Anion binding by catechols—an NMR, optical and electrochemical study†

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The X-ray structure of the ClC chloride channel made it clear that O–H · · · chloride interactions play a key role in important biological membrane-bound systems, however, surprisingly this type of interaction has only been rarely exploited for the development of synthetic anion receptors. This paper therefore reports the anion binding strengths and selectivities of some simple commercially available bis-phenols. In particular, we compare catechol (1,2-dihydroxybenzene) and resorcinol (1,3-dihydroxybenzene) which show interesting and different selectivities between the halide anions in acetonitrile solution. Catechol binds tetrabutylammononium (TBA) chloride almost 30 times more strongly than TBA bromide, whilst for resorcinol, this difference drops to a factor of *ca.* 3.5. It is suggested that this is a consequence of the bite angle of the chelating hydrogen bonding groups of catechol being particularly appropriate for effective binding of the smaller anion. The oxidation of catechol to *ortho*-quinone is perturbed by the addition of chloride anions, as probed *via* cyclic voltammetry, and this compound can therefore be considered to act as an electrochemical sensor for chloride. Nitrocatechol is able to bind chloride anions more strongly than catechol as a consequence of its enhanced acidity and hence greater hydrogen bond donor character. Furthermore, nitrocatechol senses the bound anion *via* changes in its UV-visible spectrum. Notably, binding still occurs even in the presence of small amounts of competitive solvents (*e.g.* water). This observation has biomimetic importance as wet acetonitrile has some similarity in terms of overall polarity and hydrogen bond competition to the solvent shielded interiors of biological macromolecules and membranes—such as the environment within the ClC chloride channel itself. Finally, we report that catechol undergoes a unique colorimetric response on the addition of basic anions, such as fluoride. We can assign this response as being due to oxidative degradation of catechol catalysed by the basic anions (which bind to, and deprotonate, the catechol). This process is somewhat analogous to the well-known metal catalysed oxidation of catechol which can take place in aqueous solution. The speed of response and easily monitored and distinctive colour change induced by fluoride anions indicates this may be a useful mechanism for exploitation in the development of selective fluoride sensors.

Introduction

The field of anion recognition has seen remarkable progress over the past three decades.[1] However, it is still a significant challenge to develop receptors which show controllable anion selectivities. Generally, the most successful approach has been to synthesise sophisticated macrocyclic systems in order to generate well-defined cavities capable of exhibiting a good degree of anion discrimination.[2] Furthermore, binding anions in competitive media is still a significant challenge, and thus far, the vast majority of systems which operate in competitive hydroxylic solvents require a positive charge in order to snare an anionic guest.[3]

Neutral anion receptors are of considerable interest,[4] partly because it was realised relatively early that neutral binding proteins play a key role in the transport of sulfate and phosphate anions through membranes in biological systems.[5] In these proteins, high specificity for the target anion is achieved by using a recognition site in which the anion is completely desolvated, and is bound *via* neutral hydrogen bonds. In addition, a macrodipole effect contributes to the stability of the complex. Recently, there has been intense focus on chloride transport processes in biological systems. This is primarily because the mis-regulation of chloride channels plays a key role in the pathology of cystic fibrosis.[6] The recent structural elucidation of a ClC chloride channel was particularly significant.[7] Interestingly, this structure (Fig. 1) illustrated that in addition to the ubiquitous N–H · · · anion interactions found in biological systems, O–H · · · anion interactions were also vital. In particular, the side chains of tyrosine and serine amino acids play key roles in forming O–H · · · chloride hydrogen bond interactions. Once again, it is noteworthy that the binding site of this transport protein contains no full positive charge—presumably to avoid the creation of a deep energy well, which would bind chloride too strongly and prevent transport of the anion. Furthermore, mutagenesis studies on the cystic fibrosis transmembrane conductance regulator have indicated that a threonine residue (T338), which also possesses a hydroxyl side chain, plays a key role in controlling the anion permeability sequence.[8] It was suggested that entry of the anion to the conductance channel occurred through this hydroxylated region of the protein. Yellow variants

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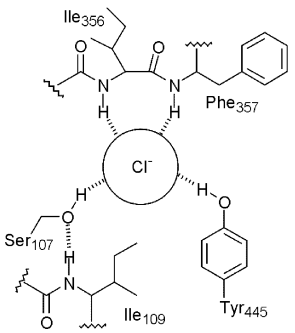

Fig. 1 Schematic taken from the X-ray structure of the ClC chloride channel indicating the hydrogen bond interactions at the chloride binding site—including the crucial OH · · · anion hydrogen bond interactions from Ser_{107} and Tyr_{445}.[7] It should be noted there are also some close hydrophobic contacts between the protein and the chloride anion.

of green fluorescent proteins have also previously been shown to act as halide sensors, with the hydrogen bond interaction between a tyrosine OH group and the chloride anion proving to be indispensable (in combination with an electrostatic interaction from another residue) in both the anion binding and sensing process.[9]

Thus far, the majority of synthetic systems[1] have employed neutral N–H · · · anion hydrogen bond interactions as the method of choice for achieving anion binding. In general, chloride selective receptors employ relatively complex frameworks in order to organise the functional groups capable of recognising the relevant halide anion.[10] An enhanced degree of size selectivity for chloride can be obtained by carefully controlling the dimensions of the receptor binding site—for example by using macrocyclic ligands. A number of groups have employed chloride binders to achieve the transport of chloride anions across membranes—once again these studies have potential biomedical relevance.[11]

Given the biological importance of O–H · · · anion interactions as described above, it is surprising that there has only been very limited work describing the ability of hydroxylated compounds to interact with anionic guests as a consequence of hydrogen bond formation (especially in comparison with the huge body of work dealing with N–H · · · anion interactions). Given the biomimetic importance of O–H · · · anion interactions, we find it particularly surprising therefore that there has never been any systematic investigation of this kind of anion binding interaction, whereas amides and ureas have been extensively studied in this way.[12] Crystal structures from the 1980s showed that if phenols and catechols were crystallised in the presence of tetrabutylammonium halides, the O–H groups would form hydrogen bond interactions with the halide anion.[13] However, it was not until the early 1990s that solution studies began to be performed, with the groups of Aoyama and Koga reporting that phenolic groups could help bind anions which were predominantly bound as part of an ion pair with a pyridinium cation.[14] A number of other groups have subsequently reported the ability of OH · · · anion interactions to supplement an anion binding process. Davis and co-workers made use of steroid cryptands, which supplemented amide N–H groups capable of hydrogen bonding to anions with steoridal O–H groups (in non-polar solvents, *e.g.* $CDCl_3$).[15] Kondo and co-workers used alcohols to augment the binding strength of simple sulfonamide based anion receptors.[16] It has been shown that phenolic groups on calixarenes can interact with anions,[17] and phenolic compounds have also been employed as anion sensors.[18]

We recently used a high-throughput assay[19] to screen the ability of a number of simple bisamides and phenols to bind chloride anions in acetonitrile solution. This assay identified catechol as a potentially useful chloride anion binding fragment.[20] Indeed the binding strengths observed using catechol were significantly higher than those found for flexible bis-amide derivatives which have been systematically studied as anion receptors.[21] We therefore decided to build on our discovery, and in this paper, we report that simple bis-phenols such as **1**–**3** can exhibit relatively high degrees of tunable anion selectivity. Furthermore they are able to detect the presence of a variety of anions *via* electrochemical and optical responses. Indeed, fluoride causes a colorimetric response with catechol, a process which occurs *via* a new mechanism. We also report that effective anion binding and sensing is possible *via* O–H · · · anion hydrogen bond interactions, even in the presence of small amounts of water. Binding anions under these conditions of polarity and hydrogen bond competition is somewhat analogous to anion binding within the partly solvated active sites of enzymes and proteins as well as within membrane environments.

Results and discussion

NMR titration studies with halide anions

Initially, we decided to compare the ability of catechol (**1**) and resorcinol (**2**) (Fig. 2) to bind different anions (as their tetrabutylammonium salts) in CD_3CN solution using ^1H NMR titration methods.[22] We reasoned that the different organisation of the OH groups on the aromatic framework may modify the selectivities of these receptors. Compounds **1** and **2** exhibited anion binding under fast exchange on the NMR timescale, with the O–H and Ar–H peaks shifting downfield on the addition of aliquots of tetrabutylammonium halide (Table 1). Chloride gave rise to the largest downfield shifts (as would be expected for the most charge

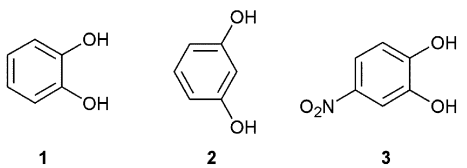

Fig. 2 Phenolic compounds used for anion binding and sensing studies: catechol (**1**), resorcinol (**2**) and nitrocatechol (**3**).

Table 1 NMR shifts (ppm) induced by the addition of 6 eq. of different anions as their tetrabutylammonium salts to catechol (**1**) and resorcinol (**2**) (concentration = 2 mM) in CD_3CN solution. Data are an average of at least two titrations

$\Delta\delta$ (ppm)				
	O–H	Ar–H	Ar–H	Ar–H
1 + Cl^-	2.097	−0.036	−0.020	—
1 + Br^-	0.415	−0.017	0.033	—
1 + I^-	buried	*ca.* −0.007	0.013	—
2 + Cl^-	0.913	0.160	0.021	−0.037
2 + Br^-	0.200	*ca.* 0.06	0.014	−0.010
2 + I^-	0.037	0.024	0.004	−0.003

dense anion). In all cases, the NMR signal for the OH protons of **1** and **2** remained visible during the titration. This indicates that halide anions are not simply deprotonating the acidic phenolic groups. It is noteworthy that when titrating anions into resorcinol (**2**), relatively large shifts were observed for one of the aromatic protons (for further discussion of this see below).

The NMR titration curves were fitted to a 1 : 1 stoichiometry of binding with a commercial program (HypNMR)[23] using non-linear least squares methods in order to obtain binding constants. All binding constants were determined in undried CD_3CN using catechol–resorcinol concentrations of 2 mM.[24] As reported previously,[20] **1** was significantly more effective as a chloride anion binder than **2**, exhibiting a respectable binding constant with chloride of 1570 mol^{-1} dm^3 (Table 2). Compound **1** bound bromide significantly more weakly ($K = 55$ $mol^{-1}dm^3$) than chloride. Indeed, this is a difference in binding strength of a factor of *ca.* 30. Catechol (**1**) therefore shows a remarkable degree of size selectivity for chloride and bromide anions—well over an order of magnitude. This selectivity is in spite of the fact that catechol has relatively little structural organisation when compared with many of the macrocyclic receptors employed in the literature for selective chloride binding.[9] In the case of resorcinol (**2**), however, bromide was only bound a factor of *ca.* 3.5 less strongly than chloride—indicating a much lower degree of size selectivity. Iodide binding was very weak for both catechol and resorcinol.

It can be proposed, in analogy with chelating ligands for transition metals,[25] that the 'bite angle' of the chelating hydrogen bonding groups is important in determining the binding strengths with different halide anions (Fig. 3). This would explain the difference in halide anion selectivity observed between catechol (**1**) and resorcinol (**2**), with the OH groups of catechol **1** being particularly appropriate for chloride binding. This proposal is also consistent with the observation of a single shifting NMR peak corresponding to *both* of the catechol O–H protons. A chelate mode for chloride anion binding has previously been demonstrated crystallographically for catechol[13a] but has not been detailed in solution phase studies. For all of the experiments using resorcinol, the aromatic proton located between the OH groups was strongly perturbed in the NMR titration ($\Delta\delta = 0.160$, 0.06 and 0.024 ppm for Cl^-, Br^- and I^- binding, respectively, Table 1). The shift of 0.160 ppm induced by chloride anion binding is a very significant shift for an Ar–H proton. Notably, the other aromatic protons of resorcinol were not affected in this way (NMR shifts <0.040 ppm). This observation is consistent with the O–H protons of resorcinol binding the halide anions in a chelate binding mode, hence perturbing the Ar–H proton between them. Furthermore, the large shift in Ar–H may even indicate the presence of a weak Ar–H $\cdots$ anion hydrogen bond interaction. Such C–H $\cdots$ anion hydrogen bonds have been shown to sometimes play important roles in halide anion binding.[26] The aromatic protons of catechol (**1**), on the other hand, only exhibited minor shifts on halide binding, consistent with the fact that they do not point into the chelate binding site and therefore probably have no direct interaction with the bound anion.

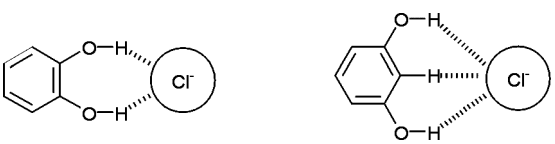

Fig. 3 Proposed chelate binding modes of catechol (**1**) and resorcinol (**2**) with chloride anions.

Table 2 Binding constants (K, mol^{-1} dm^3, ± 15%) determined for 1 : 1 complexes between receptors **1** and **2** and a variety of anions in CD_3CN solution, determined using ^1H NMR titration methods, fitting the data with HypNMR.[24] Data are an average of at least two titrations

	Cl^-	Br^-	I^-
1	1570	55	<5
2	110	30	<5

Electrochemical studies

Catechol is a redox-active unit, undergoing oxidation to *ortho*-quinone which is reversible in aqueous solution. We, therefore, became interested in whether the inherent redox chemistry of this molecule would enable it to act as an electrochemical chloride sensor.[27] In acetonitrile, catechol possesses an irreversible oxidation wave at 1.210 V (Fig. 4a) corresponding to the oxidation of catechol to *ortho*-quinone.[28] In the same solvent, chloride undergoes a quasi-reversible oxidation process at a similar potential, with the oxidation peak at 1.075 V (Fig. 4b). It was anticipated that this would make the electrochemical titration difficult to interpret, however, the experiment was still carried out.

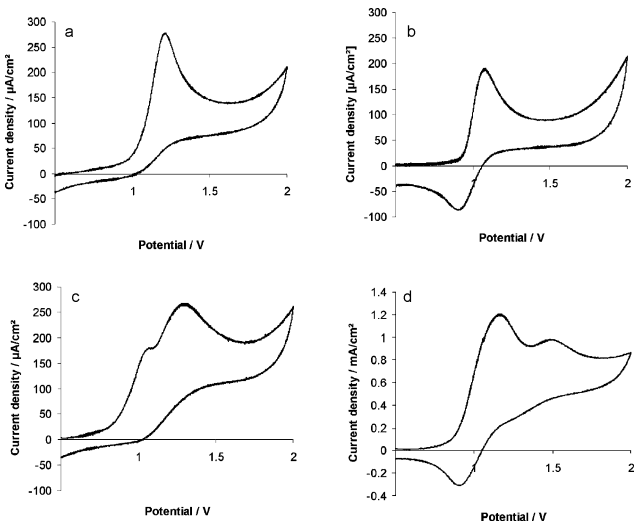

Fig. 4 Cyclic voltammograms of (a) catechol (1 mM), (b) tetrabutylammonium chloride (1 mM), (c) catechol (1 mM) and tetrabutylammonium chloride (1 mM), (d) catechol (1 mM) and tetrabutylammonium chloride (10 mM). All voltammograms measured in acetonitrile containing tetrabutylammonium tetrafluoroborate (200 mM) as supporting electrolyte. Scan rate = 100 mV s^{-1}.

On the addition of tetrabutylammonium chloride to catechol, a redox wave for chloride oxidation was, as expected, observed to grow into the voltammogram. In the presence of one equivalent of tetrabutylammonium chloride (Fig. 4c), the chloride oxidation appeared as a shoulder at *ca.* 1.085 V (effectively unchanged within the errors of the electrochemical experiment). However, the oxidation wave associated with the catechol unit was shifted to higher potential. In the presence of one equivalent of chloride,

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this oxidation wave appeared at *ca.* 1.315 V—a significant shift of 105 mV. This would indicate that the presence of tetrabutylammonium chloride perturbs the oxidation of the catechol unit making it thermodynamically more difficult.[29] Indeed, the presence of ten equivalents of chloride anion (Fig. 4d) appeared to shift the redox potential yet further in an anodic direction, with a broad oxidation wave being observed at 1.520 V (a shift of just over 300 mV).

A similar study was performed with tetrabutylammonium iodide. As expected, the redox wave for iodide appears at lower potential than that for chloride (iodide is more easily oxidised). In this case, the oxidation wave associated with catechol appeared to be much less affected than on the addition of chloride. Indeed, in the presence of ten equivalents of tetrabutylammonium iodide (Fig. 5), although the catechol oxidation peak broadened significantly, it appeared at a potential of *ca.* 1.23 V—a relatively insignificant shift (20 mV). This indicates that unlike chloride anions, which have a significant effect on the oxidation of catechol, iodide anions do not cause any real observable perturbation. The electrochemistry of tetrabutyl ammonium bromide is more complex, but once again, no significant perturbation of the catechol oxidation wave was observed.

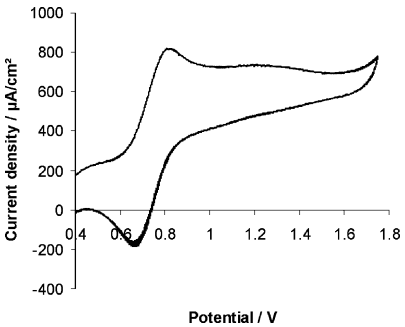

Fig. 5 Cyclic voltammogram of catechol (1 mM) in the presence of tetrabutylammonium iodide (10 mM). Measured in acetonitrile containing tetrabutylammonium tetrafluoroborate (200 mM) as supporting electrolyte. Scan rate = 100 mV s^{-1}.

It is therefore possible that catechol groups may be useful for the development of anion selective redox sensors—however, it should be noted that the overlap between halide and catechol redox processes, and the irreversibility of the redox process observed for catechol in acetonitrile, may ultimately limit this application.

UV-Vis spectrometric studies

Given our developing interest in sensors for the presence of chloride anions, we turned our attention to nitrocatechol (**3**), reasoning that the electron withdrawing nitro group should enhance the ability of the OH groups to form hydrogen bond interactions with the chloride anion. Indeed, it has been reported that the pK_a values for catechol (**1**) are 9.2 and 13.0,[30] whilst those for nitrocatechol (**3**) are significantly lower at 6.7 and 10.8.[30c,31] Lower pK_a values are consistent with a greater ability to act as hydrogen bond donors.

Initially, we performed an NMR titration experiment using nitrocatechol (**3**) in deuterated acetonitrile. The data fitted well to a 1 : 1 binding profile, and HypNMR fitting gave a K_a of 3800 mol^{-1} dm^3 (±15%). This binding of chloride is therefore approximately 2.5 times stronger than that observed with simple catechol (**1**). This is in agreement with our expectations and also with what we found for simple phenols in our previous paper using NMR screening methods.[20] For example, phenol itself bound chloride anions with a K value of 48 mol^{-1} dm^3, whilst nitrophenol bound chloride much more strongly ($K = 555$ mol^{-1} dm^{-3}). Indeed, it has previously been shown that Hammett-type relationships (with aromatic substituents graded according to their electron donating/withdrawing character) can be applied to anion binding events in which hydrogen bonding interactions play a primary role.[32]

We then went on to investigate the anion sensing capability of nitrocatechol (**3**) in CH_3CN solution using UV-visible titration methods. In CH_3CN, compound **3** has a band in its UV-visible spectrum at *ca.* 330 nm. On the addition of anions (as their tetrabutyl ammonium salts), a decrease in the intensity of the band at 330 nm was observed (Fig. 6a). The data were fitted to a 1 : 1 stoichometry using a non-linear least squares method, and a satisfactory fit of the experimental data was obtained. This gave a K_a value of 4400 mol^{-1} dm^3, ±15% for chloride binding. This is in agreement with the NMR titration data, and once again indicates the advantage of attaching a nitro group for increasing chloride binding strength.

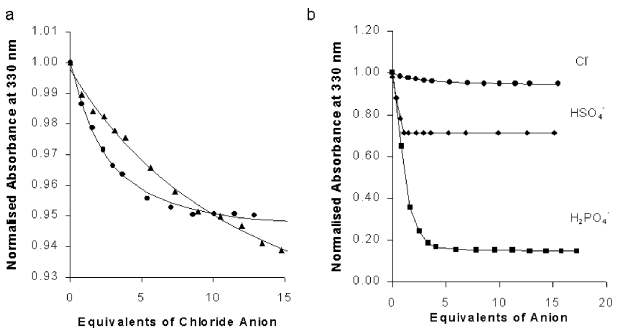

Fig. 6 (a) UV-Vis titration curves for nitrocatechol **3** with tetrabutylammonium chloride in CH_3CN (circles) and in CH_3CN–H_2O (99.5 : 0.5) (triangles). (b) UV-Vis titration curves for nitrocatechol **3** with tetrabutylammonium chloride (circles), hydrogensulfate (diamonds) and dihydrogenphosphate (squares), all in CH_3CN.

The sensory response to chloride anions was admittedly small (*ca.* 5% decrease in intensity, Fig. 6a), but chloride gave rise to a clearer and more reproducible response than bromide or iodide anions. Indeed, the small perturbations in the UV-vis spectrum induced by the larger halide anions could not be reliably fitted to give K_a values. Once again, this indicates that the organisation of the OH hydrogen bond donors on catechols such as **1** and **3** is particularly appropriate for binding the chloride anion.

Given the strength of binding being observed with chloride anions we decided to investigate the ability of **3** to sense this anion in the presence of significant amounts of competitive solvents. We used CH_3CN and added 0.5% H_2O (*ca.* 1400 equivalents relative to nitrocatechol). On titrating chloride anions into **3**, a decrease in the intensity of the band at 330 nm was once again observed (Fig. 6a). Remarkably, relatively strong anion binding was still observed. Once again, fitting to a 1 : 1 stoichiometry gave acceptable results, and in this case, a K_a value of 330 mol^{-1} dm^3 (±15%) was obtained.

Many synthetic neutral anion receptors struggle to achieve any halide anion binding in the presence of hydrogen bond competitive

water molecules. It may be considered that the O–H groups on nitrocatechol are particularly able to compete with water molecules for the anion because:

(i) the O–H groups on nitrocatechol (**3**) are more acidic than H_2O and hence able to form enthalpically stronger hydrogen bonds with chloride anions

(ii) catecholic O–H groups have the potential to bind anions in a chelate mode (Fig. 3, unlike water) and hence have an entropic advantage binding chloride anions.

Compound **3** therefore is capable of binding chloride anions under wet acetonitrile conditions, and indicates that this type of interaction may be of biological relevance. We believe this solvent system models, to some extent, the microenvironment experienced within the solvated active site of an enzyme (*i.e.* moderate polarity with a small number of hydrogen bonding water molecules being present). Indeed, encapsulated protein interiors and enzyme active sites experience a significant degree of shielding from hydrogen bond competitive water molecules. Furthermore, membrane bound systems, such as chloride transport channels,[7,8] also experience significant degrees of water exclusion.

Oxo-anions HSO_4^- and $H_2PO_4^-$ were then investigated for their ability to interfere with halide anion binding. The $H_2PO_4^-$ anion caused a very large response in the UV-Vis spectrum (85% decrease in intensity at 330 nm, Fig. 6b) and gave very strong binding ($>10^4$ M^{-1}). Indeed, the shade of the yellow solution was observed to visibly change. This response was markedly different to that observed for halide binding. We therefore propose that in this case, the anion interacts *via* a different mechanism with the catechol subunit. We argue that the relatively acidic nitrocatechol is deprotonated by the basic anion. Indeed, the UV-Vis data are consistent with deprotonation of the catechol as a very intense, new absorption band emerges at *ca.* 430 nm on the addition of $H_2PO_4^-$ anions.[33] It is possible that once deprotonated, the catechol binds directly to the phosphorus centre *via* covalent bond formation, in analogy to the mode of binding observed between catechols and molybdate anions.[34] However, it is also worth noting that under basic conditions, oxidation of the catechol unit also becomes more likely, and this process could potentially be occurring in this case.[33]

The HSO_4^- anion also gave strong binding and perturbed the UV-Vis spectrum to a significant degree (25% decease in intensity at 330 nm, Fig. 6b). It is noteworthy that the end-point of the titration was different to that obtained with $H_2PO_4^-$, indicating that the resultant complex is different—perhaps having the catechol oxygen atoms bound directly to the sulfur.

Catechol also exhibited a UV-response on the addition of $H_2PO_4^-$ and HSO_4^- anions, with its absorption band at 280 nm increasing in intensity. Once again, the two anions gave rise to different levels of response, with $H_2PO_4^-$ leading to greater perturbation of the spectrum. The titration profiles were not as sharp as those observed for nitrocatechol, probably reflecting the lower acidity of catechol.

We therefore propose that the role of oxo-anions in binding to acidic nitrocatechol (**3**) is significantly different to that of halide anions. Whilst halide anions bind to this compound as a consequence of hydrogen bond interactions, giving rise to small perturbations in the UV-vis spectrum, and NMR shifts of the O–H protons, oxo-anions become involved in acid–base processes with the relatively acidic nitrocatechol **3**. We attempted NMR titration with the oxo-anions, but the resonances corresponding to the O–H protons always disappeared during the titration—supportive of our proposal of proton transfer in this case. It is worth noting, in analogy with these results, that proton-transfer (acid–base) processes are often important in anion binding (*e.g.* when using basic anions such as F^- or $H_2PO_4^-$ and receptors containing moderately acidic N–H groups).[35]

Catechol with fluoride—a rapid and selective colorimetric response

Given the observations from titrations of compound **3** with $H_2PO_4^-$ and HSO_4^- anions reported above, we decided to return to investigating the behaviour of simple catechol (**1**) with a wider range of anionic guests than the three halides initially studied. We therefore carried out a screening experiment, in which catechol was dissolved in acetonitrile with a ten-fold excess of tetrabutylammonium salts of different anions.

Fig. 7 illustrates the situation immediately after adding tetrabutylammonium anion salts to solutions of catechol (2 mM). Clearly the fluoride anion has induced a dramatic and rapid change on the catechol solution, leading to an intense blue colour, whilst the other anions apparently have no effect. Sensors and receptors with selectivity for the fluoride anion have received much attention over recent years[36] on environmental and medical grounds—partly due to the fact that fluoride anions are released during the hydrolysis of the nerve gas sarin.[37]

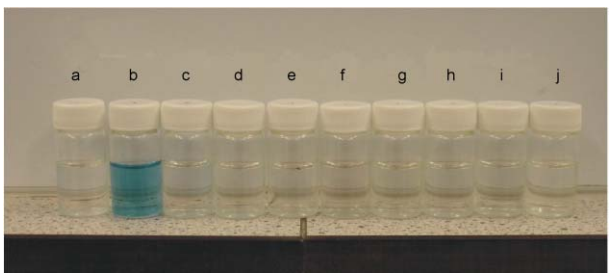

Fig. 7 Visible changes induced on solutions of catechol (2 mM) in acetonitrile by the addition of (a) no guest, (b) fluoride (blue), (c) chloride, (d) bromide, (e) iodide, (f) acetate, (g) dihydrogenphosphate, (h) hydrogensulfate, (i) nitrate, and (j) benzoate. All anions present as their tetrabutylammonium salts at concentrations of 20 mM.

NMR titrations between catechol and fluoride were performed and this gave rise to the titration profile shown in Fig. 8a. As can be seen, the titration curve does not fit to a 1 : 1 profile, with a significant distortion being observed. This titration profile is consistent with a two step process. Such a system has recently been proposed by Fabbrizzi and co-workers,[38] who demonstrated that

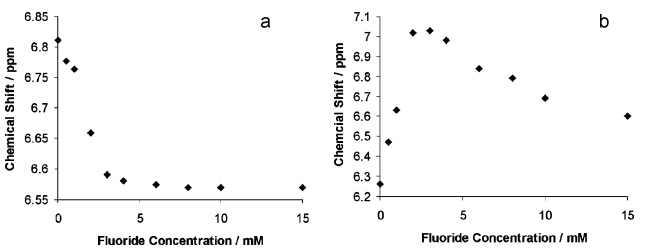

Fig. 8 ^{1}H NMR titration curves for the addition of tetrabutylammonium fluoride to: (a) catechol (**1**), (b) resorcinol (**2**) in CH_3CN solution.

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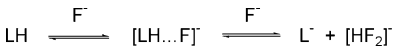
for neutral hydrogen bonding anion receptors, a hydrogen bonded complex can be formed with the first equivalent of anion, and that subsequently, the second equivalent of anion abstracts the HX fragment from the molecule to give $[HX_2]^-$ in solution (Scheme 1). Gale and co-workers previously reported a fluoride sensor which exhibited a colour change associated with deprotonation.[35a]



Scheme 1 Schematic of two-step process leading to receptor deprotonation proposed with basic fluoride anions.

We therefore propose that the basicity of the fluoride anion promotes such a process in this case. Indeed, the data for resorcinol titrated with fluoride (Fig. 8b) demonstrates this even more clearly, with a maximum downfield $\Delta\delta$ being observed after the addition of 1 equivalent of fluoride, and the NMR peak then shifting back upfield on the addition of further fluoride anion.

The intense blue colour induced by the fluoride anion, however, cannot simply be assigned to the deprotonation of catechol, by the basic anion, as the expected product catecholate anion is not coloured. On prolonged standing (*ca.* 1 h), some of the other basic anions (*i.e.*, acetate, benzoate, *etc.*) induced slow colour changes—although they did not turn blue, instead changing to pink and subsequently green (Fig. 9).

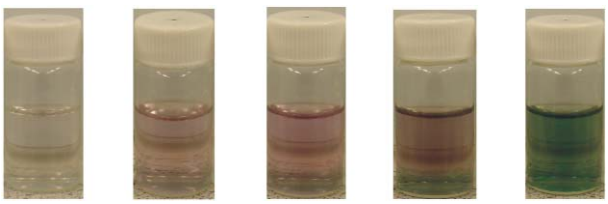


Fig. 9 Visible changes in colour from colourless to pink to green over time (increasing time from left to right) induced on a solution of catechol (2 mM) in acetonitrile by the addition of tetrabutylammonium acetate (20 mM). Total time = 1 h.

When the same qualitative experiment was performed using resorcinol with a variety of different anions, no colour changes were observed—even though resorcinol exhibits a NMR titration profile which is consistent with deprotonation taking place in the presence of fluoride (Fig. 8b).

Further experiments were therefore required to determine the origin of the colorimetric response of catechol induced by the fluoride anion, and the following conclusions were noted:

(i) the more basic the anion, the faster the colour change,

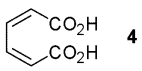
(ii) using more competitive solvents slows down the colour change,

(iii) using less anion made the colour change slower,

(iv) under an inert atmosphere the colour changes induced by basic anions were slower.

Observations (i) and (ii) would indicate that deprotonation of the catechol is a key step in the colorimetric response, and observation (iii) might indicate that deprotonation of the anion is the first stage in a multi-step process. Most importantly, observation (iv) indicates that atmospheric O_2 (or H_2O or CO_2) is probably playing a key role in the colorimetric response. It is also worth noting that the process still occurred in the dark and so it is unlikely that the colorimetric response is photoinitiated.

Mass spectrometry (MS) performed on the mixture of catechol and fluoride was very informative. Electrospray MS indicated the presence of a peak with *m*/*z* of 142 (refer to the ESI). Interestingly, this peak at *m*/*z* 142 corresponds to *cis*,*cis*-muconic acid (**4**, Fig. 10). This is a further oxidation product of *ortho*-quinone, and interestingly, has previously been observed in aqueous Cu^{2+} catalysed aerobic oxidations of catechol,[39] as well as in enzyme/microbially catalysed oxidative degradations of catechol.[40] It has also been noted previously that oxidation of catechols can, in addition to yelding *ortho*-quinone and *cis*,*cis*-muconic acid, give rise to a range of coloured acidic and polymeric byproducts.[41] We also observed a major peak at *m*/*z* 450, which can tentatively be assigned as an ester dimer formed from the combination of *cis*,*cis*-muconic acid and catechol ($C_{24}H_{18}O_9$). In contrast, mass spectrometry performed on a mixture of catechol and tetrabutylammonium acetate gave rise to a complex array of peaks, none of which could be definitively assigned.



4

Fig. 10 *cis*,*cis*-Muconic acid—a product of oxidative degradation of catechol—found from mixtures of catechol and tetrabutylammonium fluoride in acetonitrile *via* mass spectrometry.

We therefore propose that in acetonitrile solution, in the presence of basic anions, deprotonation of catechol occurs, and that subsequently, an oxidative degradation process takes place. This ultimately leads to oxidised catechol and coloured product(s)—the unambiguous identification of the product(s) repsonsible for the blue coloration is difficult,[40] although it has previously been proposed that polynuclear condensation products of quinone and semi-quinone fragments can arise.

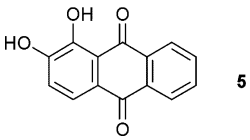
It is well-known that in water, catechol derivatives are more susceptible to oxidation in more basic conditions (*i.e.*, higher pH values).[33] Furthermore, it is known that metals can catalyse the oxidation process by assisting in deprotonation of the catechol (and binding it). We therefore propose that in aprotic media, basic anions such as fluoride can play a similar role to that played by metal ions in aqueous media, and that by binding and deprotonating the catechol motif, they are capable of catalysing its oxidative degradation by atmospheric oxygen. We can also state that it seems likely that in our system, the anion plays an active mechanistic role in this oxidative degradation pathway—this would explain why fluoride and carboxylate anions give rise to qualitatively different colorimetric responses (blue and pink/green respectively).

Resorcinol (**2**) is less sensitive to oxidation than catechol (**1**), and consequently, our proposal would also explain why resorcinol does not exhibit a colorimetric response even though it does undergo a deprotonation process as evidenced by NMR titration.

These results indicate that in solvents such as acetonitrile, catechol (**1**) has the potential to be a useful colorimetric sensor for basic anions. The reversible binding and deprotonation of the receptor is coupled to an irreversible oxidation process which ultimately gives rise to coloured products. Therefore the pK_a of the anion controls the rate of colorimetric response. This colorimetric response with fluoride anions was very reproducible and catechol exhibits good solution stability—further development of the sensor potential of catechol would focus on an investigation of

colorimetric response in the presence of complex mixtures of analytes.

It is worth noting that Miyaji and Sessler investigated commercially available hydrogen bonding systems (including some phenols) as anion sensors, and reported that alizarin (Fig. 11), which contains a catechol-type unit, was capable of qualitatively sensing anionic guests in apolar CH_2Cl_2 solution through a colour change.[18a] However, the mechanism of this response was not discussed.



5

Fig. 11 Structure of alizarin (**5**).

Conclusions

In summary, this paper reports that simple, commercially available bis-phenols, such as catechol (**1**), can give useful binding selectivities and reasonable binding affinities. Interestingly, for halide binding, these factors are controlled by the relative positions of the O–H groups on the aromatic ring, with catechol showing much greater selectivity for chloride than resorcinol—a consequence of a more effective arrangement of chelating hydrogen bond donors (Fig. 3).

Furthermore, we have demonstrated the ability of this class of compound to act as electrochemical sensors for anion binding. Tetrabutylammonium chloride causes a much greater response in redox properties than bromide or iodide salts. In particular, the addition of chloride leads to a significant perturbation of catechol electrochemistry as visualised *via* cyclic voltammetric methods (*i.e.*, oxidation to *ortho*-quinone).

We have demonstrated that nitrocatechol **3** exhibits stronger halide binding as a consequence of the electron withdrawing NO_2 group. Furthermore, this compound senses chloride anions *via* a change in its UV-Vis spectrum and interestingly, is still capable of sensing chloride anions in the presence of competitive solvents such as H_2O. We argue that this observation supports the recent biological X-ray structures which have demonstrated the crucial importance of O–H $\cdots$ anion hydrogen bond interactions in partly solvated biological superstructures such as enzyme interiors and membranes.

Finally, we report that simple catechol itself shows a selective and rapid colorimetric response on the addition of fluoride anions. This response can be assigned to a base induced deprotonation, followed by an oxidative degradation of catechol. This process mirrors to some extent the well-known metal catalysed decomposition of catechol in aqueous solutions. Other basic anions such as carboxylates caused a qualitatively similar, albeit slower, colorimetric response, with the rate of response appearing to correlate with the basicity of the added anion.

Taken in combination, these results explore in detail for the first time the behaviour of bis-phenols with a variety of anions, and demonstrate their potential to act as both anion receptors and sensors *via* a variety of different mechanisms. Our observations provide us with optimism that by constructing more complex anion receptors based on phenolic building blocks, we may be able to access receptors, sensors and perhaps even chloride transport agents with biologically useful anion binding affinities and selectivities.

Experimental

All bis-phenol compounds are commercially available and were used without further purification. All tetrabutylammonium salts were stored in a desiccator.

NMR titration method

NMR titrations were performed in undried CD_3CN solution[24] with concentration of host bis-phenol of 2 mM. A solution containing the anionic guest (as its tetrabutylammonium salt) at a concentration of 50 mM, and phenol at a concentration of 2 mM (in order to ensure a constant concentration of bis-phenol) was made up in the same solvent. This solution was added in aliquots to the host solution and NMR spectra recorded. Data were analysed by non-linear least squares fitting methods.

Electrochemical titration method

Electrochemical titrations were performed in analytical grade CH_3CN which had been dried over molecular sieves with tetrabutylammonium tetrafluoroborate present as base electrolyte at a concentration of 0.2 M. The concentration of catechol was 1 mM. A solution containing the anion (as its tetrabutyl ammonium salt) at a concentration of 110 mM and electrolyte (0.2 M) and catechol (1 mM) was made up in the same solvent (ensuring constant concentration of electrolyte and catechol). This solution was added in aliquots to the host solution and cyclic voltammograms recorded. Electrochemistry was performed out on an EG & G Princeton Applied Research potentiostat/galvanostat model 273 with a standard three electrode configuration, consisting of platinum working and counter electrodes and an Ag/AgCl reference electrode.

UV-visible titration method

UV-vis titrations were performed in analytical grade CH_3CN solution (or 99.5 : 0.5, CH_3CN–H_2O) using a concentration of host bis-phenol of 0.2 mM. A solution containing the anion (as its tetrabutylammonium salt) at a concentration of 15 mM, and phenol at a concentration of 0.2 mM (in order to ensure a constant concentration of bis-phenol) was made up in the same solvent. This solution was added in aliquots to the host solution and UV-Vis spectra recorded. Data were analysed by non-linear least squares fitting methods on the intensity at 330 nm.

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