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Quinoxaline-oligopyrroles: Improved pyrrole-based anion receptors†

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Novel quinoxaline derivatives bearing dipyromethane or tripyrromethane substituents act as improved anion receptors as compared to the unsubstituted dipyrrylquinoline line 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 calixpyrrole NH core.6 Recently we reported that dipyrrolylquinolinehydrogen bond donor site that complements that present in the phosphate well precisely because they provide an additional 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 substituted by a SEM protecting group displayed anion affinities that were dramatically decreased compared to the finding that a DPQ derivative wherein one of the nitrogens was replaced by a formyl-substituted 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 cooperation of both pyrrolic subunits with the bound anion via hydrogen bonds. Consistent with this suggestion was the finding that a DPQ derivative wherein one of the quinoxaline and attached tether, respectively.

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[n]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 dipyrrylquinolinaxaline (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 cooperation of both pyrrolic subunits with the bound anion via hydrogen bonds. Consistent with this suggestion was the finding that a DPQ derivative wherein one of the quinoxaline and attached tether, respectively. 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 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 × 10−3 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 compounds 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/
fitting gave an association constant, \( K_a \), for 1:1 binding of (3.2 ± 0.4) \times 10^4 mol \cdot 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 \cdot dm\(^3\)), the degree of increase is not appreciable when compared to the ca. 100-fold increase in binding affinity seen 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 \cdot 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 \cdot dm\(^3\)) and 4 (\( K_a = 5800 ± 600 \) mol \cdot 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 \cdot dm\(^3\) and 3.0 ± 0.6 \times 10^4 mol \cdot dm\(^3\) are calculated in the case of 3 and 4, respectively.

### Table 1

<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>32000</td>
<td>&gt;1000000</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(_a)/K(_a)'</td>
<td>360</td>
<td>58</td>
<td>&gt;170</td>
</tr>
<tr>
<td>K(_a)/K(_a)''</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 greater number of pyrrole NH donors required to bind the larger dihydrogenphosphate anion as compared to a small spherical substrate such as F\(^-\). Here again, downfield shifts without assignment spectral changes seen in CH\(_2\)Cl\(_2\) upon the addition of TBA salts of the anion in question.

[Scheme 1](#) Proposed anion binding modes for receptor 4.

Notes and references

1. N. J. Sessler, H. Maeda, T. Mizuno, V. M. Lynch and H. Furuta, *J. Am. Chem. Soc.*, 1998, 120, 6200. (only) slight deviations from a strict 1 binding isotherm, \( GOF = 0.103 \).
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