyclic systems.

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**Notes and references**

1 Crystallographic data for 3: C$_{30}$H$_{22}$N$_6$. $M_r = 418.50$, monoclinic, $P2_1/c$ (no 14), $a = 22.265(9)$, $b = 5.3668(2)$, $c = 17.3911(7)$, $\beta = 96.131(2)^\circ$, $V = 2066.29(16)$ Å$^3$, $D_i = 1.345$ g cm$^{-3}$, $Z = 4$, $R = 0.103$, $GOF = 1.185$ ($t > 2\sigma(t)$), $R_{w} = 0.214$ (all data); CCDC 176723. See http://www.rsc.org/suppdata/cc/b1/b111708d/ for electronic files in .cif or other electronic format.

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

3 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 5.90 ± 800 mol$^{-1}$ dm$^3$ was obtained.

4 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$_2$PO$_4^-$ binding or, in the case of 4, for any of the anions tested at least under the conditions of the UV–vis experiments.


