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1,3,5-Tris(2-butyrylaminophenyl)benzene: a simple, acyclic chloride anion receptor

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Abstract—A simple, acyclic, amide-functionalized tripodal receptor was synthesized, and shown to bind chloride anions with high selectivity relative to dihydrogenphosphate and other halide anions.

The binding and sensing of anionic species by artificial receptors is an expanding area of supramolecular chemistry. Recent progress in this field has led to the development of effective receptors for fluoride, carboxylates and dihydrogenphosphate anions.[1] In contrast, relatively few efficient receptors for biologically and/or environmentally important anions such as sulfate,[2] nitrate[3] and chloride[4] have been reported. Chloride anions, which are the dominant anionic species present in extracellular fluid (100 mM) play an important physiological role in the stabilization of membrane potential, synaptic inhibition, cell volume regulation, transepitheral transport, extracellular and vesicular acidification and endocytotic trafficking.[5] Thus, it is not surprising that considerable effort has been devoted to the synthesis of systems that selectively and effectively bind chloride anions. While, there are examples of molecular receptors that bind chloride strongly,[4] few of them show preferential binding of chloride versus dihydrogenphosphate and acetate anions.[4b,d] Some of the very effective chloride receptors have complex structures that require multistep syntheses.[4b,f–j] Herein, we present the design and synthesis of a simple, acyclic, tripodal receptor and demonstrate that it binds chloride anions with high selectivity relative to dihydrogenphosphate and other halide anions.

In contrast to cyclic molecular receptors, acyclic, podand systems are usually easier to synthesize and offer faster kinetics of complexation/decomplexation.[6] Thus, podand receptors have been successively applied in the recognition of anionic species.[4a,e,h–k,7] Moreover, the anion induced conformation changes of appropriate substituted podand receptors can produce optical signals which can be used for anion sensing.[4c,8] The construction of podand type molecular receptors is usually based on functionalization of rigid molecular scaffolds. The most versatile example of such a scaffold is 1,3,5-tris(aminomethyl)-2,4,6-trialkylbenzene.[9] This molecular platform has been used extensively for the construction of numerous receptor systems that require appended functional groups and these systems are known to bind and/or detect various anionic species.[10]

Recently, we reported the synthesis of 1,3,5-tris(2-aminophenyl)benzene (**2**), a novel, rigid, molecular scaffold (Scheme 1).[11] Trisamine **2** is available in excellent yield in one synthetic step via palladium-catalyzed coupling of 2-aminophenylboronic acid with 1,3,5-triiodobenzene. DFT calculations reveal that the energy difference between the lowest energy conformations in which two of the amino groups are oriented 'up' and one amino group is oriented 'down' (partial cone) and cone conformation is 0.19 kcal/mol.[12] These results suggest that the entropic penalty for preorganization of compound **2**, as well as receptors based on it, should be relatively low. Encouraged by these computational studies we reacted triamine **2** with acyl chlorides, bearing various alkyl chains, which resulted in the formation of trisamides of type **1**. It is known that molecular receptors containing amide groups often exhibit limited solubility in nonpolar organic solvents which precluded their practical application as ionophores or extracting agents. Thus, by varying the length of the alkyl chains we tuned the solubility of receptors of type **1** in organic solvents.

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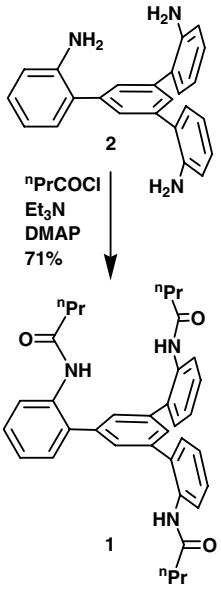

Scheme 1. The synthesis of receptor **1**.

From a family of triamide compounds 1,3,5-tris(2-butyrylaminophenyl) benzene **1** was chosen for further investigation because it was readily soluble in most organic solvents and could be obtained in crystalline form which simplified purification and sample preparation.[13] Moreover, single crystals suitable for X-ray diffraction analysis were grown from an acetone/diisopropyl ether solution of **1**.[14]

The asymmetric unit contains two crystallographically unique molecules that adopt similar geometries. The structure of one geometry is shown in Figure 1. Receptor **1** adopts a two arms 'up', one arm 'down' (partial cone) conformation. Such a conformation is stabilized by a total of six intermolecular hydrogen bonds. The amide hydrogen atoms of one molecule of **1** are H-bond to the oxygen atoms of three others molecules. The oxygen atoms, in turn, accept amide hydrogen atoms of adjacent molecules. Thus each amide bond serves as an acceptor and a donor of intermolecular hydrogen bonds.

The interaction of receptor **1** with various anions was investigated in acetonitrile-d_3 using a ^{1}H NMR titration technique.[15] As a control, dilution studies were carried out in the concentration range of 1.4–8.0 mM and no evidence for self-association was observed. The receptor-anion stoichiometries were determined via a continuous variation method (Job plots) and proved to be 1:1 for all anions.[16]

The addition of anions (as tetrabutylammonium salts) to the 2.4 mM acetonitrile-d_3 solutions of receptor **1** led to large downfield shifts of the amide N–H resonance ($\Delta\delta$ 0.4–3.0 ppm). These large downfield shifts of the N–H signal are consistent with the presence of a hydrogen-bonding interaction between the anion and amide protons. Moreover, only one signal corresponding to three N–H protons was observed during these titration experiments which suggests that each N–H atom is equally involved in the anion binding process. To determine the association constants for **1** with anions, the binding isotherms were analyzed by a nonlinear regression method.[17] The results of those determinations are shown in Table 1.

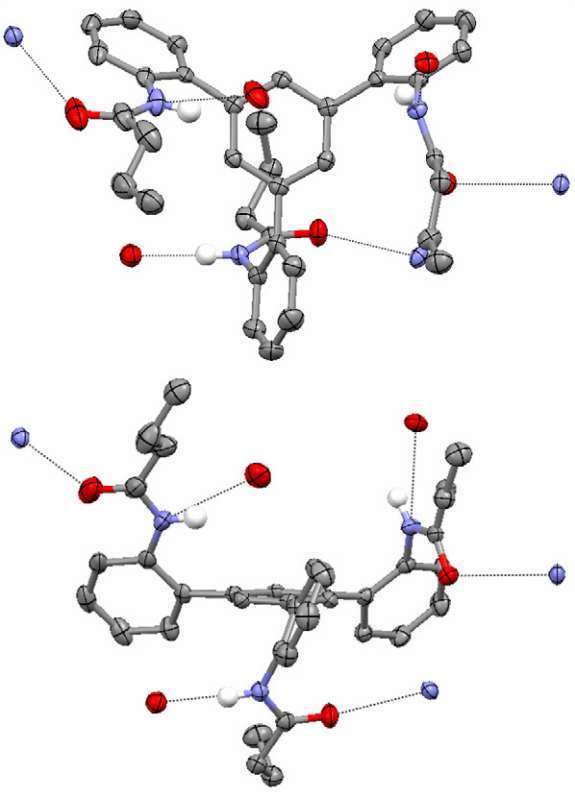

Figure 1. The crystal structure of 1,3,5-tris(2-butyryl-aminophenyl) benzene. The heteroatoms of adjacent receptor molecules involved in intermolecular hydrogen bonding are shown. Hydrogen atoms other than those of amide groups have been omitted for clarity.

Inspection of Table 1 reveals that receptor **1** shows a high affinity for chloride anions with an association constant of 1540 M^{-1}. Receptor **1** also proved to be selective for chloride anions over bromide and iodide anions. Whereas chloride anions interact strongly with receptor **1** the highest association constant was determined for **1** with an acetate ion (K_a 2410 M^{-1}). However, acetate binds by only a factor of roughly 1.5

Table 1. Association constants (M^{-1}) for the binding of anions by receptor **1** as determined from ^{1}H NMR titrations in acetonitrile-d_3

Anion	K_a (M^{-1})	pK_a[a]
Cl^-	1540	−6.1
Br^-	450	−8
I^-	120	−9
AcO^-	2410	4.7
$H_2PO_4^-$	120	2.1
HSO_4^-	60	−9
NO_3^-	180	−1.4

The anions were formulated as tetrabutylammonium salts.
[a] In water at 25 °C, $I = 0$.[18]

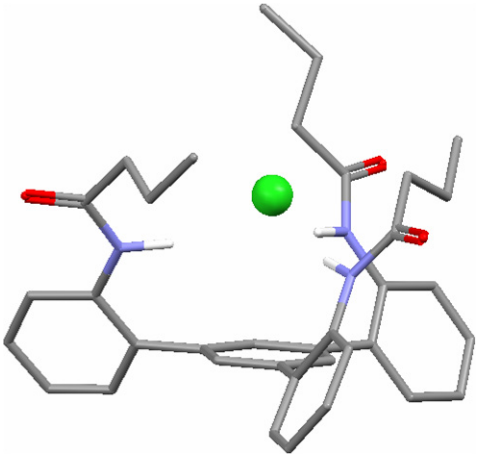

Figure 2. Proposed binding mode of chloride by 1,3,5-tris(2-butyryl-aminophenyl) benzene. The geometry optimization was performed at the B3LYP level of theory using 3-21G basis set.

times better than chloride, although it is 10^{10} more basic. Further, dihydrogenphosphate is also significantly more basic than chloride, yet it has much lower affinity. Weak binding interactions were seen in the case of hydrogen sulfate and nitrate anions.

DFT calculations provide some insight into the chloride complex geometry.[12] The optimized structure of receptor **1** bound to chloride revealed a preference to adopt a cone conformation (Fig. 2). This conformation produced a cavity filled by a chloride anion. The anion is located 3.38 Å above the central phenyl ring of the ligand and is hydrogen bonded to the three amide hydrogen atoms. The NH to chloride distances are in the range 3.36–3.37 Å, and nitrogen–hydrogen–chloride angles are in the range 158.4–159.9°.

In conclusion, the readily prepared 1,3,5-tris(2-butyryl-aminophenyl)benzene **1** has proven to be an effective anion-binding receptor. Receptor **1** binds chloride anions with high affinity and selectivity relative to dihydrogenphosphate and other halide anions in a polar organic solvent. We expect that by varying the nature of the appended functional group we can tune the binding properties of receptors based on the 1,3,5-tris(2-aminophenyl)benzene scaffold. Investigations in this context are currently underway.

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12. The geometry optimization was performed at the B3LYP level of theory using 3-21G and 6-31G basis sets for compound **1** and **2**, respectively.
13. *Analytical data for* **1**: Mp 179–181 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 8.04 (broad d, 3H, $J = 7.0$ Hz), 7.42 (s, 3H, central Ar), 7.38 (td, 3H, $J = 8.0$ Hz, $J = 1.5$ Hz), 7.32–7.30 (m, 3H), 7.27 (broad s, 3H, D_2O exchangeable, amide NH) 7.22–7.25 (m, 3H), 2.18 (t, 6H, $J = 7.5$ Hz), 1.52 (sextet, 6H, $J = 7.5$ Hz), 0.79 (t, 9H, $J = 7.5$ Hz); ^{13}C (50 MHz, $CDCl_3$) δ (ppm) = 171.5 (C=O), 140.2, 134.8, 133.0, 130.0, 129.2, 128.9, 125.3, 123.5, 39.4, 19.2, 13.8; ESI+MS (*m*/*z*) 584.3 $(M+Na)^+$; ESI−MS (*m*/*z*) 560.6 $(M-H)^-$, HRMS calcd for $C_{36}H_{39}N_3O_3Na$ 584.2889, found (*m*/*z*) 584.2876. Anal. Calcd for $C_{36}H_{39}N_3O_3$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.22; H, 7.31; N 7.37.
14. Crystallographic data (excluding structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 639957. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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