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Ortho-Substituted Catechol Derivatives: The Effect of Intramolecular Hydrogen-Bonding Pathways on Chloride Anion Recognition

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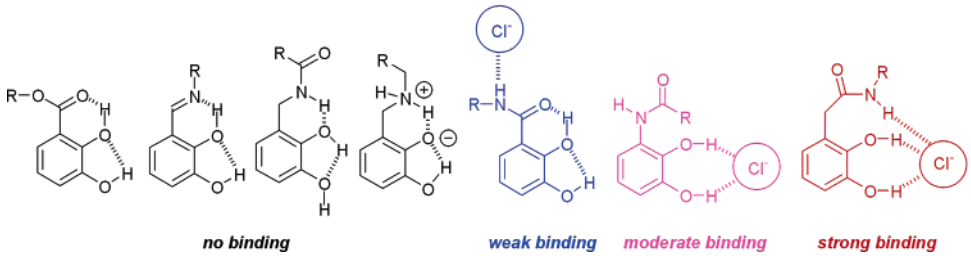

This paper reports a series of chloride anion receptors containing two catechol head groups connected through their ortho-positions via a spacer chain. The linking group chosen to attach the spacer chain to the catechol units has a major impact on the anion-binding potential of the receptor. Linking groups that are capable of forming stable six-membered intramolecular hydrogen-bonded rings with the catechol O−H groups significantly inhibit the ability of the catechol units to hydrogen bond to chloride anions. However, where the linking groups are only capable of forming five- or seven-membered intramolecular hydrogen-bonded rings, then anion binding via hydrogen bonding through the catechol O−H groups becomes a possibility. This process is solvent dependent; the presence of competitive solvent (e.g., DMSO-d_6) disrupts the intramolecular hydrogen-bonding pattern and enhances anion binding relative to simple unfunctionalized catechol. The most effective receptor is that in which the hydrogen-bonding linker (−CH_2CONH−) is most distant from the catechol units and can only form a seven-membered intramolecular hydrogen-bonded ring. In this case, the receptor, which contains two catechol units, is a more effective chloride anion binder than simple unfunctionalized catechol, demonstrating that the two head groups, in combination with the N−H groups in the linker, act cooperatively and enhance the degree of anion binding. In summary, this paper provides insight into the hydrogen-bonding patterns in ortho-functionalized catechols and the impact these have on the potential of the catechol O−H groups to hydrogen bond to a chloride anion.

Introduction

Catechol derivatives have been the subject of intense interest over recent years, in no small measure due to their ability to act as chelating ligands, in analogy with naturally occurring siderophores, such as enterobactin, which use catechols as ligating groups for metals.[1] This bio-inspiration has led many research groups to synthesize synthetic analogues of siderophore structures and explore their potential as ligands for metal cations.[2] Over the past 10 years, there has been significant interest in linked bis-catechol-type ligands as metal binders.[3] Depending on the nature of the linking group connecting the catechol units together, such systems can either use both catechol

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groups to bind a single metal or each catechol can bind a separate metal, with multiple ligand strands assembling in a helical manner around the metals.

Recently, Duhme-Klair and co-workers have demonstrated that synthetic catechol derivatives also have potential in anion binding, in particular recognizing molybdate anions using a binding mode in which the deprotonated catecholate binds directly to the molybdenum center;[4] a similar binding mode has also been employed for the recognition of boric acids.[5] In contrast, we have been exploiting the ability of protonated catechol to bind anions, in particular the chloride anion,[6] as a consequence of hydrogen bonds between the O−H groups and the chloride anion. This binding mode of catechol is also biologically relevant, as O−H···anion interactions are observed in the crystal structure of the ClC chloride transport channel, with the amino acid side chains of serine and tyrosine being involved.[7]

Anion binding is of intense current interest,[8] in particular the ability of receptor species to act as transport agents for anions across synthetic membranes.[9] The importance of defective chloride transport channels in the pathology of cystic fibrosis means this research has biomedical relevance.[10] Given the biomimetic importance of O−H···anion interactions, we find it particularly surprising that there have been only limited systematic investigations of this kind of anion-binding interaction, whereas amides and ureas have been extensively studied in this way.[11] Indeed, only a few studies over the past 20 years have reported the use of O−H groups as a key component in achieving anion binding. Crystal structures from the 1980s showed that phenols and catechols crystallized in the presence of tetrabutylammonium halides had hydrogen-bond interactions between the O−H groups and the halide anion.[12] However, it was only in the early 1990s that solution studies began to be performed. The groups of Aoyama and Koga reported that phenols could help bind anions, which were predominantly bound as part of an ion pair with a pyridinium cation.[13] A number of other groups subsequently also reported the ability of OH···anion interactions to supplement an existing anion-binding process. Davis and co-workers made use of steroid cryptands, in which steroidal O−H groups supplemented the anion binding afforded by amide N−H groups (in nonpolar solvents, e.g., $CDCl_3$).[14] Meanwhile, Kondo and co-workers used alcohols to augment the binding strength of simple sulfonamide-based anion receptors.[15] It has also been shown that phenolic groups on calixarenes can interact with anions[16] and that simple phenolic compounds can be employed as anion sensors.[17] In a recent study, Scott and Libra demonstrated that metal salens functionalized with phenolic groups showed effective anion binding via hydrogen-bond interactions.[18] Furthermore, Maitra and co-workers have recently demonstrated that macrocylic steroids can bind anions in apolar media using O−H groups, supplemented by C−H···anion interactions.[19]

In 2003, we first reported that catechol was a surprisingly effective chloride binder,[6a] and, in 2006, we went on to investigate this process in more detail and demonstrate that it could optically sense fluoride anions.[6b] We therefore became interested in combining multiple catechol units to try and enhance the anion-binding event. We reasoned that this approach would be analogous to the development of siderophore ligands for metal cations, only in the case of siderophores, the active ligand contains deprotonated catecholates, whereas in our case, anion binding would be achieved using the protonated catechol form of the ligand to ultimately yield "siderophores" for anions. In this paper, we report the synthesis of a range of catechol derivatives and uncover the factors that control their anion-binding potential. We report that these receptors, which bind anions via hydrogen bonding, are remarkably sensitive to the internal hydrogen-bonding possibilities of the receptor framework.

Results and Discussion

Strategy. We aimed to synthesize a library of potential catechol-based anion receptors with different linking groups in

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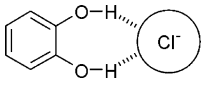


FIGURE 1. Chelate binding mode between catechol and chloride anions leads to effective anion binding.

TABLE 1. Summary of Binding Constants (K, mol^{-1} dm^3, ±10%) Determined by Fitting NMR Titration Data to a 1:1 Model for Receptors with Chloride Anions in Different Solvent Systems[a]

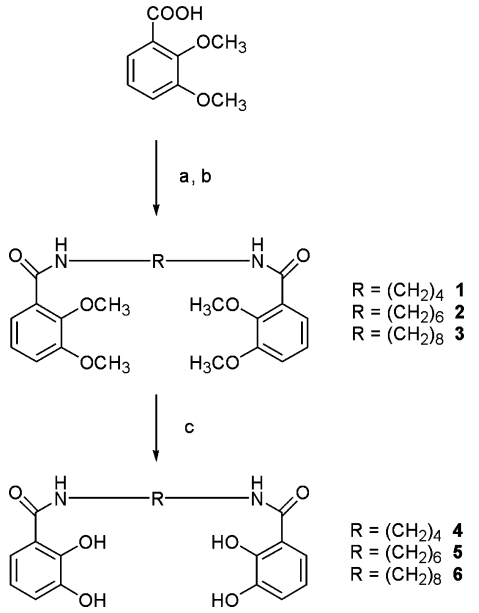
receptor	type of linkage	K (mol^{-1} dm^3) CD_3CN	K (mol^{-1} dm^3) CD_3CN:DMSO-d_6 (9:1)
catechol	none	**1575**	100
4	amide (−CONH−)	−	25
5	amide (−CONH−)	−	25
6	amide (−CONH−)	−	25
11	ester (−COO−)	−	<5
12	imine (−C═N−)	5[b]	−
14	amide (−CH_2NHCO−)	−	<5
18	amine (−CH_2NH−)	<5	−
21	amide (−NHCO−)	270	110
22	amide (−NHCO−)	185	115
24	amide (−CH_2CONH−)	−	**235**

[a] The symbol "−" represents "not measured", usually due to lack of solubility. Bold amounts represent the optimum binding in a given solvent. [b] Binding measured in $CDCl_3$ due to insolubility in CD_3CN.

the ortho-position and investigate their ability to bind chloride anions in apolar media. We hoped that these studies would allow us to determine the effect of the linking group on the ability of the catechol head groups to bind a simple anionic target, and we also hoped to improve on the ability of simple unfunctionalized catechol to bind anions. For purposes of comparison, the ability of simple catechol to bind chloride anions was initially determined by NMR titration. NMR titrations were the method of choice in this paper as they enable the effects of hydrogen bonding in anion binding to be clearly visualized; furthermore, other techniques, such as UV−vis titrations, only led to small changes in intensity. We have previously reported the binding affinity of catechol for chloride anions in CD_3CN solution, where the K_a value was relatively high, 1575 mol^{-1} dm^3 (Figure 1).[6a] For this new study, we also determined the binding strength in CD_3CN:DMSO-d_6 (9:1). Fitting the data to a 1:1 binding model gave a binding constant, K_a, of 100 mol^{-1} dm^3 (Table 1). This expected drop in binding strength is a consequence of the higher polarity of DMSO-d_6, and its greater ability to form competitive intermolecular hydrogen bonds with the O−H protons. We anticipated that on comparison with simple catechol, our new linked bis-catechol receptors, although flexible, should exhibit an enhanced degree of anion-binding potential due to the presence of multiple hydrogen-bonding catechol units capable of cooperating in anion recognition.

Catechols Linked via Amide (−CONH−) Groups. Our initial target receptors each contained two ortho-substituted catechol units connected with flexible spacer groups via amide (−CONH−) linking groups. The synthesis of three compounds with spacer chains of different lengths was achieved via methyl ether protected intermediates. 2,3-Dimethoxybenzoic acid was converted to the acid chloride with neat thionyl chloride and then reacted with the appropriate diaminoalkane in the presence of triethylamine to give protected compounds **1**−**3** in acceptable yields. Methyl ethers **1**−**3** were subsequently deprotected using BBr_3 in dry CH_2Cl_2 to provide receptors **4**−**6** (Scheme 1). Purification was achieved using washing/recrystallization protocols and yielded the target materials in low, but acceptable yields. It should be noted that compounds **4** and **5** have

SCHEME 1. Synthesis of Amide (CONH)-Linked Receptors 4−6[a]



[a] (a) $SOCl_2$; (b) H_2N−R−NH_2 Et_3N, CH_2Cl_2, 25% (**1**), 43% (**2**), 64% (**3**); (c) BBr_3, CH_2Cl_2, 14% (**4**), 21% (**5**), 27% (**6**).

previously been synthesized and investigated as metal sequestration agents by Raymond and co-workers,[20] while **4**−**6** have been investigated to the same end by Bhargava et al.[21]

A crystal of compound **6** was grown from methanol (Figure 2). It is worth noting that the two catechol head groups are involved in intramolecular hydrogen-bonding networks with the amide group of the linker unit (C═O···H−O···H−O). The C═O group of the amide forms a hydrogen bond with the ortho O−H group of the catechol, while the meta O−H group forms a hydrogen-bond interaction with the oxygen atom in the ortho location (Figure 3). This type of hydrogen-bonding pattern is well-known for amide-functionalized catechol units,[22] with the intramolecular C═O···H−O hydrogen bond constituting a stable six-membered ring. There is also solution-phase evidence for the existence of this intramolecular hydrogen-bonding pattern. Two discrete O−H resonances were observed in the ^{1}H NMR spectrum of compound **6**, and in DMSO-d_6 solution, at ca. 12.9 and 9.2 ppm. The strongly downfield shifted O−H proton at 12.9 ppm indicates a strongly deshielded environment, consistent with the presence of a very stable intramolecular hydrogen bond in solution.

In unfunctionalized catechol, one of the O−H groups forms an O−H···O intramolecular hydrogen bond with the other oxygen. This leaves the other hydrogen atom available, and crystallography has previously shown that the presence of a chloride anion is sufficient to break the intramolecular O−H···O hydrogen bond, and the two O−H groups then hydrogen bond to the chloride anion in a chelate manner.[12]

We investigated the ability of compounds **4**−**6** to bind tetrabutylammonium chloride. The studies were performed in

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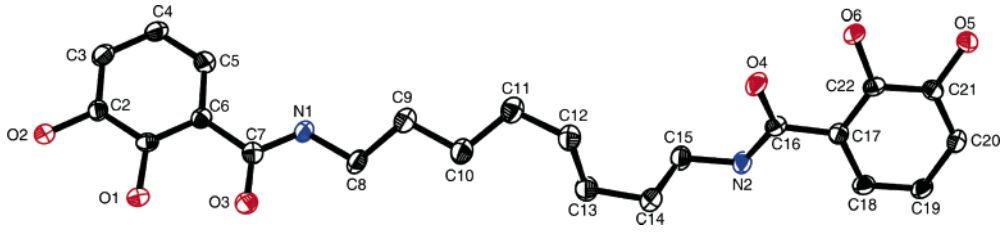


FIGURE 2. Crystal structure of compound **6** grown from methanol solution, illustrating the intramolecular C═O···H−O···H−O hydrogen-bond pathway.

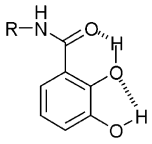


FIGURE 3. Intramolecular hydrogen-bond pathway proposed for compounds **4**−**6**, which inactivates the ability of the catechol O−H groups to hydrogen bond with anionic guests.

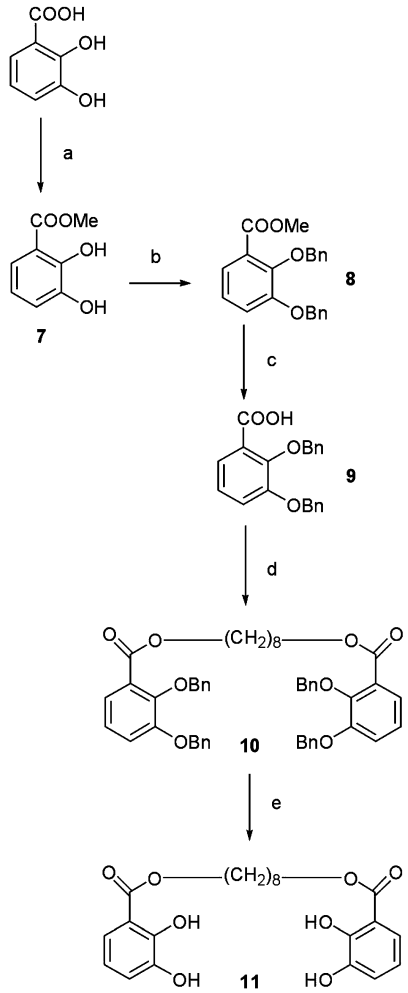
CD_3CN:DMSO-d_6 (9:1) due to lack of solubility in 100% CD_3-CN. Disappointingly, when the data were fitted to a 1:1 binding model, these receptors exhibited weaker chloride binding than simple unfunctionalized catechol (Table 1). Furthermore, there was no noticeable effect of the spacer chain on the binding affinity for chloride; it might have been expected that changing the length of this unit would modify the strength or stoichiometry of halide anion binding.[23]

We therefore postulate that in receptors **4**−**6** the presence of the amide unit in the linking group prevents initial binding of either catechol O−H group to the anion and hence switches off binding. We argue that the small amount of residual binding observed for compounds **4**−**6** (K_a ca. 25 mol^{-1} dm^3) can be attributed to interaction of the amide N−H groups with the anion, rather than the catechol O−H groups. In support of this hypothesis, it is worth noting that the NH resonance was the most perturbed peak during the NMR titration. Notably, the induced shift of the N−H peak (on addition of 5 equiv of tetrabutylammonium chloride) was significantly greater for the compounds with shorter spacer chains (**4**, $\Delta\delta = 0.332$ ppm; **5**, $\Delta\delta = 0.276$ ppm; **6**, $\Delta\delta = 0.208$ ppm). This indicates that the two amide (N−H) protons may act cooperatively in binding the chloride anion.

Catechols Linked via Ester (−COO−) Groups. To explore the hypothesis proposed above, we decided to synthesize an ester-linked receptor (**11**) analogous to amide-linked compound **6**. We reasoned that the C═O group should still form the intramolecular hydrogen bond, which inactivates the catechol O−H groups, but in this case there would be no N−H group to provide residual anion binding.

For the synthesis of an ester-linked receptor (Scheme 2), we could not employ a methyl ether protection−deprotection scheme analogous to that used to synthesize amide-linked **4**−**6**, as we were concerned about potential ester hydrolysis during the final BBr_3-mediated deprotection step. As a consequence, we made use of a benzyl ether protecting group strategy. 2,3-Dihydroxybenzoic acid was protected as a methyl ester (**7**) using thionyl chloride in methanol.[24] The hydroxy groups were then

SCHEME 2. Synthesis of Ester-Linked Compound 11[a]



[a] (a) $SOCl_2$, MeOH, 50%; (b) BnBr, NaI, K_2CO_3, DMF, 81%; (c) NaOH, MeOH, 1,4-dioxane, 50%; (d) $HO(CH_2)_8OH$, DCC, DMAP, CH_2Cl_2, 47%; (e) H_2, 10% Pd−C, EtOH, 71%.

benzylated with benzylbromide in dry DMF, using K_2CO_3 as base and NaI to enhance reactivity of the bromide, providing compound **8** in excellent yield.[24] Hydrolysis of the methyl ester to give carboxylic acid **9** was achieved using standard basic conditions and proceeded in acceptable yield.[24] Ester coupling to yield compound **10** was achieved using dicyclohexylcarbodiimide (DCC) and a catalytic amount of dimethylaminopyridine (DMAP). Finally, the benzyl ether protecting groups were removed by hydrogenation with 10% Pd/C to provide ester-linked target compound **11**.

On investigating the chloride binding ability of this compound via the NMR titration method, there were no significant shifts in the NMR spectrum, and the binding constant was therefore

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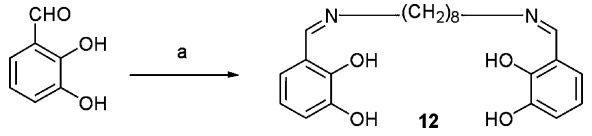
SCHEME 3. Synthesis of Imine (C═N)-Linked Compound 12[a]



[a] (a) $H_2N(CH_2)_8NH_2$, MeOH, 90%.

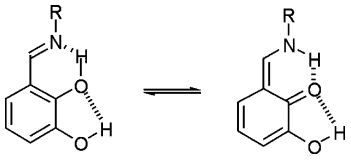


FIGURE 4. Proposed intramolecular hydrogen-bond pathway in imine-linked receptor **12**.

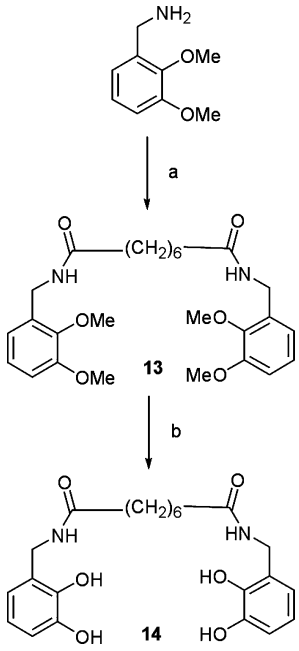
considered to be negligible (Table 1). This was in agreement with our hypothesis that the intramolecular C═O···H−O···H−O hydrogen-bond pathway completely inactivates the anion-binding potential of both catechol O−H groups and supports the argument that the only reason compounds **4**−**6** show some weak affinity for chloride is due to the residual affinity of the N−H protons for the anion.

Catechols Linked via Imine Groups. Imine-linked compound **12** was synthesized in excellent yield by the simple condensation of 2,3-dihydroxybenzaldehyde and 1,8-diaminooctane (Scheme 3). Related catechol imines have previously been reported by Albrecht and co-workers with regard to their metal binding ability.[25] This compound would be expected to form a C═N···H−O intramolecular hydrogen-bonded six-membered ring (Figure 4). Indeed, it has be shown that certain ortho-substituted catechol imines have such strong intramolecular hydrogen bonds that proton exchange and tautomerization can occur.[25,26]

As may have been predicted based on the hypothesis above, the chloride affinity of this receptor was very low. Solubility limited the chloride binding studies to chloroform, but even in this noncompetitive solvent, the observed shifts were very small (<0.01 ppm), and a binding constant could not be determined (Table 1). Once again, this illustrates the role the ortho-substituent plays in deactivating the hydrogen-bonding potential of the catechol O−H groups, making them unavailable for chloride binding.

Catechols Linked via Amide and Amine (−CH_2NHCO− and −CH_2NH−) Groups. We then decided to synthesize compounds in which the hydrogen-bond (C═X) acceptor present in compounds **4**−**6**, **11**, and **12** was replaced with a potential hydrogen-bond donor group (N−H). We therefore targeted substituted catechols in which a CH_2NH group was located in the ortho position. Albrecht and co-workers have recently employed this type of −CH_2NHCO− linkage in the synthesis of various catechol-derived metal-binding ligands.[27] First, 2,3-dimethoxyphenylaniline was reacted with bis-acid chloride to yield compound **13**, which on BBr_3-mediated deprotection gave rise to target amide-linked compound **14** (Scheme 4).

SCHEME 4. Synthesis of Amide (−CH_2NHCO−)-Linked Receptor 14[a]



[a] (a) $ClOC(CH_2)_6COCl$, Et_3N, CH_2Cl_2, 58%; (b) BBr_3, CH_2Cl_2, 32%.

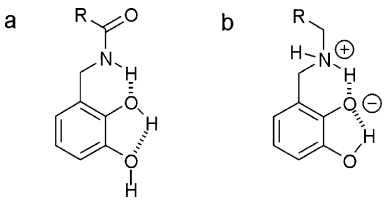


FIGURE 5. Proposed intramolecular hydrogen bonds in (a) amide-linked **14** and (b) amine-linked **18**.

Compound **14** has an N−H group in an appropriate position to form an N−H···O−H hydrogen bond. This has not previously been reported by Albrecht for the neutral catechols with this type of ortho-linkage, although it is known that the N−H group interacts with the deprotonated catechol in this manner.[27] This pattern of intramolecular hydrogen bonding should leave a single O−H group of the catechol uninvolved in the hydrogen-bonding network and hence available for binding to chloride (Figure 5a). Our NMR evidence supported this proposal, with one of the O−H protons being more sensitive to changes in solvent than the other. We reasoned initial chloride binding might then encourage the intramolecular hydrogen-bond network to break and yield high affinity chelate-mode anion binding. However, when the binding of compound **14** with chloride was investigated in CD_3CN:DMSO-d_6 (9:1), the shifts in NMR peaks were negligible, and a binding constant could not be determined. It seems likely that, once again, the six-membered intramolecular hydrogen-bonded ring is too stable and cannot be disrupted by the presence of chloride anions.

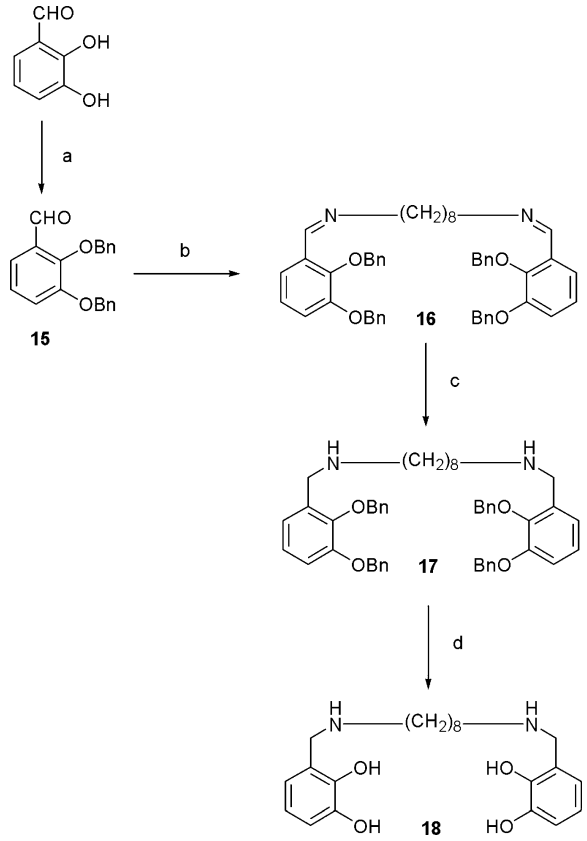
To synthesize amine-linked compound **18** (Scheme 5), attempts were initially were made to reduce imine **12**; however, decomposition was observed during the reduction step. We next attempted a synthetic strategy that made use of methyl-ether

(25) Albrecht, M.; Janser, I.; Fröhlich, R. *Chem. Commun.* **2005**, 157−165 and references therein.

(26) Pizzala, H.; Carles, M.; Stone, W. E. E.; Thevand, A. *J. Chem. Soc., Perkin Trans. 2* **2000**, 935−939 and references therein.

(27) (a) Albrecht, M.; Napp, M.; Schneider, M.; Weis, P.; Fröhlich, R. *Chem.-Eur. J.* **2001**, *7*, 3966−3975. (b) Albrecht, M.; Zauner, J.; Eisele, T.; Weis, P. *Synthesis* **2003**, 1105−1111.

SCHEME 5. Synthesis of Amine (−CH_2NH−)-Linked Receptor 18[a]



[a] (a) BnBr, K_2CO_3, NaI, DMF, 74%; (b) $H_2N(CH_2)_8NH_2$, MeOH, 90%; (c) $NaBH_4$, MeOH, 35%; (d) H_2, 10% Pd/C, EtOH, 80%.

protecting groups. However, the final BBr_3-mediated deprotection yielded the target amine (**18**) in protonated form; this could not be deprotonated without also deprotonating the catechol O−H groups. We therefore synthesized the amine-linked compound using an alternative approach in which the catechol OH groups were protected as benzyl ethers. 2,3-Dihydroxybenzaldehyde was benzylated using benzyl bromide in dry DMF with K_2CO_3 and NaI to give compound **15** in excellent yield.[28] This compound was then converted to imine **16** in 90% yield by reaction with 1,8-diaminooctane in methanol. Reduction of this imine with $NaBH_4$ over a period of 2 h gave compound **17** in moderate yield. Finally, debenzylation using H_2 and 10% Pd/C in ethanol yielded target amine **18**. However, it should be noted that this compound had a relatively limited shelf life (ca. 1 week).

On titration with tetrabutylammonium chloride, compound **18** also exhibited very small NMR shifts, and once again a reliable binding constant could not be determined. For this compound, the amine N−H group can act either as a hydrogen-bond donor (through the H atom) or as a hydrogen-bond acceptor (through the N atom). The lack of anion binding is consistent with a model in which the nitrogen accepts a hydrogen bond from the ortho catechol O−H group. Indeed, intramolecular proton transfer can then occur, to yield a protonated amine and a deprotonated catechol unit (Figure 5b). Experimental support for this proposal comes from the observation that in the ^{1}H NMR spectra of methyl-ether protected compound **17** the Ar−CH_2−NH protons appear at 3.78 ppm, while in compound **18**, with free O−H groups, this resonance has shifted downfield to 3.95 ppm. Crystallographic evidence for the interaction of catechol O−H groups with basic nitrogens has also previously been reported.[29] This proposal is also supported by the observed instability of compound **18**, as deprotonated catechols are known to be oxidized more readily than their protonated analogues.[30] Such an intramolecular hydrogen-bonded system (Figure 5b) has no free O−H protons available for hydrogen bonding to chloride anions.

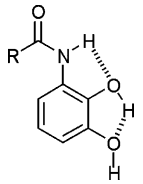


FIGURE 6. Proposed hydrogen-bonding pattern in receptors **21** and **22** incorporating a five-membered intramolecular hydrogen-bonded ring.

Catechols Linked via Amide (−NHCO−) Groups. We then targeted the synthesis of amide-linked catechols in which the amide functional group was directly attached to the catechol ring, but inverted (i.e., NHCO rather than CONH). In this system, only five-membered intramolecular hydrogen-bonded rings would be expected, rather than six-membered rings, and we were interested in the impact of this on the anion-binding process (Figure 6). References reporting the synthesis of catechols with this type of ortho-linkage are surprisingly limited.[31] Amide (−NHCO−)-linked compounds **19** and **20** were formed by simply reacting the appropriate bis-acid chloride with 2,3-dimethoxyaniline in the presence of Et_3N, using CH_2Cl_2 as solvent. Boron tribromide-mediated deprotection of **19** and **20** gave rise to linked-catechol target compounds **21** and **22** (Scheme 6).

It was noted that in the ^{1}H NMR spectrum of compound **21**, the N−H (amide) peaks appeared downfield of their expected position (ca. 9.5 ppm for compound **21** in DMSO-d_6 as compared to 8.8 ppm for compound **6** in the same solvent). This is consistent with the amide N−H group of compound **21** being involved in an intramolecular N−H···O−H hydrogen bond, forming a five-membered ring (Figure 6), although it should be noted the N−H group is also now directly attached to the aromatic ring. In this hydrogen-bond pattern, the O−H group in the ortho position would form a hydrogen bond with the O−H group in the meta position. However, the proton of the meta O−H group would not be involved in the hydrogen-bond pathway.

This proposal was further supported by measuring the ^{1}H NMR spectra of compound **22** in different solvents (Figure 7). On changing the solvent from CD_3CN to CD_3CN:DMSO-d_6 (9:1), one of the O−H protons (proton 2) shifted ca. 1.7 ppm downfield (appearing from underneath an aromatic signal), while the other O−H proton (proton 1) only moved about 0.2 ppm, and in this case was shifted upfield. Proton 2 shifts 1.7 ppm

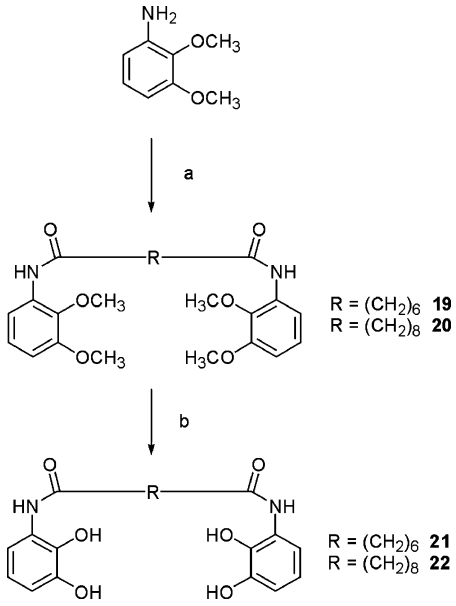
(28) Vériot, G.; Dutasta, J.-P.; Matouzenko, G.; Collet, A. *Tetrahedron* **1995**, *51*, 389−400.

(29) Bazzicalupi, C.; Bencini, A.; Bianchi, A.; Fusi, V.; Giorgi, C.; Messori, L.; Migliorini, M.; Paoletti, P.; Valtancoli, B. *J. Chem. Soc., Dalton Trans.* **1998**, 359−367.

(30) Cornard, J.-P.; Rasmiwetti Merlin, J.-C. *Chem. Phys.* **2005**, *309*, 239−249.

(31) For an example, see: Whiteley, C. G. *Bioorg. Med. Chem.* **2002**, *10*, 1221−1227.

SCHEME 6. Synthesis of Amide (−NHCO−)-Linked Receptors 21 and 22[a]



[a] (a) $ClOC(CH_2)_nCOCl$, Et_3N, CH_2Cl_2, 71% (**19**), 33% (**20**); (b) BBr_3, CH_2Cl_2, 40% (**21**), 35% (**22**).

downfield because on the addition of 10% DMSO, an intermolecular hydrogen bond can be formed to this solvent-exposed proton. Proton 1 shifts less dramatically because this proton is already in an intramolecular hydrogen-bonded environment. We propose that the small upfield shift is observed because this intramolecular hydrogen-bond pattern is disrupted by the presence of DMSO.

Compounds **21** and **22** were then titrated with tetrabutylammonium chloride in CD_3CN:DMSO-d_6 (9:1), and significant shifts were observed in the ^1H NMR spectra (Figure 8). The N−H proton exhibited a large downfield shift, followed by a small upfield shift (Figure 8A), while the aromatic protons showed a gradual, large downfield shift (Figure 8B). The O−H protons were broadened during the titration and could not be followed directly; however, the large shift in the aromatic proton suggests the O−H groups are directly involved in binding the chloride anion.

The differences in titration curve shape for different protons indicate that the binding process cannot be a simple 1:1 binding event. However, Job plot methods indicated that the aromatic protons could be fitted to a 1:1 binding model (Figure 9), and we therefore calculated apparent 1:1 binding constants using the titration profiles for these aromatic protons (Table 1). This does not explain the shape of the binding curve for the N−H proton shown in Figure 8A (for further discussion, see below). The data for compound **21** could be handled in exactly the same way as those for compound **22**.

We performed binding experiments in both CD_3CN and CD_3-CN:DMSO-d_6 (9:1). Interestingly, both receptors are slightly more effective than unfunctionalized catechol in CD_3CN:DMSO-d_6 (9:1), but much less effective in CD_3CN. When the solvent becomes more competitive (i.e., addition of DMSO), this will disrupt the intramolecular hydrogen-bonded pattern. Therefore, we propose that, in CD_3CN:DMSO-d_6 (9:1), both catechol O−H groups can bind to anions, and the strength and mode of binding is analogous to that of catechol itself. In acetonitrile, however, the intramolecular hydrogen-bond patterns of **21** and **22** remain intact, and therefore each catechol group can only employ the one "free" O−H group (proton 2) to

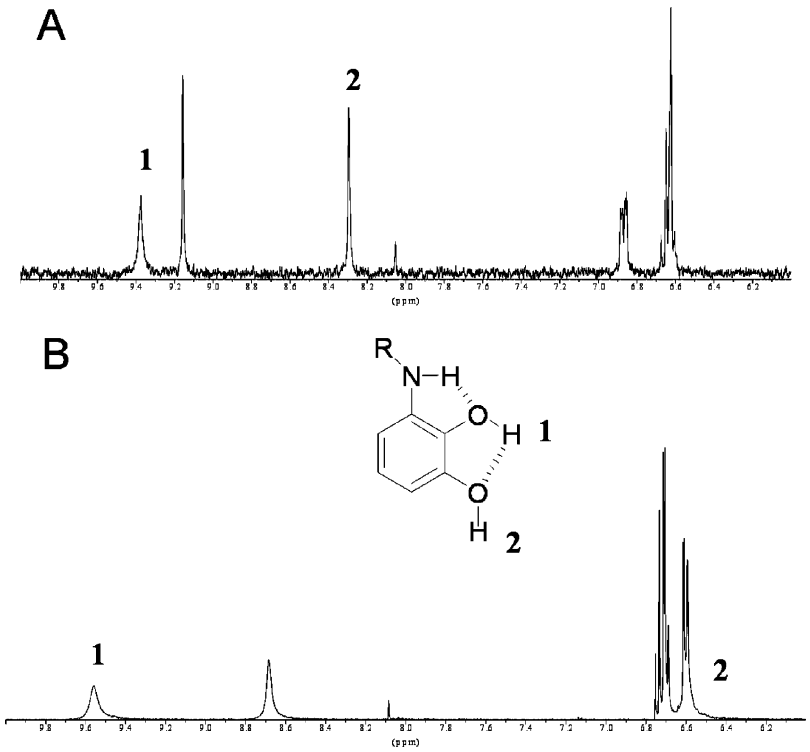


FIGURE 7. NMR spectra of compound **22** measured in (A) CD_3CN:DMSO-d_6 (9:1), and (B) CD_3CN. Note the large solvent-dependent response of proton **2**.

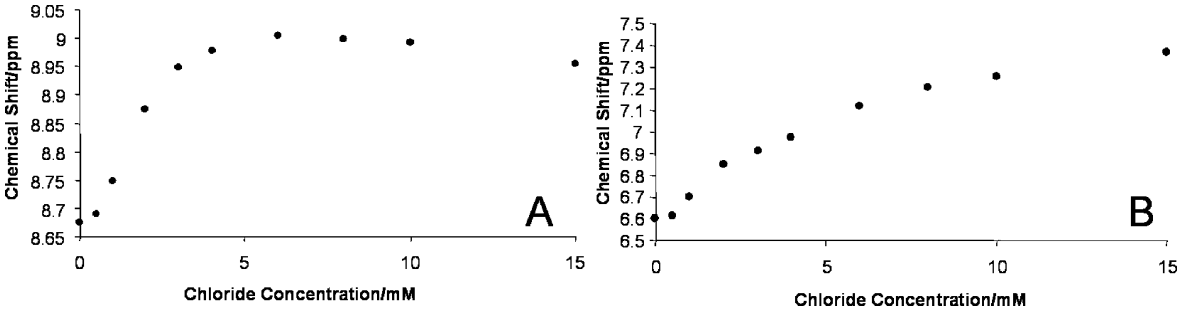


FIGURE 8. NMR titration profiles for the addition of tetrabutylammonium chloride to compound **22** in CD_3CN:DMSO-d_6 (9:1): (A) N−H proton, and (B) Ar−H proton.

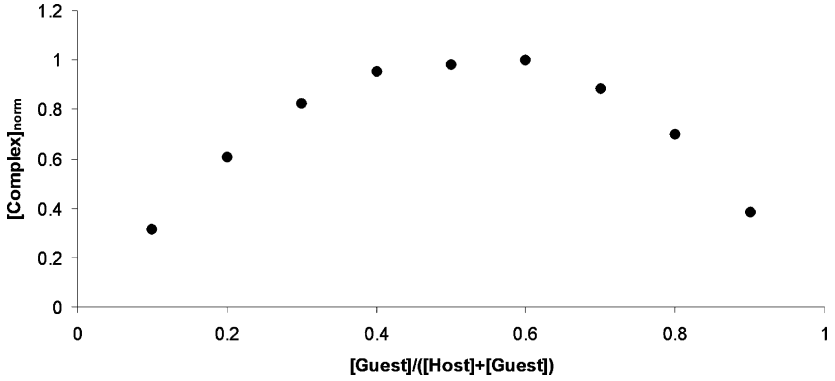


FIGURE 9. Job plot analysis for the Ar−H proton of compound **22** on the addition of tetrabutylammonium chloride in CD_3CN:DMSO-d_6 (9:1), indicating 1:1 stoichiometry is a reasonable assumption when fitting this proton.

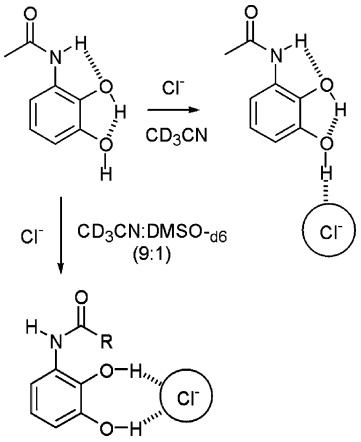


FIGURE 10. Proposed chloride binding modes for compounds **21** and **22** in different solvents.

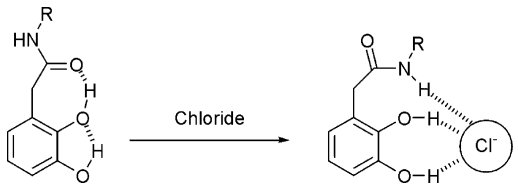
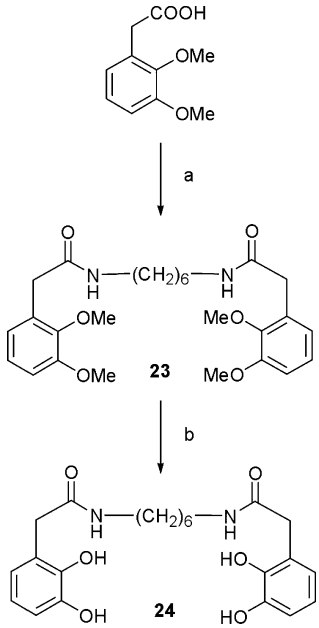


FIGURE 11. Proposed intramolecular seven-membered hydrogen-bonded ring in compound **24**.

SCHEME 7. Synthesis of Amide (−CH_2CONH−)-Linked Receptor 24[a]



[a] (a) $H_2N(CH_2)_6NH_2$, DCC, HOBt, Et_3N, CH_2Cl_2, 15%; (b) BBr_3, CH_2Cl_2, 20%.

hydrogen bond with the chloride anion; therefore, the binding is weaker (Figure 10).

We previously reported that in CD_3CN, simple phenols had binding constants typically ranging from 50 to 100 mol^{-1} dm^3.[6a] It is worth noting that in CD_3CN, both compounds **21** and **22** have higher binding constants than this, suggesting that the two catechol head groups may act cooperatively. Furthermore, compound **21**, with the shorter spacer chain, shows higher affinity chloride anion binding than compound **22**, presumably because the "free" OH groups on each of the two head groups

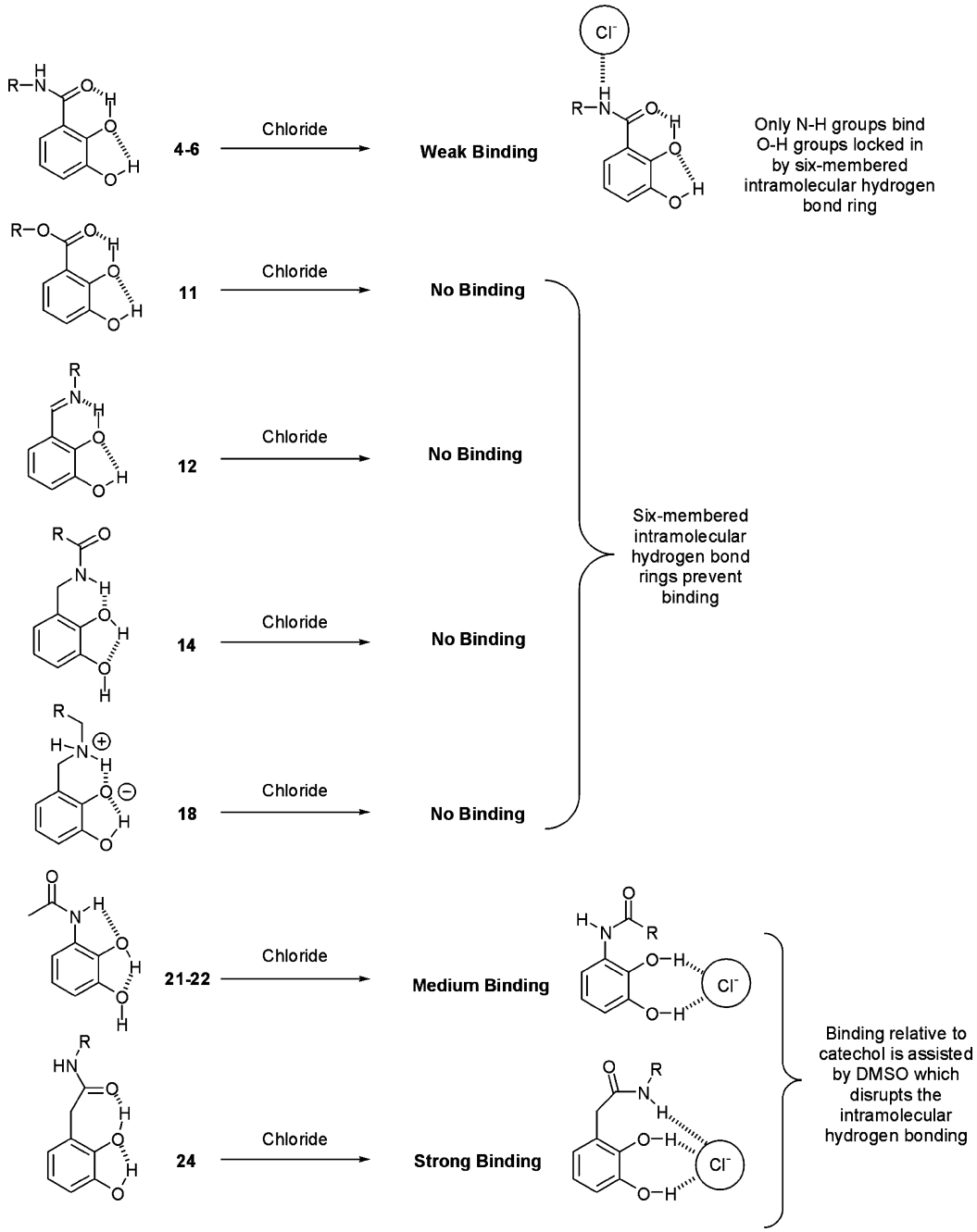


FIGURE 12. Summary of potential intramolecular hydrogen-bonding patterns and consequent chloride recognition pathways.

are closer together and are more able to bind cooperatively to the anionic guest.

The unusual titration curve shape observed for the N−H protons in compounds **21** and **22** (Figure 7A) could also be explained by this proposal. Initially, the N−H proton is involved in the intramolecular hydrogen-bond network. We propose that the addition of chloride anions has several different effects: (i) the anion binds to the O−H groups, which will also perturb the N−H resonance, (ii) the intramolecular hydrogen-bond pattern is disrupted, and (iii) residual chloride anions may also be able to interact with the "free" N−H proton (as in compounds **4**−**6**). This combination of factors will lead to more complex lineshapes, such as that observed in Figure 7A.

It is worth noting that binding can be switched on for −NHCO-linked receptors **21** and **22**, but could not be activated for analogous −CONH-linked receptors **4**−**6**. We propose this is because the five-membered intramolecular ring in receptors **21** and **22** is more labile and can therefore be disrupted by DMSO and chloride anions, unlike the six-membered intramolecular ring in receptors **4**−**6**.

Catechols Linked via Amide (−CH_2CONH−) Groups. We also targeted the synthesis of another receptor in which a CH_2 group was incorporated between the catechol ring and an amide (CONH) functionality. This unusual type of linking group prevents the formation of either five- or six-membered intramolecular hydrogen-bonded rings. 2,3-Dimethoxyphenylacetic acid was reacted with 1,6-diaminohexane under DCC/HOBt coupling conditions to give rise to compound **23**. The methyl ether protecting groups were then removed using BBr_3 in dry CH_2-

Cl_2 to provide target compound **24** (Scheme 7). These reactions only proceeded in poor yields, but provided sufficient compound for study.

Compound **24** has the hydrogen-bonding groups in the linker located further away from the catechol O−H groups. It might be expected that, in this case, a seven-membered intramolecular hydrogen-bonded ring would form between the C═O and the ortho O−H group (Figure 11). However, such a ring would not be particularly stable, and it should therefore be relatively straightforward for the catechol O−H groups to achieve chelate-type binding to the target chloride anion. In CD_3CN:DMSO-d_6 (9:1), the O−H protons resonate at 9.84 and 7.78 ppm, while in DMSO-d_6, these protons appeared at 9.30 and 8.99 ppm. This indicates that when increasing amounts of DMSO are present, the ortho O−H proton, which was involved in an intramolecular hydrogen bond, shifts upfield (by 0.54 ppm) as the hydrogen bond is broken. The meta OH proton, however, is sensitive to intermolecular hydrogen bonding with the DMSO solvent and shifts downfield by 1.21 ppm. It is worth noting that in neat DMSO-d_6, the ortho O−H proton of **24** appeared at 9.30 ppm, while in compound **6**, this proton resonated at 12.90 ppm. This indicates that the seven-membered hydrogen-bonded ring in **24** is considerably less effective than the six-membered analogue in compound **6**.

Receptor **24** showed the highest affinity for chloride anions of any of the receptors reported in this paper (Table 1), with a binding constant of 235 mol^{-1} dm^3 in CD_3CN:DMSO-d_6 (9:1). The O−H protons shifted significantly on the addition of chloride anions (5 equiv). The meta O−H proton shifted 0.340 ppm downfield, while the ortho proton sharpened and shifted slightly upfield (indicative of the intramolecular hydrogen bond being broken as the receptor binds to chloride anions). The N−H proton was also shifted downfield by 0.141 ppm, indicative that this proton may contribute to the anion-binding event (Figure 11).

This clearly demonstrates that moving the hydrogen-bonding functionalities in the linker away from the catechol ring has a positive impact on the anion-binding process by preventing the formation of the stable intramolecular hydrogen-bond networks, which deactivate the catechol O−H groups. Furthermore, receptor **24** is a somewhat more effective anion binder than unfunctionalized catechol, and this demonstrates that the multiple catechol units, in part assisted by the N−H groups, are acting cooperatively in binding to the chloride anion. It is worth noting that the improved ability of compound **24** as compared to catechol in CD_3CN:DMSO-d_6 (9:1) can be ascribed to an enhanced hydrogen-bonding ability of the modified catechol unit, the combination of two such units into a single receptor, or a combination of these effects. In any case, compound **24** can be considered as a first step toward anion-binding receptors based on catechol subunits.

Conclusions and Outlook

This paper demonstrates that, by combining catechol-type fragments, it is possible to create catechol-derived anion receptors that outperform simple unfunctionalized catechol. However, this paper also clearly demonstrates that this process is not straightforward and that the choice of linking group in the ortho position is crucial. Having hydrogen-bonding groups in this position has a direct impact on the catechol O−H groups via the formation of intramolecular hydrogen-bonding patterns and can significantly inhibit the ability of the catechol O−H groups to achieve "chelate-type" anion binding.

In particular, the formation of stable six-membered intramolecular hydrogen-bonded rings significantly inhibits anion binding; such rings are not even disturbed by the addition of competitive solvents such as DMSO-d_6. Only the receptors that are incapable of forming six-membered intramolecular rings show effective chloride anion binding. Compounds **21** and **22** form five-membered hydrogen-bonding rings; in CD_3CN, these compounds do not bind chloride anions as efficiently as catechol itself, but on the addition of 10% DMSO-d_6, binding is enhanced as compared to that of unfunctionalized catechol, as the five-membered ring intramolecular hydrogen-bond interactions are weakened. Compound **24**, which can only form a seven-membered hydrogen-bonded ring, shows the strongest binding of all, and significantly outperforms catechol in its ability to bind chloride anions in CD_3CN:DMSO-d_6 (9:1). These results are summarized in Figure 12.

In future work, we aim to develop anion receptors in which the catechol units are connected by linkers with minimal hydrogen-bonding functionality. Furthermore, we intend to explore the linkage of catechol units through their meta positions, so that any hydrogen-bonding groups in the linker cannot directly interact with the catechol O−H groups that are required for anion binding. Results of these studies will be reported in due course.

Experimental Section

Synthesis and Characterization. Compounds **1**−**6** are known in the literature.[20,21] Synthetic methods and characterization data are provided in the Supporting Information as our methods were modified and literature data are not always complete. Compounds **7**−**9**[24] and **15**[28] are also known in the literature, and the synthesis and data are not reproduced here.

General Method 1. A mixture of methyl ether protected bis-catechol (0.0014 mol) and dry dichloromethane (70 mL) was maintained under an inert atmosphere with stirring, and BBr_3 (5 mL) was added by syringe. The reaction mixture was connected to a 1 M NaOH trap to remove evolved HBr. The reaction mixture was then stirred for 3 d. The reaction mixture was quenched by the slow addition of iced water to the reaction flask until addition no longer caused the evolution of HBr. The product was evaporated to dryness and dissolved in methanol; the methanol was then evaporated under vacuum (to remove boron impurities).

1,8-Bis-(2,3-benzyloxybenzyloxy)octane (10). Compound **9** (0.71 g, 0.0021 mol) was dissolved in dichloromethane; DMAP (0.05 g), DCC (0.88 g, 0.0043 mol), and 1,8-octanediol (0.16 g, 0.0011 mol) were added to it with stirring at room temperature. The reaction mixture was left to stir overnight and then washed with deionized water, 1 M NaOH, deionized water, 1 M HCl, and finally deionized water. The product was dried with $MgSO_4$ and evaporated to dryness. The product was then extracted into toluene, filtered, and the solvent was evaporated. The product was washed with cyclohexane to give a white solid. A yield of 47% of compound **10** was obtained and used without further purification (there was some contamination of compound **10** with DCC, not listed in the NMR here). mp 74−76 °C. ^{1}H NMR ($CDCl_3$): δ 7.49−7.27 (22H, m, Ar−*H*), 7.16−7.03 (4H, m, Ar−*H*), 5.13 (4H, s, Ar−CH_2−O), 5.11 (4H, s, Ar−CH_2−O), 4.24 (4H, t, J = 6.7 Hz O−CH_2−CH_2), 1.65 (4H, quin, J = 7.0 Hz, C−CH_2−C), 1.38−1.19 (8H, m, C−CH_2−C). ^{13}C NMR ($CDCl_3$): δ 166.8 (*C*═O), 153.1 (Ar*C*−O), 148.5 (Ar*C*−O), 137.9 (Ar*C*−CH_2), 137.0 (Ar*C*−CH_2), 129.0 (Ar*C*), 128.8 (Ar*C*), 128.6 (Ar*C*), 128.5 (Ar*C*), 128.2 (Ar*C*), 127.9 (Ar*C*), 127.7 (Ar*C*), 124.3 (Ar*C*), 123.1 (Ar*C*), 118.1 (Ar*C*−CO_2R), 75.9 (Ar−*C*H_2−O), 71.7 (Ar−*C*H_2−O), 65.7 (O−*C*H_2−CH_2), 29.5 (C−*C*H_2−C), 29.0 (C−*C*H_2−C), 26.3 (C−*C*H_2−

C). ESIMS *m*/*z*: 801 ([M + Na]$^+$, 100%). ν_{max} (solid): 3067m (C−H), 3032m (C−H), 2930s (C−H), 2856s (C−H), 2118s, 1726s (C═O), 1599m, 1580m, 1499m, 1470m, 1381m, 1314m, 1248m, 1221m, 1159s.

1,8-Bis-(2,3-hydroxybenzyloxy)octane (11). Compound **10** (0.60 g, 0.00077 mol) and 10% Pd−C (25% w/w) were suspended in ethanol, and the mixture was placed under hydrogen with stirring for 48 h. The mixture was filtered, and the ethanol was evaporated under vacuum to give a brown solid. Compound **11** was obtained in a yield of 71%. mp 113 °C. ^{1}H NMR (DMSO-d_6): δ 10.54 (2H, s, O−*H*), 9.47 (2H, s, O−H), 7.25 (2H, d, J = 7.9 Hz, Ar−*H*), 7.05 (2H, d, J = 7.9 Hz, Ar−*H*), 6.78 (2H, t, J = 7.9 Hz, Ar−*H*), 4.33 (4H, t, J = 6.4 Hz, C*H*$_2$−O), 1.82−1.69 (4H, m, C*H*$_2$−CH$_2$−O), 1.51−1.29 (8H, m, C*H*$_2$). ^{13}C NMR (DMSO-d_6): 170.5 (C═O), 150.5 (Ar*C*−OH), 147.0 (Ar*C*−OH), 121.7 (Ar*C*), 120.4 (Ar*C*), 119.9 (Ar*C*), 114.0 (Ar*C*−CO$_2$R), 66.1 (O−*C*H$_2$), 29.4 (C−*C*H$_2$−C), 28.9 (C−*C*H$_2$−C), 26.3 (C−*C*H$_2$−C). ESIMS *m*/*z*: 417 ([M − H]$^-$, 85%), 439 ([M − 2H + Na]$^-$, 100%). ν_{max} (solid): 3472s (O−H), 2936m (C−H), 2859m (C−H), 1670s (C═O), 1605w, 1466s, 1400m, 1366w, 1308s, 1269s, 1153s, 1072s, 984m. HRCI: calculated for $C_{22}H_{30}NO_8$, 436.1971; found, 436.1957.

***N,N′*-Bis(2,3-bis(hydroxy)benzylidene)diaminooctane (12).** 2,3-Dihydroxybenzaldehyde (2.00 g, 0.015 mol) was dissolved in methanol, and to it was added 1,8-diaminooctane (1.05 g, 0.0073 mol) with stirring. The yellow precipitate was collected as compound **12** in a yield of ∼90%. mp 141 °C. ^{1}H NMR ($CDCl_3$): δ 8.09 (2H, s, N═C*H*), 6.91 (2H, d, J = 7.3 Hz, Ar−*H*), 6.69 (2H, d, J = 7.9 Hz, Ar−*H*), 6.56 (2H, t, J = 7.9 Hz, Ar−*H*), 3.57 (4H, t, J = 6.7 Hz, N−C*H*$_2$), 1.69 (4H, bquin, C−C*H*$_2$−C), 1.49−1.25 (8H, m, C−C*H*$_2$−C). ^{13}C NMR ($CDCl_3$): δ 164.7 (*N*═*C*H), 159.4 (Ar*C*−OH), 147.5 (Ar*C*−OH), 122.2 (Ar*C*−H), 116.1 (Ar*C*−H), 116.0 (Ar*C*−H), 115.3 (Ar*C*−C), 55.3 (N−*C*H$_2$), 30.7 (C−*C*H$_2$−C), 29.2 (C−*C*H$_2$−C), 26.9 (C−*C*H$_2$−C). ESIMS *m*/*z*: 383 ([M − H]$^-$). ν_{max} (solid): 3132m (O−H), 2924m (C−H), 2855m (C−H), 1643s (C═N), 1539m, 1512s, 1458s, 1389s, 1354s, 1227s, 1184s, 1157s, 1018s. HRCI: calculated for $C_{22}H_{29}N_2O_4$, 385.2127; found, 385.2117.

Octanedioic Acid Bis-(2,3-dimethoxybenzylamide) (13). Suberoyl chloride (0.27 mL, 1.50 mmol) was dissolved in a minimum amount of dry dichloromethane, and to it was added a solution of 2,3-dimethoxybenzylamine (0.50 g, 3 mmol) and triethylamine (0.4 mL, 3 mmol) in dry dichloromethane dropwise with stirring under an inert atmosphere. The reaction was then left to stir overnight. The product was purified by washing with deionized water, 1 M NaOH, deionized water, 1 M HCl, and finally with deionized water. The product was dried with $MgSO_4$, filtered, and evaporated to dryness, to give compound **13** as a white solid in 58% yield. mp 136 °C. ^{1}H NMR ($CDCl_3$): δ 7.01 (2H, t, J = 7.9 Hz, Ar−*H*), 6.86 (4H, m, Ar−*H*), 5.96 (2H, bt, N*H*), 4.43 (4H, d, J = 5.8 Hz, C*H*$_2$−NH), 3.86 (6H, s, O−C*H*$_3$), 3.85 (6H, s, O−C*H*$_3$), 2.13 (4H, t, J = 7.3 Hz, CO−C*H*$_2$), 1.60 (4H, b quin, C*H*$_2$), 1.39−1.21 (4H, m, C*H*$_2$). ^{13}C NMR ($CDCl_3$): δ 172.8 (*C*═O), 152.8 (Ar*C*−OMe), 147.3 (Ar*C*−OMe), 132.2 (Ar*C*), 124.4 (Ar*C*), 121.6 (Ar*C*), 112.0 (Ar*C*), 60.9 (O−*C*H$_3$), 55.9 (O−*C*H$_3$), 39.1 (*C*H$_2$), 36.7 (*C*H$_2$), 28.9 (*C*H$_2$), 25.6 (*C*H$_2$). ESIMS *m*/*z*: 495 ([M + Na]$^+$, 100%). ν_{max} (solid): 3291m (N−H), 2928m (C−H), 2847m (C−H), 1740m (C═O), 1632s, 1535s, 1481s, 1365m, 1277s, 1210s, 1076s, 1003s. HRCIMS calculated for $C_{26}H_{37}N_2O_6$, 473.2652; found, 473.2648.

Octanedioic Acid Bis-(2,3-dihydroxybenzylamide) (14). Using general method 1 with compound **13** and purifying the product by suspending in deionized water and placing in an ultrasonic bath for ∼6 h yielded compound **14** as a light brown solid in 32% yield. mp 184 °C. ^{1}H NMR (DMSO-d_6): δ 9.07 (2H, s, O*H*), 8.93 (2H, s, O*H*), 8.39 (2H, t, J = 5.8 Hz, N*H*), 6.69 (2H, dd, J = 7.3, 2.4 Hz, Ar−*H*), 6.59 (4H, m, Ar−*H*), 4.19 (4H, d, J = 5.8 Hz, C*H*$_2$−NH), 2.15 (4H, t, J = 7.3 Hz, C*H*$_2$−CO), 1.62−1.48 (4H, m, C*H*$_2$), 1.37−1.18 (4H, m, C*H*$_2$). ^{13}C NMR (DMSO-d_6): 173.1 (*C*═O), 145.3 (Ar*C*−OH), 142.9 (Ar*C*−OH), 126.1 (Ar*C*), 119.2 (Ar*C*), 118.7 (Ar*C*), 114.3 (Ar*C*), 37.8 (*C*H$_2$), 35.1 (*C*H$_2$), 28.4 (*C*H$_2$), 25.2 (*C*H$_2$). ESIMS *m*/*z*: 415 ([M − H]$^-$, 100%). ν_{max} (solid): 3325m (N−H), 3102w, 2928m (C−H), 2854w (C−H), 2731w, 2635w, 1558s (C═O), 1501m, 1481m, 1435m, 1412m, 1365m, 1339m, 1258s, 1219s, 1084m, 1049w, 1014m, 968w, 880w, 841m. HRCIMS calculated for $C_{22}H_{29}N_2O_6$, 417.2026; found, 417.2023.

***N,N′*-Bis-(2,3-bis-benzyloxybenzylidene)-octane-1,8-diamine (16).** Compound **15** (8.40 g, 0.026 mol) was dissolved in methanol, and to it was added 1,8-diaminooctane (1.87 g, 0.013 mol) with stirring. The white precipitate was collected as compound **16** in a yield of ∼90%. mp 95 °C. ^{1}H NMR ($CDCl_3$): δ 8.50 (2H, s, C*HN*), 7.56−7.52 (2H, m, Ar−*H*), 7.49−7.44 (4H, m, Ar−*H*), 7.42−7.28 (16H, m, Ar−*H*), 7.09−7.03 (4H, m, Ar−*H*), 5.16 (4H, s, O−C*H*$_2$), 5.07 (4H, s, O−C*H*$_2$), 3.50 (4H, t, J = 7.0 Hz, N−C*H*$_2$), 1.70−1.57 (4H, m, C*H*$_2$), 1.38−1.28 (8H, m, C*H*$_2$). ^{13}C NMR ($CDCl_3$): δ 157.0 (*N*═*C*H), 152.1 (Ar*C*−O), 148.4 (Ar*C*−O), 137.2 (Ar*C*−CH$_2$), 136.9 (Ar*C*−CH$_2$), 130.9 (Ar*C*), 128.8 (Ar*C*), 128.7 (Ar*C*), 128.5 (Ar*C*), 128.3 (Ar*C*), 128.2 (Ar*C*), 127.6 (Ar*C*), 124.4 (Ar*C*), 119.4 (Ar*C*), 116.1 (Ar*C*), 76.1 (O−*C*H$_2$), 71.1 (O−*C*H$_2$), 62.2 (*N*═*C*H$_2$), 31.0 (*C*H$_2$), 29.6 (*C*H$_2$), 27.5 (*C*H$_2$). ESIMS *m*/*z*: 745 ([M + H]$^+$, 100%). ν_{max} (solid): 3067w (C−H), 3032w (C−H), 2927m (C−H), 2854m (C−H), 2812m (C−H), 1643s (C═N), 1578m, 1497w, 1454s, 1385m, 1362s, 1335m, 1308s, 1265s, 1231s, 1192s, 1069s, 1053s, 1022s, 972s. HRESIMS calculated for $C_{50}H_{53}N_2O_4$, 745.4000; found, 745.3979.

***N,N′*-Bis-(2,3-bis-benzyloxybenzyl)-octane-1,8-diamine (17).** Compound **16** (3.50 g, 4.70 mmol) was suspended in methanol, and $NaBH_4$ (0.91 g, 23.5 mmol) was added with stirring. The reaction was left to stir for a period of 2 h, and the solvent was removed in vacuo. The product was dissolved in dichloromethane and washed with $NaOH_{aq}$ (0.5 M). The product was dried with $MgSO_4$, filtered, and evaporated to dryness. The product was purified using column chromatography (SiO_2) with eluent of dichloromethane and employing gradient elution until an eluent of 95:5 dichloromethane:methanol was reached. A small amount of triethylamine was added to the eluent. The product was a white solid and was obtained in a yield of 35%. mp 61 °C. ^{1}H NMR ($CDCl_3$): δ 7.48−7.46 (2H, m, Ar−*H*), 7.41−7.30 (16H, m, Ar−*H*), 7.00 (2H, t, J = 7.6 Hz, Ar−*H*), 6.95−6.90 (4H, m, Ar−*H*), 5.14 (4H, s, O−C*H*$_2$), 5.07 (4H, s, O−C*H*$_2$), 3.73 (4H, s, Ar−C*H*$_2$−NH), 2.51 (4H, t, J = 7.3 Hz, NH−C*H*$_2$−CH$_2$), 1.49−1.38 (4H, m, C*H*$_2$), 1.33−1.18 (8H, m, C*H*$_2$). ^{13}C NMR ($CDCl_3$): δ 151.9 (Ar*C*−O), 146.7 (Ar*C*−O), 137.8 (Ar*C*−CH$_2$), 137.1 (Ar*C*−CH$_2$), 134.7 (Ar*C*), 128.7 (Ar*C*), 128.5 (Ar*C*), 128.1 (Ar*C*), 128.1 (Ar*C*), 127.6 (Ar*C*), 124.0 (Ar*C*), 122.4 (Ar*C*), 113.3 (Ar*C*), 75.1 (O−*C*H$_2$), 71.0 (O−*C*H$_2$), 49.5 (*C*H$_2$−NH), 49.3 (*C*H$_2$−NH), 30.2 (*C*H$_2$), 29.6 (*C*H$_2$), 27.4 (*C*H$_2$). ESIMS *m*/*z*: 749 ([M + H]$^+$, 100%), 771 ([M + Na]$^+$, 97%). ν_{max} (solid): 3070w (C−H), 3030w (C−H), 2924m (C−H), 2851m (C−H), 2816m (C−H), 2747w (C−H), 1582m, 1497m, 1474s, 1451s, 1369m, 1335m, 1273s, 1204s, 1111w, 1084s, 1061s, 1026m, 984m. HRESIMS calculated for $C_{50}H_{57}N_2O_4$, 749.4313; found, 749.4284.

***N,N′*-Bis-(2,3-bis-hydroxy)-octane-1,8-diamine (18).** Compound **17** (0.80 g, 1.07 mmol) and 10% Pd−C (25% w/w) were suspended in ethanol, and the mixture was stirred under hydrogen for 48 h. The mixture was filtered over celite, and the solvent was removed under vacuum to give a light brown solid in a yield of 80%. This compound only had a short shelf life, ca. 1 week. ^{1}H NMR (CD_3CN): δ 6.69 (2H, dd, J = 7.9, 1.5 Hz, Ar−*H*), 6.61 (2H, t, J = 7.6 Hz, Ar−*H*), 6.52 (2H, d, J = 7.6 Hz, Ar−*H*), 3.95 (4H, s, C*H*$_2$−NH), 2.60 (4H, t, J = 7.3 Hz, NH−C*H*$_2$−CH$_2$), 1.59−1.47 (4H, m, C*H*$_2$), 1.40−1.25 (8H, m, C*H*$_2$). ^{13}C NMR (DMSO-d_6): δ 145.8 (Ar*C*−OH), 145.1 (Ar*C*−OH), 123.5 (Ar*C*), 118.8 (Ar*C*), 118.1 (Ar*C*), 114.3 (Ar*C*), 50.9 (*C*H$_2$−NH), 47.9 (*C*H$_2$−NH), 28.9 (*C*H$_2$), 28.7 (*C*H$_2$), 26.6 (*C*H$_2$). ESIMS (−ion) *m*/*z*: 387 ([M − H]$^-$, 100%). ESIMS (+ion) *m*/*z*: 389 ([M + H]$^+$, 77%), 411 ([M + Na]$^+$, 100%).

Octanedioic Acid Bis-[(2,3-dimethoxyphenyl)-amide] (19). Suberoyl chloride (0.47 mL, 2.6 mmol) was dissolved in a minimum amount of dry dichloromethane under an inert atmosphere, and to it was added a solution of 2,3-dimethoxyaniline (0.80 g, 5.2 mmol) and triethylamine (0.7 mL, 5.2 mmol) in dry dichloromethane dropwise with stirring. The reaction was left to stir overnight. The product was purified by washing with deionized water, 1 M NaOH, deionized water, 1 M HCl, and finally with deionized water. The product was dried with $MgSO_4$, filtered, and evaporated to dryness to give compound **19** as a light brown solid in a yield of 71%. mp 111 °C. ^{1}H NMR ($CDCl_3$): δ 7.99 (2H, d, J = 8.2 Hz, Ar−*H*), 7.81 (2H, s, N*H*), 7.03 (2H, t, J = 8.5 Hz Ar−*H*), 6.66 (2H, d, J = 8.2 Hz, Ar−*H*), 3.87 (6H, s, O−C*H*$_3$), 3.87 (6H, s, O−C*H*$_3$), 2.41 (4H, t, J = 7.3 Hz, C*H*$_2$−CO), 1.75 (4H, bt, C*H*$_2$), 1.44 (4H, bt, C*H*$_2$). ^{13}C NMR ($CDCl_3$): δ 171.4 (*C*═O), 152.0 (Ar*C*−OMe), 137.3 (Ar*C*−OMe) 132.3 (Ar*C*−C), 124.3 (Ar*C*−H), 112.7 (Ar*C*−H), 107.5 (Ar*C*−H), 60.8 (O−*C*H$_3$), 55.9 (O−*C*H$_3$), 38.0 (*C*H$_2$−CO), 29.0 (*C*H$_2$), 25.3 (*C*H$_2$). ESIMS *m*/*z*: 467 ([M + Na]$^+$, 100%). ν_{max} (solid): 3287m (N−H), 2935m (C−H), 2900w (C−H), 1639s (C═O), 1560w, 1535s, 1477s, 1354m, 1258s, 1169m, 1072s, 1003s, 940w, 741s. HRCIMS calculated for $C_{24}H_{33}N_2O_6$, 445.2339; found, 445.2344.

Decanedioic Acid Bis-[(2,3-dimethoxyphenyl)-amide] (20). A mixture of sebacic acid (0.66 g, 3.27 mmol) and thionyl chloride (10 mL) was allowed to react overnight under an inert atmosphere at 35 °C. The excess $SOCl_2$ was removed by distillation in vacuo at room temperature. The residue was dissolved in dry CH_2Cl_2 under an inert atmosphere, the solvent was removed as before, and this procedure was repeated again. The newly formed acid chloride was dissolved in a minimum amount of CH_2Cl_2 under an inert atmosphere, and 2,3-dimethoxyaniline (1.00 g, 6.54 mmol) and triethylamine (0.9 mL, 6.54 mmol) in dry CH_2Cl_2 were added dropwise to the solution at room temperature with stirring for a period of 2 h. The reaction was then left to stir overnight. The product was purified by washing with deionized water, 1 M NaOH, deionized water, 1 M HCl, and finally with deionized water. The product was dried with $MgSO_4$, filtered, and evaporated to dryness to give compound **20** as a red solid in a yield of 33%. mp 132 °C. ^{1}H NMR ($CDCl_3$): δ 7.99 (2H, d, J = 8.2 Hz, Ar−*H*), 7.81 (2H, s, N−*H*), 7.02 (2H, t, J = 8.2 Hz, Ar−*H*), 6.65 (2H, d, J = 8.5 Hz, Ar−*H*), 3.87 (6H, s, O−C*H*$_3$), 3.86 (6H, s, O−C*H*$_3$), 2.39 (4H, t, J = 7.6 Hz, C*H*$_2$−CO), 1.72 (4H, quin, J = 7.3 Hz, CO−CH$_2$−C*H*$_2$), 1.47−1.28 (8H, m, C*H*$_2$). ^{13}C NMR ($CDCl_3$): δ 171.5 (*C*═O), 152.0 (Ar*C*−OMe), 137.3 (Ar*C*−OMe) 132.3 (Ar*C*), 124.4 (Ar*C*), 112.7 (Ar*C*), 107.4 (Ar*C*), 60.8 (O−*C*H$_3$), 55.9 (O−*C*H$_3$), 38.2 (*C*H$_2$−CO), 29.3 (C−*C*H$_2$−C), 29.3 (C−*C*H$_2$−C), 25.7 (C−*C*H$_2$−C). ESIMS *m*/*z*: 495 ([M + Na]$^+$, 100%). ν_{max} (solid): 3341m (N−H), 2928m (C−H), 2854m (C−H), 1690s (C═O), 1604s, 1510m, 1462s, 1420s, 1296s, 1261s, 1227s, 1165s, 1080s, 980s. HRCIMS calculated for $C_{26}H_{37}N_2O_6$, 473.2652; found, 473.2646.

Octanedioic Acid Bis-[(2,3-dihydroxyphenyl)-amide] (21). Using general method 1 with compound **19** and purifying the product by suspending in deionized water and placing in an ultrasonic bath for ∼6 h yielded compound **21** as a light brown solid in 40% yield. mp 156−158 °C. ^{1}H NMR (DMSO-d_6): δ 9.51 (2H, s, N*H*), 9.08 (2H, s, O*H*), 9.05 (2H, s, O*H*), 7.02 (2H, dd, J = 7.0, 2.1 Hz, Ar−*H*), 6.69−6.59 (4H, m, Ar−*H*), 2.43 (4H, t, J = 7.3 Hz, COC*H*$_2$), 1.69−1.56 (4H, m, C*H*$_2$), 1.43−1.20 (4H, m, C*H*$_2$). ^{13}C NMR (DMSO-d_6): δ 172.3 (*C*═O), 146.5 (Ar*C*−OH), 136.5 (Ar*C*−OH), 127.2 (Ar*C*), 118.8 (Ar*C*), 113.2 (Ar*C*), 111.7 (Ar*C*), 35.8 (*C*H$_2$−CO), 28.4 (*C*H$_2$), 25.2 (*C*H$_2$). ESIMS *m*/*z*: 387 ([M − H]$^-$, 100%). ν_{max} (solid): 3518m (O−H), 3333w, 3283m (N−H), 2931m (C−H), 2858m (C−H), 1636s (C═O), 1535s, 1477s, 1358s, 1238s, 1172s, 964m. HRCIMS calculated for $C_{20}H_{25}N_2O_6$, 389.1713; found, 389.1702.

Decanedioic Acid Bis-[(2,3-dihydroxyphenyl)-amide] (22). Using general method 1 with compound **20** and purifying the product by suspending in deionized water and placing in an ultrasonic bath for ∼6 h yielded compound **22** as a light brown solid in 35% yield. mp 165 °C. ^{1}H NMR (DMSO-d_6): δ 9.51 (2H, s, N*H*), 9.06 (4H, s, O*H*), 7.02 (2H, dd, J = 7.3, 2.1 Hz, Ar−*H*), 6.67−6.55 (4H, m, Ar *H*), 2.41 (4H, t, J = 7.3 Hz, C*H*$_2$−CO), 1.71−1.55 (4H, m, C*H*$_2$), 1.42−1.25 (8H, m, C*H*$_2$). ^{13}C NMR (DMSO-d_6): δ 172.4 (*C*═O), 146.5 (Ar*C*−OH), 136.5 (Ar*C*−OH), 127.1 (Ar*C*), 118.8 (Ar*C*), 113.2 (Ar*C*), 111.6 (Ar*C*), 35.8 (*C*H$_2$−CO), 28.7 (*C*H$_2$), 28.6 (*C*H$_2$), 25.3 (*C*H$_2$). ESIMS *m*/*z*: 415 ([M − H]$^-$, 100%). ν_{max} (solid): 3518m (O−H), 3337m (N−H), 2920m (C−H), 2850m (C−H), 1636s (C═O), 1605m, 1535s, 1497s, 1470m, 1416w, 1366s, 1180s, 1157s, 1072m, 999w, 957m, 876w, 841m, 779s. HRCIMS calculated for $C_{22}H_{29}N_2O_6$, 417.2026; found, 417.2025.

2-(2,3-Dimethoxyphenyl)-*N*-{6-[2,3-dimethoxyphenyl)-acetylamino]-hexyl}-acetamide (23). 2,3-Dimethoxyphenyl acetic acid (1.00 g, 5.10 mmol) was dissolved in ∼30 mL of CH_2Cl_2. To the solution were added DCC (2.10 g, 10.2 mmol) and HOBt (1.39 g, 10.2 mmol) as a mixture of solids. The solution was stirred under a nitrogen atmosphere and cooled to 0 °C. After 10 min, 1,6-diaminohexane (0.30 g, 2.55 mmol) and triethylamine (0.7 mL, 5.10 mmol) in CH_2Cl_2 were added to the reaction. The reaction was allowed to return to room temperature and stirred for 24 h. The precipitate was removed by filtration and discarded. The filtrate was then washed with deionized water, 1 M NaOH, deionized water, 1 M HCl, and finally with deionized water. The product was dried with $MgSO_4$ and evaporated to dryness. The excess DCU was removed by multiple recrystallizations from CH_2Cl_2 to yield compound **23** as a white solid in a 15% yield. mp 135 °C. ^{1}H NMR ($CDCl_3$): δ 7.03 (2H, t, J = 7.6 Hz, Ar−*H*), 6.89−6.71 (4H, m, Ar−*H*), 5.86 (2H, b t, N−*H*), 3.87 (6H, s, O−C*H*$_3$), 3.85 (6H, s, O−C*H*$_3$), 3.54 (4H, s, Ar−C*H*$_2$CO), 3.12 (4H, q, J = 6.7 Hz, C*H*$_2$−NH), 1.42−1.30 (4H, m, C*H*$_2$), 1.22−1.10 (4H, m, C*H*$_2$). ^{13}C NMR ($CDCl_3$): 171.1 (*C*═O), 152.9 (Ar*C*−O), 146.9 (Ar*C*−O), 129.5 (Ar*C*), 124.6 (Ar*C*), 122.8 (Ar*C*), 111.7 (Ar*C*), 60.7 (O−*C*H$_3$), 55.8 (O−*C*H$_3$), 39.4 (*C*H$_2$), 38.7 (*C*H$_2$), 29.4 (*C*H$_2$), 26.3 (*C*H$_2$). ESIMS *m*/*z*: 495 ([M + Na]$^+$, 100%). ν_{max} (solid): 3283s (N−H), 2936m (C−H), 2925w (C−H), 1639s (C═O), 1539s, 1477s, 1354m, 1261s, 1238s, 1169m, 1072s, 1003s. HRESIMS calculated for $C_{26}H_{37}N_2O_6$, 473.2646; found, 473.2645.

2-(2,3-Dihydroxyphenyl)-*N*-{6-[2-(2,3-dihydroxyphenyl)-acetylamino]-hexyl}-acetamide (24). Using general method 1 with compound **23** and purifying the product by washing the solid with dichloromethane and water provided compound **24** as a light brown solid in a 20% yield. mp 110 °C. ^{1}H NMR (DMSO-d_6): δ 9.30 (2H, s, O−*H*), 8.99 (2H, s, O−*H*), 8.13 (2H, b t, N−*H*), 6.69 (2H, dd, J = 7.9, 1.8 Hz, Ar−*H*), 6.59 (2H, t, J = 7.3 Hz, Ar−*H*), 6.53 (2H, dd, J = 7.6, 1.5 Hz, Ar−*H*), 3.43 (4H, s, Ar−C*H*$_2$CO), 3.06 (4H, q, J = 6.7 Hz, C*H*$_2$−NH), 1.50−1.34 (4H, m, C*H*$_2$), 1.32−1.22 (4H, m, C*H*$_2$). ^{13}C NMR (CD_3COD): δ 175.0 (*C*═O), 146.8 (Ar*C*−O), 144.9 (Ar*C*−O), 123.8 (Ar*C*), 122.4 (Ar*C*), 120.8 (Ar*C*), 115.4 (Ar*C*), 40.4 (*C*H$_2$), 39.4 (*C*H$_2$), 30.1 (*C*H$_2$), 27.3 (*C*H$_2$). ESIMS (+ion) *m*/*z*: 439 ([M + Na]$^+$, 100%). ESIMS (−ion) *m*/*z*: 415 ([M − H]$^-$, 100%), 495 ([M + ^{79}Br]$^-$, 25%), 497 ([M + ^{81}Br]$^-$, 25%). ν_{max} (solid): 3421m (O−H), 3306m (N−H), 3109w (C−H), 2935m (C−H), 2855w (C−H), 1635s (C═O), 1593s, 1570s, 1477s, 1435s, 1362s, 1342s, 1281s, 1254s, 1180s, 1076m, 1018w, 988w. HRESIMS calculated for $C_{22}H_{27}N_2O_6$, 415.1875; found, 415.1866.

NMR Titrations. NMR titrations were performed in undried $CDCl_3$, CD_3CN, or CD_3CN:DMSO-d_6 (9:1) using a host concentration of 2 mM. A solution containing the anionic guest (as its tetrabutylammonium salt) at a concentration of 50 mM, and host at a concentration of 2 mM, was made up in the same solvent. The guest solution was added in aliquots (via Gilson pipet) to the host solution, and NMR spectra were recorded. Data were fitted to a

1:1 model by nonlinear least-squares fitting methods; the commercial program HypNMR was used.[32]

Job Plot Method. The Job plot was performed in CD_3CN:DMSO-d_6 (9:1). Host and guest solutions with concentrations of 2 mM were used. Aliquots were added to each sample to give a total volume of 1 mL and a constant total concentration of host and guest (2 mM). For data analysis, we used the relationship [complex]$\alpha\Delta\delta \times$ [host].

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Supporting Information Available: General experimental methods, synthesis and data for compounds **1**−**6**, CIF file for compound **6**, and ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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