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Linear Components for Supramolecular Networks

1.1 Flexible Components

The origins of supramolecular chemistry are intimately linked to Pedersen's pioneering work on crown ethers. His fortuitous discovery of dibenzo[18]crown-6 in 1967 occurred when he was attempting to prepare a flexible phenol-terminated polyether which was expected to bind to the vanadyl ion and thus support its catalytic activity [1]. Although the importance of the new class of cyclic polyethers was recognized across the globe, researchers were also alerted to Pedersen's original goal: the potential for acyclic polyethers to act as metal-binding ligands. Starting points for many of the experiments were the widely available polyethylene glycols that could be modified readily. Foremost among those preparing functionalized polyethers were Vögtle and Weber who coined the term 'podands' for their compounds [2].

Polyethers are well known for their abilities to wrap around metal ions, particularly those in groups 1 and 2 and the lanthanides (Figure 1.1), but the introduction of coordinating termini in concert with variable lengths of the polyether tether gave greater specificity to the ligands [3,4]. More recently, polyethers have been used to prepare coordination networks through the incorporation of transition metals. The inherent flexibility of the ether link coupled to the preferred geometry of certain metals gives rise to some very interesting nanoscale complexes, many of which have a helical motif [5].

Two methods to prepare polyether-based podands are described here. The first is a direct modification of polyethylene glycols and comes originally from the work of Piepers and Kellogg [6], later modified by Hosseini [7]. A simple reaction between hexaethylene glycol and isonicotinyl chloride, as shown in Figure 1.2, results in the formation of podand **1** in good yield. When treated with silver salts

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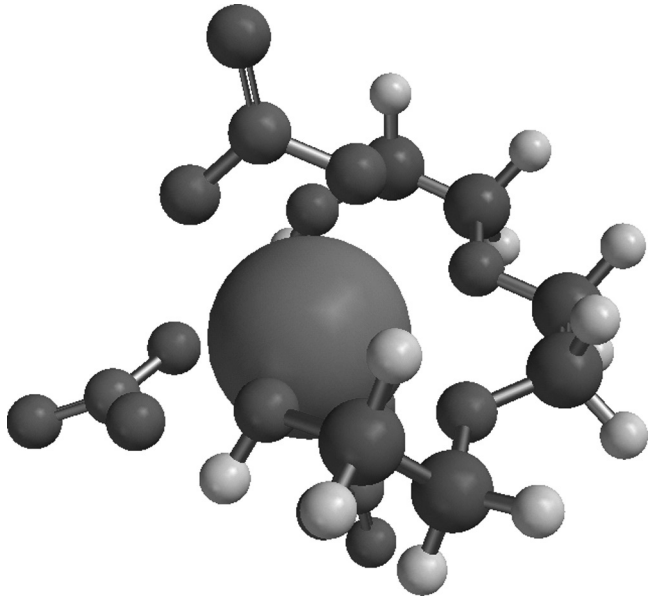

Figure 1.1 A triethylene glycol complex of europium(III) nitrate

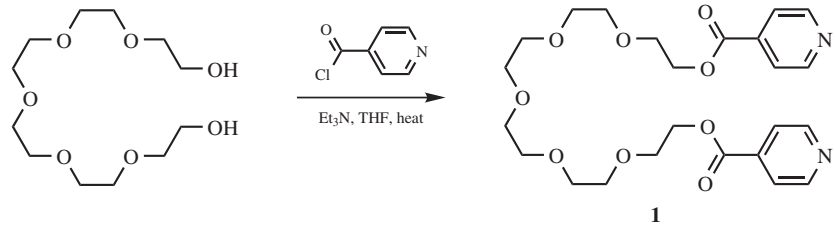

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Figure 1.2 Synthesis of 1,19-bis(isonicotinyloxy)-4,7,10,13,16-pentaoxaheptadecane (**1**)

its bifunctional nature becomes apparent: while the polyether wraps around the metal ion, the donor groups of the isonicotinyl termini coordinate axially to give a self-assembling linear polymer as illustrated in the computational simulation of the X-ray structure (Figure 1.3). As shown by later work by the Hosseini group, many variations of the synthesis can be envisaged [8]. This method gives a yield that is in close agreement with the published 86 per cent.

The second method can be used to synthesize Vögtle-type podands [9,10] in two high-yielding steps from polyethylene glycol ditosylates. The ditosylate derivatives, which are also precursors of cyclic crown ethers, azacrown ethers and lariat ethers, can be prepared with pyridine as the base [11]. However, they are synthesized more effectively in higher yields using aqueous sodium hydroxide and tetrahydrofuran (Figure 1.4) [12]. These conditions also remove the necessity to

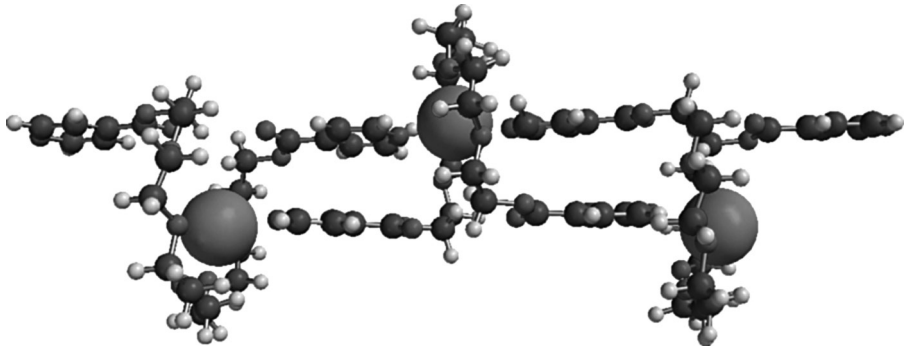

Figure 1.3 Part of the infinite linear cationic chain formed by **1** with silver

Figure 1.4 Syntheses of triethyleneglycol ditosylate (**2**) and tetraethyleneglycol ditosylate (**3**)

work with large amounts of an unpleasant solvent. Furthermore it avoids problems inherent in the removal of excess pyridine from the reaction. Once the ditosylates have been prepared they can be treated with simple metal salts such as sodium 8-hydroxyquinolinate, as shown in Figure 1.5, to introduce useful termini. Although the products have high conformational mobility, the termini converge on alkali metals while the oxygen donors in the polyether backbone wrap around the metals as shown in crystal structures of related compounds and illustrated in Figure 1.6 [13,14].

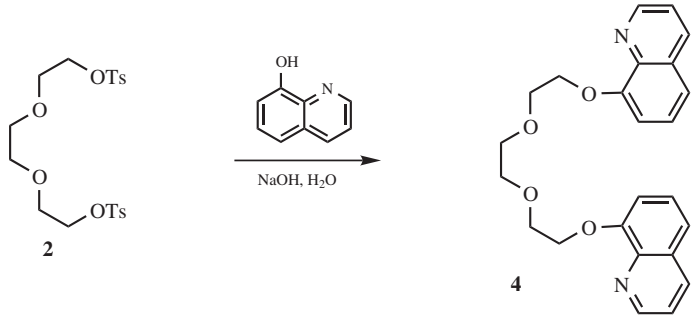

Figure 1.5 Syntheses of 1,9-bis(8-quinolinyloxy)-3,6-dioxanonane (**4**)

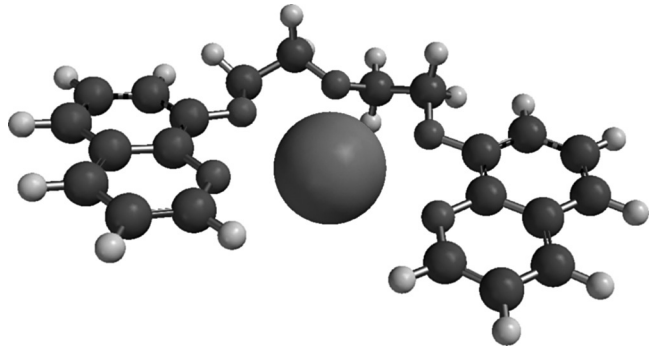

Figure 1.6 Simulation of a complex formed between a bis(quinoline) podand and sodium

Tosyl derivatives are widely used in polyether chemistry as the tosylate anion makes a good leaving group. Diiodopolyethers are often encountered too; however, iodide is no better as a leaving group under the conditions used in the examples given here. Tosylate derivatives have three clear advantages. First, they are often crystalline (though unfortunately not in the case of tetraethylene glycol ditosylate) and can therefore be obtained in high purity. Second, they add significantly to the mass of the parent compound (a mole of triethylene glycol weighs 150 g, its ditosylate derivative, 458 g) making transfer more accurate in the laboratory. Finally, the tosylate salts form as insoluble precipitates upon reaction with the alkali metal salts of alcohols and phenols in non-aqueous solvents. As a result, simple filtration followed by solvent removal is often all that is necessary to isolate the functionalized polyether.

Syntheses of ditosylates **2** and **3** are representative of the procedures required to make crystalline and non-crystalline polyether derivatives: continuation to bis(quinoline) **4** is typical of the method used to prepare a range of symmetrically substituted polyethers with aromatic termini.

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[7] Double stranded interwound infinite linear silver coordination network, B. Schmaltz, A. Jouaiti, M. W. Hosseini and A. De Cian, *Chem. Commun.*, 2001, 1242.
[8] Design and structural analysis of metallamacrocycles based on a combination of ethylene glycol bearing pyridine units with zinc, cobalt and mercury, P. Grosshans, A. Jouaiti, V. Bulach, J.-M. Planeix, M. W. Hosseini and N. Kyritsakas, *Eur. J. Inorg. Chem.*, 2004, 453.
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[10] Open-chain polyethers. Influence of aromatic donor end groups on thermodynamics and kinetics of alkali metal ion complex formation, B. Tümmler, G. Maass, F. Vögtle, H. Sieger, U. Heimann and E. Weber, *J. Am. Chem. Soc.*, 1979, **101**, 2588.
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[14] Consequences of the Pedersen papers on crown type chemistry at Wurzburg and Bonn-Universities–from heteroaromatic crowns and podands to large molecular and crystalline cavities including multisite receptors, cascade molecules, chromoionophores, siderophores, surfactant-type, and extreme ligands, F. Vögtle and E. Weber, *J. Inclusion Phenom. Mol. Rec. Chem.*, 1992, **12**, 75.

Preparation of an isonicotinyl podand

1,19-Bis(isonicotinyloxy)-4,7,10,13,16-pentaoxaheptadecane (1)

Reagents	**Equipment**
Hexaethylene glycol	2-Necked round-bottomed flask (250 mL)
Triethylamine [FLAMMABLE]	Pressure equalized dropping funnel
Isonicotinyl chloride hydrochloride	Reflux condenser
Tetrahydrofuran (THF) [FLAMMABLE]	Heating/stirring mantle and stirrer bar
Diethyl ether [FLAMMABLE]	Inert atmosphere line
Distilled water	Glassware for filtration and work up
Hexane [FLAMMABLE]	
Dichloromethane [TOXIC]	
Magnesium sulphate	

Note: Wherever possible all steps of this synthesis should be carried out in a fume hood.

In a 250 mL two-necked round-bottomed flask, stir finely powdered isonicotinyl chloride hydrochloride (3.56 g, 20 mmol) in dry THF* (50 mL) under an inert atmosphere and add triethylamine (7.0 mL, 5.0 g, 50 mmol). Immediately the cream hydrochloride salt dissolves and a white precipitate of triethylamine hydrochloride forms. After 30 min add hexaethylene glycol (2.5 mL, 2.82 g, 10 mmol) in dry THF (30 mL) dropwise from a pressure-equalized dropping funnel. Once all the hexaethylene glycol solution has been added stir for a further 30 min then heat to reflux for 1 h. Allow the mixture to cool to room temperature and stir for a further 48 h. Filter the mixture and remove the THF under reduced pressure. (Place the precipitate in a fume hood as it may appear to smoke due to residual HCl. It should be dissolved in distilled water and neutralized with base prior to disposal.) Add distilled water (50 mL) to the residue and wash with hexane to remove any unreacted hexaethylene glycol. If the THF was dried with sodium hydride in mineral oil this process will also remove the oil. Extract the aqueous solution with dichloromethane (50 mL then twice with 25 mL). Dry the organic phase over anhydrous magnesium sulphate (*ca.* 1 g), filter and remove the solvent under reduced pressure to give the product, 1,19-bis(isonicotinyloxy)-4,7,10,13, 16-pentaoxaheptadecane (**1**), as an orange oil.

Yield: 3.8 g (80%); IR (υ, cm^{-1}): 3440, 3035, 2875, 1955, 1730, 1410, 1285, 1120, 760, 710, 680; ^{1}H NMR (δ, ppm; $CDCl_3$) 8.8, 7.9 (dd, 8 H, Ar*H*), 4.5 (t, 4 H, C*H*$_2$OC(O)Ar), 3.85 (t, 4 H, C*H*$_2$CH$_2$OC(O)Ar), 3.75–3.6 (m, 16 H, OC*H*$_2$C*H*$_2$O).

*For this reaction THF can be dried effectively using sodium hydride. Add about 1 g, in small portions, to a flask containing about 100 mL fresh reagent-grade THF, swirling after each addition, and repeat until no more effervescence is seen. Decant the solvent for use in the experiment but leave the remaining solid under enough solvent to stop it from drying out. To dispose of the residue (a mixture of sodium hydroxide and a small amount of unreacted sodium hydride) carefully add it a little at a time to a large volume of water. Once all the solid has dissolved check the pH of the solution and neutralize with dilute hydrochloric acid. Unless local safety regulations forbid it, the neutralized solution may be safely disposed of in a laboratory sink.

Preparation of polyethylene glycol ditosylates

Triethyleneglycol ditosylate (2)

Reagents	**Equipment**
Triethylene glycol	2-Necked round-bottomed flask (2 L)
Sodium hydroxide [CORROSIVE]	Pressure equalized addition funnel
p-Toluenesulphonyl chloride	Thermometer (−10 to 100 °C)

[CORROSIVE]	Magnetic stirrer and stirrer bar
Tetrahydrofuran (THF) [FLAMMABLE]	Ice bath
Distilled water	Glassware for recrystallization
Ethanol [FLAMMABLE]	

Note: Work in a fume hood wherever possible, particularly when handling *p*-toluenesulphonyl chloride and when recrystallizing the product.

Prepare a solution of sodium hydroxide (40 g, 1 mol) in distilled water (200 mL) and cool to room temperature. Place the solution in a 2 L two-necked round-bottomed flask fitted with a thermometer and add a solution of triethylene glycol (56.5 g, 50 mL, 0.35 mol) in THF (200 mL) while stirring. Put the flask in an ice bath and cool to 0 °C. Place a solution of *p*-toluenesulphonyl chloride (145 g, 0.76 mol) in THF (200 mL) in a pressure-equalized addition funnel and add dropwise to the stirred glycol solution over 3 h or so. Carefully monitor the temperature of the solution and keep below 5 °C throughout the addition.* Once the addition of the *p*-toluenesulphonyl chloride solution is complete continue to stir the solution for a further 1 h below 5 °C. Pour onto a mixture of ice and water (250 g/250 mL) and continue to stir. After all the ice has melted filter the product, which forms as a white powder. Although the crude ditosylate could be used directly it is worthwhile recrystallizing from a minimum quantity of hot ethanol (*ca*. 2 mL per g). Note that the ditosylate will only dissolve when the ethanol is boiling, whereupon it becomes extremely soluble. Filter the boiling solution as quickly as possible to remove any insoluble matter, cool to room temperature, filter again to isolate the precipitate and dry thoroughly to remove residual ethanol. The product, triethylene glycol ditosyate (**2**), is obtained as a colourless microcrystalline solid or white powder.

Yield: 100+ g (60%); m.p.: 77–79 °C; IR (υ, cm^{-1}): 3060, 2940, 1460, 1375, 1350, 1300, 1175, 1100; ^{1}H NMR (δ, ppm; $CDCl_3$) 8.8, 7.3 (dd, 8 H, Ar*H*), 4.2 (m, 4 H, CH_2OSO_2), 3.7 (m, 4 H, $CH_2CH_2OSO_2$), 3.9–3.8 (m, 8 H, OCH_2CH_2O), 2.4 (s, 6 H, $ArCH_3$).

*This takes some patience and it is advisable to keep a good supply of ice at hand.

Tetraethyleneglycol ditosylate (3)

Reagents	**Equipment**
Tetraethylene glycol	Two-necked round-bottomed flask (2 L)
Sodium hydroxide [CORROSIVE]	Pressure equalized addition funnel
p-Toluenesulphonyl chloride	Thermometer (−10 to 100°C)
[CORROSIVE]	Magnetic stirrer and stirrer bar

Tetrahydrofuran (THF) [FLAMMABLE]	Ice bath
Distilled water	Glassware for recrystallization
Dichloromethane [TOXIC]	Rotary evaporator
Calcium sulphate	

Note: Work in a fume hood wherever possible, particularly when handling *p*-toluenesulphonyl chloride.

Prepare a solution of sodium hydroxide (40 g, 1 mol) in distilled water (200 mL) and cool to room temperature. Place the solution in a 2 L two-necked round-bottomed flask fitted with a thermometer and add a solution of tetraethylene glycol (68 g, 60 mL, 0.35 mol) in THF (200 mL) while stirring. Put the flask in an ice bath and cool to 0 °C. Place a solution of *p*-toluenesulphonyl chloride (145 g, 0.76 mol) in THF (200 mL) in a pressure-equalized addition funnel and add dropwise to the stirred glycol solution over 3 h or so. Carefully monitor the temperature of the solution and keep below 5 °C throughout.* Once the addition of the *p*-toluenesulphonyl chloride solution is complete, continue to stir the solution for a further 1 h at below 5 °C. Pour onto a mixture of ice and water (250 g/250 mL) and continue to stir. When all the ice has melted, remove most of the THF by rotary evaporation and extract the product into dichloromethane (3×100 mL). Dry the dichloromethane extract over calcium chloride, filter and remove the solvent by rotary evaporation. The product, tetraethylene glycol ditosylate (**3**), is obtained as a colourless oil.

Yield: ~160 g (95+%); IR (υ, cm^{-1}): 3060, 2930, 1460, 1375, 1350, 1300, 1175, 1120; ^1H NMR (δ, ppm; $CDCl_3$) 8.8, 7.3 (dd, 8 H, Ar*H*), 4.2 (m, 4 H, CH_2OSO_2), 3.7 (m, 4 H, $CH_2CH_2OSO_2$), 3.9–3.8 (m, 12 H, OCH_2CH_2O), 2.4 (s, 6 H, $ArCH_3$).

*See compound **2**.

Preparation of a quinoline podand

1,9-Bis(8-quinolinyloxy)-3,6-dioxanonane (4)

Reagents	**Equipment**
Triethylene glycol ditosylate (**2**)	2-Necked round-bottomed flask (250 mL)
8-Hydroxyquinoline	Heating/stirring mantle and stirrer bar
Sodium hydride (50% oil suspension)	Pressure equalized addition funnel
[CORROSIVE; REACTS VIOLENTLY	Inert atmosphere line
WITH WATER]	Rotary evaporator
Tetrahydrofuran (THF) [FLAMMABLE]	Glassware for column chromatography

Distilled water
Dichloromethane [TOXIC]
Anhydrous sodium sulphate
Acetone [FLAMMABLE]
Silica (for chromatography)

Note: Work in a fume hood wherever possible and exercise due caution when handling sodium hydride.

Under an inert atmosphere, prepare a suspension of sodium hydride (0.96 g, 20 mmol [50 per cent in mineral oil]) in dry THF* (50 mL) in a 250 mL two-necked round-bottomed flask fitted with a reflux condenser and pressure equalized addition funnel. Stir for 30 min under an inert atmosphere. Slowly add a solution of 8-hydroxyquinoline (2.90 g, 20 mmol) in dry THF (50 mL) to this through the addition funnel. Make up a solution of triethylene glycol ditosylate, **2**, (4.60 g, 10 mmol) in dry THF (50 mL), ensuring that no solids remain (filter if necessary) or the addition funnel may become blocked. Once the effervescence subsides following the formation of the sodium 8-hydroxyquinolinate salt, add the ditosylate solution and reflux for 24 h. After 24 h, allow the solution to cool to room temperature, filter off the precipitated sodium tosylate and remove the THF by rotary evaporation. Dissolve the residue in dichloromethane (30 mL) and wash with distilled water (3×30 mL). Dry the organic phase over anhydrous sodium sulphate, filter and remove dichloromethane by rotary evaporation to give the crude product, 1,9-bis(8-quinolinyloxy)-3,6-dioxanonane (**4**) as a pale brown oil. Further purification may be afforded by column chromatography (silica, elute with acetone/dichloromethane).

Yield: 2.0 g (50%); IR (υ, cm^{-1}): 3060, 2950, 1600, 1460, 1375, 1175, 1125; ^1H NMR (δ, ppm; $CDCl_3$) 8.9 (dd, 2 H, Ar*H*), 8.1 (dd, 2 H, Ar*H*), 7.4 (m, 6 H, Ar*H*), 7.1 (d, 2 H, Ar*H*), 4.4 (t, 4 H, OCH_2CH_2OAr), 4.1 (m, 4 H, OCH_2CH_2OAr), 3.8 (s, 4 H, OCH_2CH_2O).

*See compound **1** for drying method.

1.2 Rigid Components from Schiff Bases

While the flexibility of polyethers may be advantageous in many instances, it is often necessary to have a greater degree of preorganization in the ligands in order to entice guests, usually transition metals, into complex formation. Examples of this type include sexipyridine ligands used by Constable for metal complexation within a double helix [1] and Sauvage's copper-assisted formation of molecular trefoil knots from ligands derived from 1,10-phenanthroline [2].

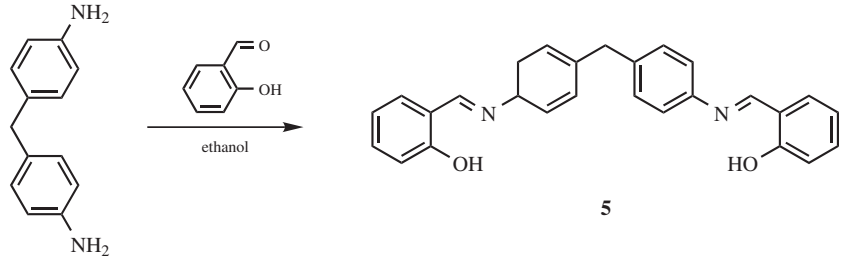

Figure 1.7 Synthesis of *N,N′*-(4,4′-methylenebiphenyl)bis(salicylideneimine) (**5**)

Hannon's group has prepared a range of rigid Schiff base ligands based on inexpensive starting materials [3]. The synthesis of these compounds is based on the addition of an aldehyde to a diamine (a method long used by coordination chemists to prepare ligands such as salens) with convergent binding sites, as shown in Figure 1.7. Coordination to transition metals results in highly coloured triple helical complexes containing two metal centres as can be seen in a simulation of Hannon's Ni_2L_3 complex, where L = bis(4-(2-pyridylmethyliminephenyl)methane) (Figure 1.8). Here, the diamine has divergent functionality leading to an extended ligand with an enforced twist.

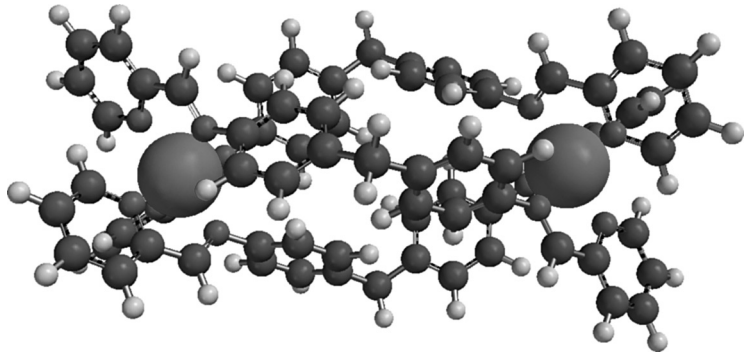

Figure 1.8 Simulation of Hannon's triple helical Ni_2L_3 complex

A single example is given here. Originating from Hannon's work on Schiff base compounds, but substituting salicylaldehyde for pyridine-2-carbaldehyde, compound **5** is extremely easy to prepare and can be used to bind various transition metals. Multifunctional ligands, with the potential for extended hydrogen bonding or metal mediated polymerization may be prepared from 1, 3- or 1, 4-dihydroxybenzaldehyde. The general method given will work for most combinations of methylenedianiline and aromatic aldehydes.

[1] Oligopyridines as helicating ligands, E. C. Constable, *Tetrahedron*, 1992, **48**, 10013.
[2] A synthetic molecular trefoil knot, C. O. Dietrich-Buechecker and J.-P. Sauvage, *Angew. Chem. Int. Ed. Engl.*, 1989, **28**, 189.
[3] An inexpensive approach to supramolecular architecture, M. J. Hannon, C. L. Painting, A. Jackson, J. Hamblin and W. Errington, *Chem. Commun.*, 1997, 1807.

Preparation of a Schiff base helicate component

N,N′-*(4,4′-Methylenebiphenyl)bis(salicylideneimine) (5)*

Reagents	**Equipment**
4,4-Methylenedianiline	Conical flask (100 mL)
Salicylaldehyde	Magnetic stirrer and stirrer bar
Ethanol [FLAMMABLE]	

Note: This compound can be prepared in a well-ventilated laboratory but will stain easily: take care when handling the product.

Place 4,4-methylenedianiline (1.6 g, 8 mmol) and ethanol (25 mL) in a 100 mL conical flask equipped with a stirrer bar. Stir at room temperature for about 20 min or until all the solid has dissolved. Add a solution of salicylaldehyde (1.9 g, 1.7 mL, 15 mmol) in ethanol (25 mL) and continue to stir. The solution turns an intense yellow colour before the product precipitates over 30 min as a yellow powder. The product is isolated in quantitative yield by filtration and washed with small quantities of ethanol to remove any unreacted starting materials. *N*,*N*′-(4,4′-methylenebiphenyl)bis(salicylideneimine) (**6**) is isolated as a yellow microcrystalline powder. Further purification should not be necessary, however, the product can be recrystallized from a minimum volume of boiling ethanol.

Yield: 3.2 g (quantitative); m.p.: 195–198 °C; IR (υ, cm^{-1}): 3020, 1615, 1595, 980, 865; ^{1}H NMR (δ, ppm; $CDCl_3$/DMSO-d_6) 13.3 (s, 2 H, ArO*H*), 8.95 (s, 2 H, −NC*H*Ar), 7.55–7.2 (m, 10 H, Ar*H*), 6.85 (m, 4 H, Ar*H*), 3.25 (s, 2 H, ArCH_2Ar).

1.3 Flexible Tripods

The podands described in Section 1.1 are essentially linear molecules that encapsulate metals through conformational changes which allow electron donor atoms to converge upon the guest. Conformational change in solution requires a rearrangement of the solvation sphere around the ligand as well as the physical change in the ligand's conformation. While this is not necessarily an energy intensive process, ligands in which the donor groups are already preorganized for the guests will always be more effective complexants for metals, particularly where high binding constants are required.

The tripodal molecules prepared here are derivatives of tris(2-aminoethyl)-amine, more commonly known as *tren*, a readily available compound well known for its ligating abilities [1]. The primary amine termini of the ligand are ideally suited to reaction with aromatic aldehydes, forming Schiff base derivatives easily, and the central nitrogen may later act as a donor atom [2,3]. As the three amine termini diverge from the central nitrogen, trisubstitution occurs without one *tren* arm influencing the rate of reaction at any other arm. N^1,N^1,N^1-Tris(2-(2-aminoethylimino)methylphenol) has been used to bind a variety of metals, notably lanthanides, that can achieve high coordination numbers [4]. It has also been used to chelate ^{99m}Tc, providing yet another complex that can be considered for use in nuclear medicine [5]. Methoxy derivatives of this ligand can be used to bind two lanthanides at the same time, as the simulation in Figure 1.9 illustrates, to yield

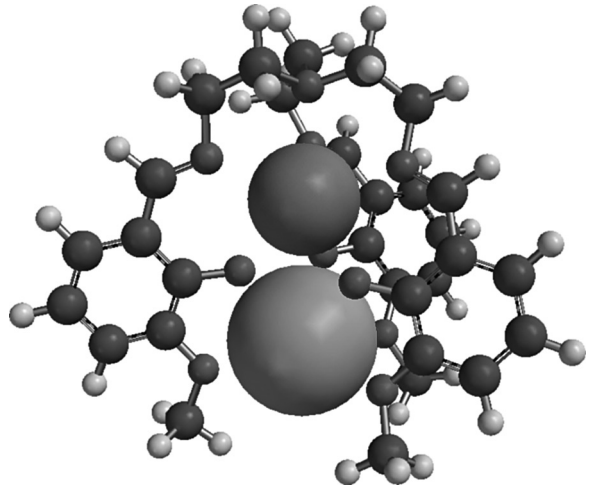

Figure 1.9 A bimetallic complex formed between a *tren*-derived ligand, gadolinium and neodymium

compounds with unusual magnetic properties [6]. Compounds based on the reduced forms of *tren*-derived ligands have also found widespread use as lanthanide chelators and as anion binding agents. The latter are discussed in the next section.

The syntheses of two very similar *tren*-derived podands are given here, N^1,N^1,N^1-tris(2-(2-aminoethylimino)methylphenol) (**6**) and N^1,N^1,N^1-tris(3-(2-aminoethylimino)methylphenol) (**7**), as shown in Figure 1.10. Both have phenolic termini: in the first they are in the 2-position and have the potential to converge on a guest, particularly a small transition metal, and in the second they are in the more divergent 3-position. By analogy with the extensive list of Schiff base ligands derived from ethylenediamine and aromatic aldehydes, many other tripodal ligands can be prepared using variations on the simple protocols given here.

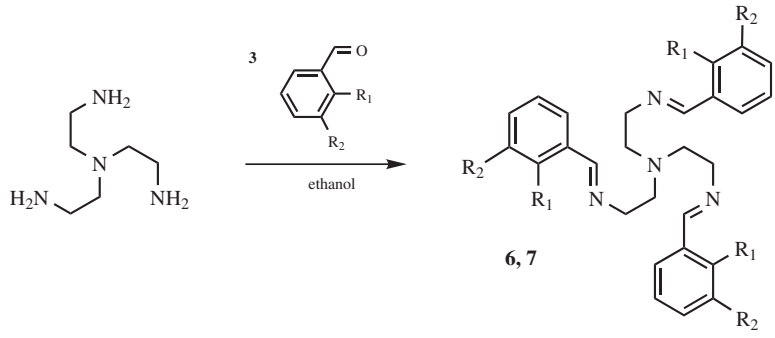

Figure 1.10 Syntheses of N^1,N^1,N^1-tris(2-(2-aminoethylimino)methylphenol) (**6**, $R_1 = OH$, $R_2 = H$) and N^1,N^1,N^1-tris(3-(2-aminoethylimino)methylphenol) (**7**, $R_1 = H$, $R_2 = OH$)

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Preparation of *tren*-derived tripods

N^1,N^1,N^1-*Tris(2-(2-aminoethylimino)methylphenol) (6)*

Reagents	**Equipment**
Tris(2-aminoethyl)amine (*tren*)	Round-bottomed flask (250 mL)
Salicylaldehyde	Heater/stirrer and stirrer bar
Ethanol [FLAMMABLE]	Reflux condenser
	Rotary evaporator

Note: Wherever possible this reaction should be carried out in a fume hood.

Dissolve salicylaldehyde (2.7 g, 2.4 mL, 21 mmol) in ethanol (50 mL) and place in a 250 mL round-bottomed flask equipped with a stirrer bar. Add a solution of tris(2-aminoethyl)amine (1.0 g, 1.0 mL, 7 mmol) in ethanol (50 mL) and stir at room temperature for 5 min while the pale yellow colour of the solution intensifies. Add a condenser and reflux the solution for 4 h. Upon completion cool the reaction mixture to room temperature and reduce the volume of solvent by *ca*. 80 per cent under vacuum. Place the concentrated solution in a refrigerator to precipitate the product. Filter the product, which forms as pale yellow fibrous crystals, and wash with a small amount of cold ethanol to give N^1,N^1,N^1-tris(2-(2-aminoethylimino)-methylphenol) (**6**) as a yellow microcrystalline powder. The product is pure by NMR and should not require recrystallization.

Yield: 3.0 g (∼95%); m.p.: 82–83 °C; IR (υ, cm^{-1}): 3055, 2940, 2900, 2820, 1635, 1615, 1585, 1500, 1280, 755; ^{1}H NMR (δ, ppm; $CDCl_3$) 13.8 (s, 3 H, ArO*H*), 7.8 (s, 3 H, ArC*H*=N), 7.3 (m, 3 H, Ar*H*), 6.9 (d, 3 H, Ar*H*), 6.6 (m, 3 H, Ar*H*), 6.1 (m, 3 H, Ar*H*), 3.6 (t, 6 H, =NCH_2CH_2–), 2.8 (t, 6 H, =NCH_2CH_2–).

N^1,N^1,N^1-*Tris(3-(2-aminoethylimino)methylphenol) (7)*

Reagents	**Equipment**
Tris(2-aminoethyl)amine (*tren*)	Round-bottomed flask (100 mL)
3-Hydroxybenzaldehyde	Magnetic stirrer and stirrer bar
Methanol [FLAMMABLE]	Heat gun
Ice	Ice bath
Diethyl ether [FLAMMABLE]	Glassware for filtration

Note: Wherever possible this reaction should be carried out in a fume hood.

Prepare a solution of 3-hydroxybenzaldehyde (10.0 g, 82 mmol) in methanol (30 mL) in a 100 mL round-bottomed flask equipped with a stirrer bar. The mixture may require a little gentle warming with a heat gun to aid dissolution. Add a solution of tris(2-aminoethyl)amine (4.0 g, 7 mmol) in methanol (50 mL) and stir at room temperature for 10 min. The reaction is slightly exothermic; upon completion the reaction mixture cools to room temperature. Unusually for a Schiff base condensation of this type there is very little change in colour. Place an ice bath under the reaction vessel and stir until the product precipitates as a cream solid. Filter the product and wash with a small amount of cold ethanol to give N^1,N^1,N^1-tris(3-(2-aminoethylimino)methylphenol) (**7**) as a cream microcrystalline powder.

Yield: 3.4 g (quantitative); m.p.: 172–174 °C; IR (υ, cm^{-1}): 2925, 2855, 2595, 1645, 1585, 1455, 1295; ^{1}H NMR (δ, ppm; $CDCl_3$) 9.5 (broad s, 3 H, ArO*H*), 8.1 (s, 3 H, ArC*H*=N), 7.2 (m, 3 H, Ar*H*), 7.1 (s, 3 H, Ar*H*), 7.0 (d, 3 H, Ar*H*), 6.8 (m, 3 H, Ar*H*), 3.6 (t, 6 H,=NCH_2CH_2–), 2.8 (t, 6 H,=NCH_2CH_2–).

1.4 Simple Anion Hosts

The natural world is concerned with binding anionic species just as much as cations and neutral molecules. It will not have escaped the notice of even the least biologically minded chemist that both DNA and RNA are polyanions. Vital biological processes involve the recognition and transport of anions such as sulphate, phosphate, carbonate and chloride. Impairment of the mechanisms by which these processes occur can have devastating effects for the organism concerned. For example, the deletion of three nucleotides from a particular gene results in the omission of a single phenylalanine from a transcribed protein. As a result the transmembrane transport of chloride across cells that form the lining of the lung is greatly reduced. This apparently trivial example is responsible for over 70 per cent of the incidents of cystic fibrosis, the most common lethal genetic defect in the Caucasian population. Another example of the importance of anion recognition is in the movement of phospholipids such as those with negatively charged phosphatidylserine head groups. Nature effects this with proteins that incorporate strongly bound calcium cations together with convergent recognition sites for carbonyl and amide groups [1].

A common motif for biological anion binding is the arginine residue which contains a terminal guanidinium group. This group is able to remain protonated over the entire physiological pH range and therefore provides an ideal monodentate or bidentate anion binding site. This motif is seen in the reversible phosphorylation of tyrosine. Protein tyrosine phosphatases that contain several convergent arginine residues are responsible for removing terminal phosphate groups from phosphotyrosine residues on proteins. The reverse process, transfer of a terminal phosphate from a nucleoside triphosphate to a tyrosine residue within a protein, is carried out by protein tyrosine kinases. The kinases were first identified in 1980 [2] and the phosphatases in 1988 [3]. Imbalance between the two processes has been implicated in many disease states including type-2 diabetes. One form of protein tyrosine phosphatase, YopH, is secreted by the bacterium *Yersinia pestis* responsible for the bubonic plague and may be a critical component in the virulence of that infection as it can translocate from the bacterium to the host organism [4]. Given the widespread biological occurrence of arginine as an anion-binding motif, it is no surprise that unnatural anion receptors have been designed to incorporate the related guanidinium cation, such as those in Figure 1.11. Guanidinium-based receptors have been prepared by several groups, most notably those of Lehn [5,6] and Schmidtchen [7]. Two excellent reviews are available covering general aspects of abiotic guanidinium groups in molecular recognition [8] and the more specific interactions between guanidinium groups and the oxyanions of phosphorus and sulphur [9].

The earliest anion-binding ligands to be prepared were those of Park and Simmonds [10,11] whose katapinands were similar to Lehn's later, and better known, cryptands but lacked coordinating oxygen atoms in the linkages connecting the

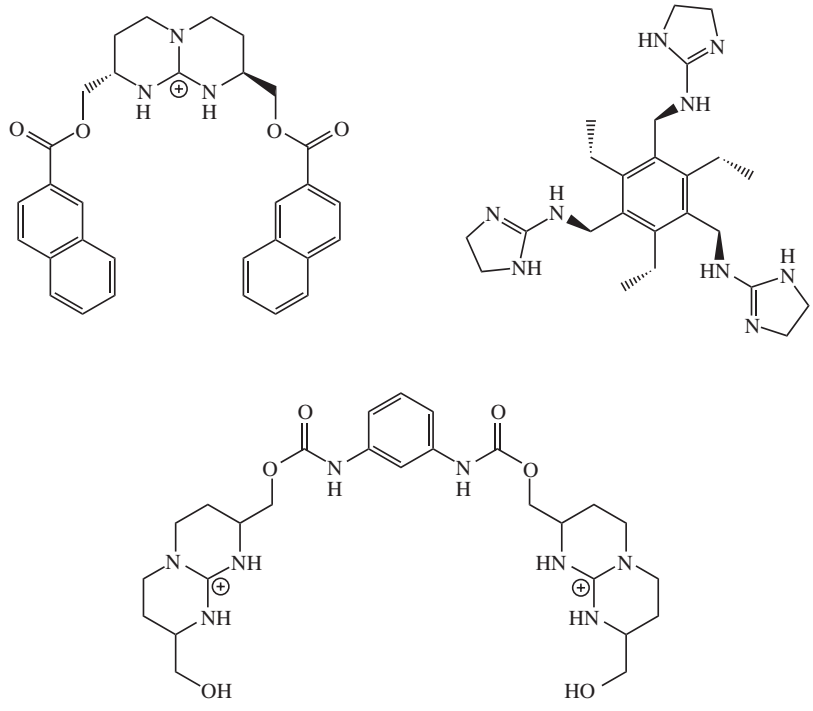

Figure 1.11 Guanidinium-based receptors

nitrogen atoms (Figure 1.12). In the diprotonated form this ligand was able to encapsulate chloride as shown by the X-ray structure of the complex. Graf and Lehn later reported that the tetraprotonated form of a tricyclic encapsulating ligand was able to bind both fluoride and chloride [12]. Similar compounds have been used to complex ATP through recognition of the polyphosphate residue by protonated regions in mixed oxa- and azacrown ethers that incorporate a pendent acridine group which is believed to π-stack with adenosine [13]. Many polyammonium-containing ligands, mostly macrocycles, have since been prepared. A particular design twist was incorporated by Schmidtchen who prepared molecular tetrahedra containing quaternary ammonium groups at the vertices [14].

An alternative approach is to design a proton-rich cavity that is flexible yet predisposed to bind to a particular anion. Examples of this type include the metal-containing polyazacryptands reported by Lehn [15] and Nelson [16] that encapsulate guests such as succinate and nitrate. A more flexible approach has been taken by Reinhoudt [17], Beer [18] and Bowman-James [19] who have used tris(aminoethyl)amine, *tren*, as the basis for preorganized anion binding and whose derivatives as shown in Figure 1.13. Most recently this theme has been extended to include *tren*-derived, Schiff-base podands that have subsequently been reduced to form trisamines capable of binding anions, from phosphate to bromide, with a range of specificities [20]. The preparation of reduced Schiff-base podands is not

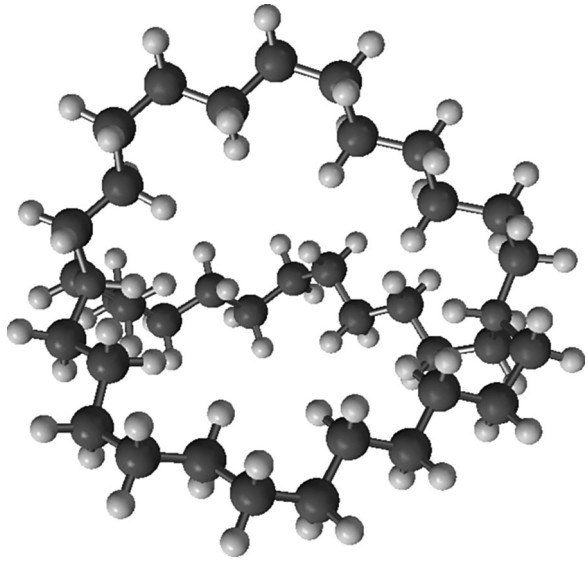

Figure 1.12 A katapinand in the 'in–in' conformation

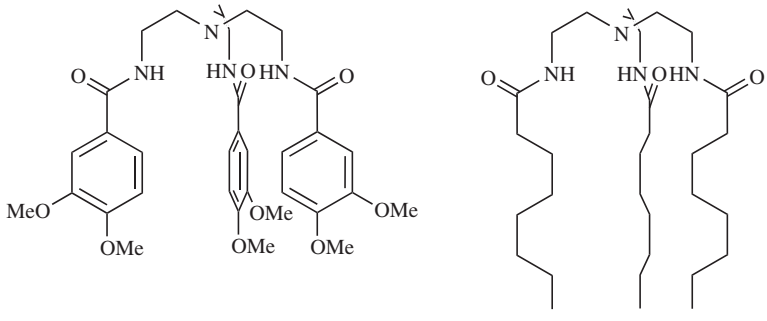

Figure 1.13 *Tren*-derived anion-binding podands

new [21–23], however, their application to the field of anion recognition is becoming more widespread. One example given here uses potassium borohydride to reduce the podand N^1,N^1,N^1-tris(2-(2-aminoethylimino)methylphenol) (**6**) and the other gives a one-pot synthesis of N^1,N^1,N^1-tris((2-aminoethylamino)methylbenzene) (**9**). The synthesis of the former can be found in a preceding section. Note that the reduction of triphenol **7** yields a derivative that can only be extracted into chloroform (dichloromethane is not polar enough) and is hydroscopic. As a result redissolution of the isolated product is difficult. The reduced ligands, shown in Figure 1.14, have the ability to bind a variety of guests but, due to the presence of amine groups, are ideal for tetrahedral oxyanions such as phosphate (Figure 1.15). Many variations are possible with this class of podands, most obviously in the aromatic substitution pattern. The most basic example [20]

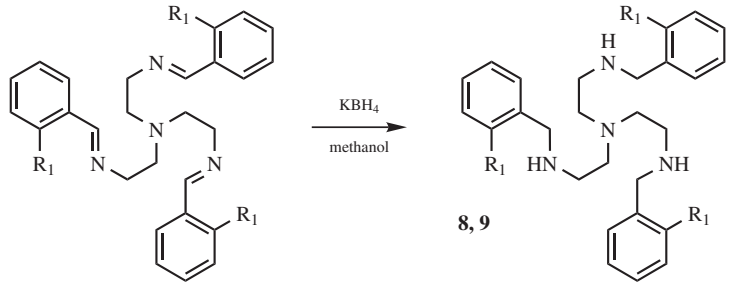

Figure 1.14 Syntheses of N^1,N^1,N^1-tris(2-(2-aminoethylamino)methylphenol) (**8**, $R_1 = OH$) and N^1,N^1,N^1-tris(2-aminoethylamino)methylbenzene) (**9**, $R_1 = H$)

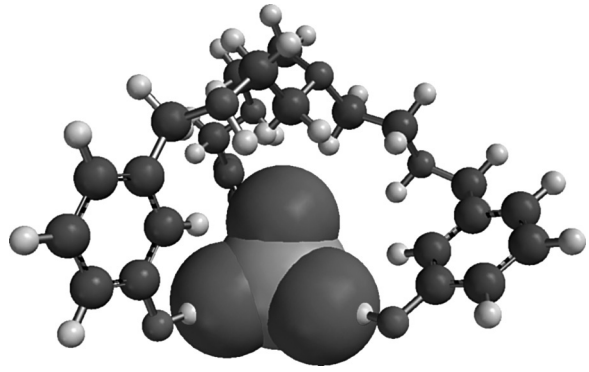

Figure 1.15 Phosphate binding by a tripodal ligand

employs benzaldehyde to give unsubstituted benzene termini; other examples use hydroxynaphthaldehyde and *o*-vanillin to introduce naphthyl and methoxybenzene functionality, respectively. The amine core of these tripodal ligands also has the potential to aid in ligand preorganization by binding metal ions. The resulting cationic species will attract anions of the correct size and complementary geometry. The copper complex of a more complex reduced *tren*-derivative, incorporating benzylamine termini, has been shown to bind a variety of anionic guests [24]. In summary, the reduced forms of the *tren*-derived ligands can complex a remarkable range of species from simple anions to lanthanides. It would be surprising if they did not also complex a range of transition and main group metals.

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Reduction of *tren*-derived tripods

N^1,N^1,N^1-*Tris(2-(2-aminoethyamino)methylphenol) (8)*

Reagents
N^1,N^1,N^1-Tris(2-(2-aminoethylimino)-methylphenol) (**7**)
Potassium borohydride [CORROSIVE; REACTS VIOLENTLY WITH WATER]
Methanol [FLAMABLE]
Ammonium chloride (2 M, aqueous solution)
Chloroform [TOXIC; CARCINOGEN]
Distilled water
Anhydrous magnesium sulphate

Equipment
Round-bottomed flask (250 mL)
Magnetic stirrer and stirrer bar
Heat gun
Rotary evaporator
Glassware for extraction and work up

Note: This reaction should be carried out in a well-ventilated laboratory. Exercise due care when handling potassium borohydride.

Dissolve N^1,N^1,N^1-tris-(2-(2-aminoethylimino)methylphenol) (**7**) (1 g, 2.2 mmol) in methanol (100 mL) in a 250 mL round-bottomed flask equipped with a stirrer bar. Gentle heating may be necessary to effect complete dissolution. Add potassium borohydride (0.4 g, 7.4 mmol) in small portions to the bright yellow solution. During the addition the solution completely decolorizes. Continue to stir at room temperature for a further 1 h after the last portion of potassium borohydride has been added. Upon completion remove the solvent under vacuum to leave a white solid. Add a solution of ammonium chloride (20 mL of a 2 M aqueous solution) to the crude product, cautiously at first, to ensure all the potassium borohydride has been consumed. Extract with chloroform (50 mL

then 2 × 25 mL), wash with distilled water (30 mL) and dry the organic phase with magnesium sulphate (*ca*. 1 g). Filter the solution and remove the solvent under vacuum to give N^1,N^1,N^1-tris(2-(2-aminoethylamino)methylphenol) (**8**) as a colourless, hydroscopic oil that solidifies when held under high vacuum for several hours.

Yield: 0.8 g (∼80%); m.p.: 45–46 °C; IR (υ, cm^{-1}): 3310, 3010, 2825, 1630, 1590, 1490, 1255; ^{1}H NMR (δ, ppm; DMSO-d_6) 7.1–7.0 (m, 6 H, Ar*H*), 6.8–6.7 (m, 6 H, Ar*H*), 3.8 (s, 6 H, NCH_2Ar), 2.6–2.4 (m, 12 H, NCH_2CH_2N).

N^1,N^1,N^1-*Tris((2-aminoethylamino)methylbenzene) (9)*

Reagents
Tris(2-aminoethyl)amine (*tren*)
Benzaldehyde
Methanol [FLAMMABLE]
Potassium borohydride [CORROSIVE; REACTS VIOLENTLY WITH WATER]
Sodium hydroxide [CORROSIVE]
Chloroform [TOXIC; CARCINOGEN]
Distilled water
Anhydrous magnesium sulphate

Equipment
Round-bottomed flask (250 mL)
Magnetic stirrer and stirrer bar
Calcium chloride guard tube
Glassware for extraction and work up
Rotary evaporator

Note: This reaction should be carried out in a well-ventilated laboratory. Exercise due care when handling potassium borohydride.

Prepare a solution of tris(2-aminoethyl)amine (1.95 g, 2.0 mL, 13 mmol) in methanol (75 mL) in a 250 mL round-bottomed flask equipped with a stirrer bar. Dissolve benzaldehyde (4.2 g, 4.0 mL, 40 mmol) in methanol (25 mL), add slowly to the *tren* solution, stopper the flask and stir at room temperature for 24 h while the pale yellow colour intensifies. Upon completion, remove the stirrer bar and reduce the volume of solvent by *ca*. 50 per cent under vacuum. To this methanolic solution of N^1,N^1,N^1-tris(2-(2-aminoethylimino)methylbenzene) add potassium borohydride (4.9 g, 90 mmol) in small portions while stirring vigorously. After the final addition, fit a calcium chloride guard tube. A slightly exothermic reaction ensues and the mixture effervesces for several hours. Stir at room temperature for 24 h while the solution fades in intensity and a pale yellow solid precipitates. Cautiously add an aqueous solution of sodium hydroxide (8 g in 50 mL) and stir for a further 1 h. Extract the resulting white emulsion with chloroform (1 × 100 mL then 2 × 50 mL), wash with distilled water (50 mL), dry with magnesium sulphate, filter and remove solvent using a rotary evaporator. Note that the addition of water leads to the formation of a white suspension; addition of magnesium sulphate

clarifies the solution. The product, N^1,N^1,N^1-tris((2-aminoethylimino)methylbenzene) (**9**) is isolated as a yellow oil and is suitably pure for further experimentation.

Yield: 4.9 g (90%); IR (υ, cm^{-1}): 3025, 2815, 1450, 1050, 730, 695; ^{1}H NMR (δ, ppm; $CDCl_3$) 7.4–7.2 (m, 15 H, Ar*H*), 3.7 (s, 6 H, ArCH_2), 2.7 (t, 6 H, NHCH_2CH_2N), 2.5 (t, 6 H, $NHCH_2CH_2$N).

1.5 Rigid Platforms

Other 'molecular tripods' have been prepared, such as those based on 1,3,5-trisubstituted cyclohexane, including a wide range of ligands that have evolved from Kemp's triacid, in particular those devised by Rebek [1] and the related work of the Walton group [2,3]. This motif is of particular interest to those investigating self-replication of small molecules. *N*,*N*′,*N*″-Trisubstituted triazacyclononane, [9]aneN_3, also makes an excellent platform for further functionalization. The binding pockets present in these compounds make their metal complexes interesting mimics for a range of enzymes, particularly those incorporating zinc or copper. Some representative examples of rigid tripodal ligands are shown in Figure 1.16.

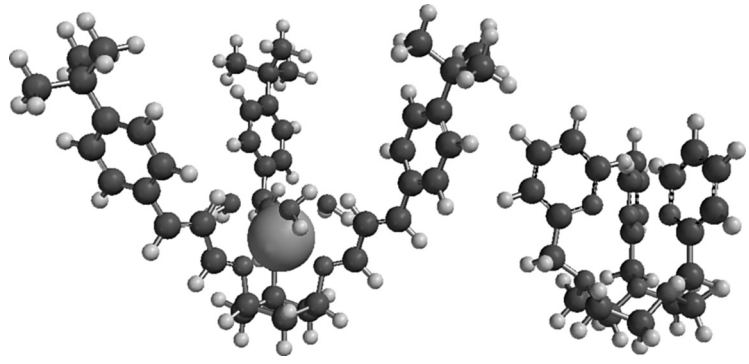

Figure 1.16 Rigid tripodal ligands based on 1,3,5-trisubstituted cyclohexane (left) and 1,3,9-triazacyclononane (right)

In addition to the tripodal structural motifs mentioned above, one obvious choice to imbue a ligand with threefold symmetry is to use 1,3,5-trisubstituted benzene as a base. The formation of the alternating conformation for substituents on a hexasubstituted benzene is a well-known phenomenon: an early example where this was used in a supramolecular context was by Harshorn and Steel in 1996 [4]. Subsequently the principle has been used widely particularly in the detection of anions [5–8]. The parent 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene is fairly complex to prepare [9], however, the corresponding mesitylene

derivative, 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene, can be made on a multigram scale in yields approaching 100 per cent [10]. From this derivative Sato [11], and later Howarth [12], were able to prepare tripodal anion receptors. An excellent review was published by Anslyn, which charts the development of these compounds up to 2002 [13]. More recently, Itoh has shown that a variety of different topologies may result from the reaction of a related 1,3,5-tris[2-(pyridin-2-yl)ethyl]-2,4,6-triethylbenzene with copper, zinc or palladium [14].

The example given here is derived from 1,3,5-tri(bromomethyl)-2,4,6-trimethylbenzene (**10**), as it is significantly easier to prepare than the 2,4,6-triethylbenzene analogue (Figure 1.17). The choice of benzene as a base for the tripod gives a

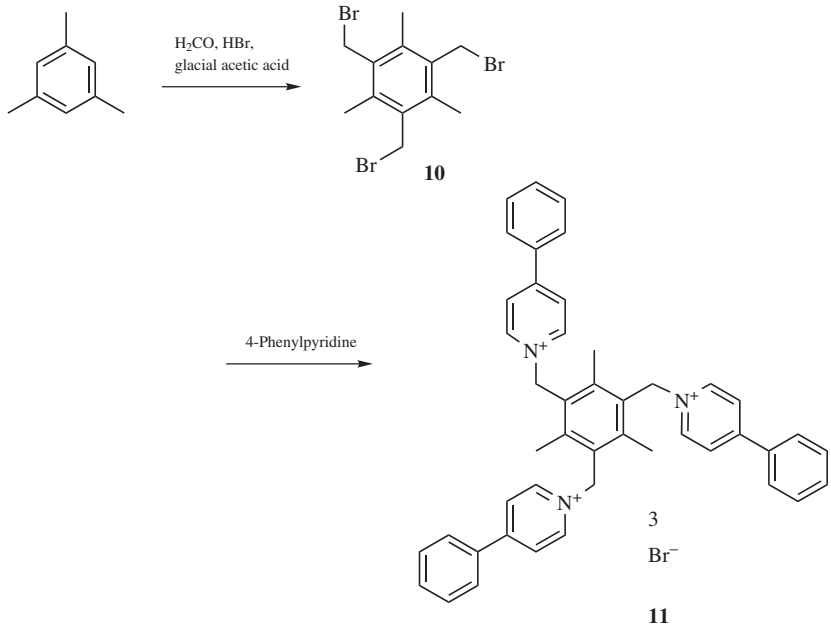

Figure 1.17 Synthesis of tripodal ligand **11** via tribromide **10**

sterically hindered product in which the ideal structure has 1,3,5-substituents and 2,4,6-substituents directed in opposite directions from face of the aromatic ring. Coordinating groups can then be focused in a convergent fashion towards a point perpendicular to the centre of the aromatic ring to give a well-defined binding site as shown in Figure 1.18. The range of tripyridyl compounds that could be prepared from 1,3,5-tri(bromomethyl)trimethylbenzene is probably only limited by the solubilities of the pyridine derivatives in dichloromethane. The method described for the tri(4-phenylpyridine) derivative (**11**) should be applicable to numerous variations on the example given.

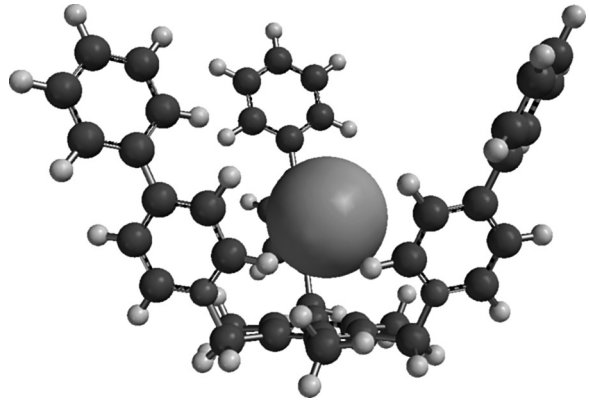

Figure 1.18 A rigid anion binding tripodal ligand based on 1,3,5-trisubstituted benzene

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Preparation of 1,3,5-trisubstituted benzene tripods

1,3,5-Tri(bromomethyl)-2,4,6-trimethylbenzene (10)

Reagents	**Equipment**
1,3,5-Trimethylbenzene (mesitylene)	Round-bottomed flask (100 mL)
Paraformaldehyde [TOXIC; CARCINOGENIC]	Heating mantle/stirrer and stirrer bar
Glacial acetic acid [CORROSIVE]	Reflux condenser
Hydrogen bromide in acetic acid (31%) [CORROSVE]	Glassware for filtration
Distilled water	
Diethyl ether [FLAMMABLE]	

Note: This reaction should be carried out in a fume hood.

Add mesitylene (6.0 g, 50 mmol), paraformaldehyde (5 g, 170 mmol) and glacial acetic acid (25 mL) to a 100 mL round-bottomed flask and stir at room temperature. Add a solution of hydrogen bromide in acetic acid (35 mL, 31 per cent v/v), heat to 90 °C and stir for 12 h. At this temperature the paraformaldehyde dissolves to give an orange solution. When the reaction is complete a white solid remains. Pour this into water (100 mL) and rinse out the reaction flask with more water (100 mL). Stir vigorously to break up the precipitate and filter to give 1,3,5-tri(bromomethyl)trimethylbenzene (**10**) as a white solid. Further purification can be afforded by stirring the solid in boiling diethyl ether (200 mL) and filtering. Although this process reduces the yield slightly it also removes coloured impurities. Note that this compound starts to decompose if left under ambient conditions for more than a week and should be used immediately to prepare derivative **11**.

Yield: 14 g (70%); m.p.: 186 °C; IR (υ, cm^{-1}): 3025, 1560, 1080, 1010, 785, 575; ^1H NMR (δ, ppm; $CDCl_3$) 4.6 (s, 6 H, ArCH_2Br), 2.5 (s, 9 H, ArCH_3).

1,3,5-Tris[(4-phenylpyridine)methyl]-2,4,6-trimethylbenzene tribromide (11)

Reagents	**Equipment**
1,3,5-Tri(bromomethyl)-trimethylbenzene (**10**)	Round-bottomed flask (250 mL)
4-Phenylpyridine	Pressure-equalized dropping funnel
Dichloromethane [TOXIC]	Inert atmosphere line
	Glassware for work-up

Note: This reaction should be carried out in a fume hood.

Stir a solution of 4-phenylpyridine (1.16 g, 7.5 mmol) in dichloromethane (50 mL) in a 250 mL round-bottomed flask at room temperature under an inert atmosphere. Add a solution of 1,3,5-tri(bromomethyl)trimethylbenzene (1 g, 2.5 mmol) in dichloromethane (50 mL) dropwise from a pressure-equalized dropping funnel. A white precipitate forms after an hour or so, however, it is worth stirring for a further 12 h to ensure the reaction goes to completion. When the reaction is complete, filter and wash with dichloromethane (25 mL) to give 1,3,5-tris[(4-phenylpyridine)methyl]-2,4,6-trimethylbenzene tribromide (**11**) as a white powder.

Yield: 2.1 g (95%); m.p.: >250 °C; IR (υ, cm^{-1}): 3100, 3025, 1635, 1555, 1135, 850, 765, 715, 695; ^{1}H NMR (δ, ppm; CD_3OD) 8.85 (m, 6 H, Ar*H*), 8.45 (m, 6 H, Ar*H*), 8.05 (m, 6 H, Ar*H*), 7.65 (m, 9 H, Ar*H*), 4.9 (s, 6 H, CH_2), 2.6 (s, 9 H, CH_3).