Chapter 5

Photophysical Measurements for Fluorescent Anion Sensors and the Binding Constants for the Host-Guest Interactions

5. Photophysical measurements for fluorescent molecular sensors and the binding constants for the host-guest interactions

5.1. Summary of the findings from the preliminary fluorescence studies and the host-guest binding studies using ^{1}H NMR

The preliminary fluorescence studies have shown that the ligands, **146**, **170-172**, undergo a partial revival of fluorescence upon protonation and complexation, in accordance with a PeT mechanism. The quantum yields of the receptor complexes, however, are still well below unity, indicating that further perturbation in either an upward or downward direction, as a guest molecule binds to the receptor complex, is a possibility. From the use of ^{1}H NMR titration experiments, for the investigation of host-guest interactions, it was shown that Cd(II) complexes of the fluorescent ligands (**146**, **170-172**), do act as strong receptors for a variety of guests, **9-16, 178, 25-29**, in DMSO-d_6, even though one of the O-H hydrogen bond donors at the base of the binding cavity present **1** is compromised by converting it to N-H or eliminated by converting it to N-R. Guest molecules so far identified can be divided up into five basic types; phenolates, benzoates, acetates, amino acids and sulfonates. Trends were discovered revealing that within the individual classes, the guests with the higher pK_a values tend to bind more strongly, which can be related to the charge density at the oxygen atoms of the anions. It was also observed that the longer guests, such as histidinate, bind more strongly in receptor **4** than in receptor **5**, which is methylated on the upper rim of the cavity. Dioxoanions, such as phenoxyacetate, generally have larger log$K$ values in receptors **4** and **5** than in receptors **6** and **7**, in which the anthrylamine is tertiary.

A limitation of the NMR method for determining host-guest binding constants is that because they have to be determined at millimolar concentrations of

reagents, an upper limit to its usefulness is reached when log*K* becomes equal to *ca* 4.8. At this value the uncertainty on the measurement becomes disturbingly large, as was seen, for example, in **Table 3.2.** This limitation can be eased by using related methods where the sensitivity of the signal being monitored is higher. This allows the titrations to be conducted at lower concentrations of reagents (in this work, 10^{-4} mol dm^{-3} for UV-visible absorption spectroscopy, and down to 10^{-6} mol dm^{-3} for fluorescence) where the level of host-guest association for a given *K* value reduces commensurately. Thus, the range of binding constant values that can be determined with reasonable certainty extends to *ca* log*K* = 5.5 if a UV signal is monitored for a 10^{-4} mol dm^{-3} solution or up to *ca* log*K* = 7.5 if a fluorescence signal is monitored using a 10^{-6} mol dm^{-3} solution. Titration curves for the differing reagent concentrations have been modelled for differing log*K* values and may be seen in **Appendix A**, **Figures A2** and **A3**.

With the fluorescence properties of the receptor ligands and receptor complexes examined, and in the knowledge that these receptor complexes do indeed include small molecules, the study of the fluorescence perturbations induced in the receptor complex by the inclusion of guest anions could now be undertaken.

5.2. Guest inclusion within metal ion activated molecular sensors

There are many ways by which the fluorescence of the receptor complexes may be either quenched or sensitised. Quenching is the deactivation of the excited fluorophore by an external (usually ground-state) component, known as the quencher.[264] Sensitising is the increase of fluorescent de-excitation of an excited fluorophore. There are at least seven processes associated with guest molecule

inclusion within the fluorescent receptors under discussion that may cause its fluorescence to undergo perturbation. These are as follows:

Process 1 is perturbation of the receptors' fluorescence by **solvent displacement** from the receptor cavity on guest entry. Fluorescence is known to be solvent dependent[188,265], especially in cases where water is present, such as is the case here where the work to be described is in 20% aqueous 1,4-dioxane. Although this process is not well understood, there is the potential for O-H $\cdots$ π hydrogen bonding of the water to the aromatic rings of the fluorophore, which would allow energy exchange and quenching of the fluorescence. Any displacement of water by the guest anion (that was a less effective quencher) would result in an **increase of fluorescence**.

Process 2 is **PeT interference due to anthryl N-H hydrogen bond donation** towards the guest. The formation of a hydrogen bond between the anthrylamine of receptor complexes **4** and **5** and the guest oxoanion results in the pushing back of electron density onto the amine, as the proton becomes more associated with the oxoanion. The increase of electron density on the amine should increase PeT, and would result in a **quenching** of fluorescence.

Process 3 is **PeT interference through space**. Fluorescence quenching due to a host$\rightarrow$guest or guest$\rightarrow$host electron transfer process, is possible with guests such as nitrobenzoate and dimethylaminobenzoate, for which the electron acceptor and donor tendencies, respectively, are well known.[165,264] Thus, the fluorescence can be **quenched** upon guest inclusion, if the formation of the host-guest complex results in electron transfer between fluorophore and guest, as shown in **Figure 5.1**.[266,267]

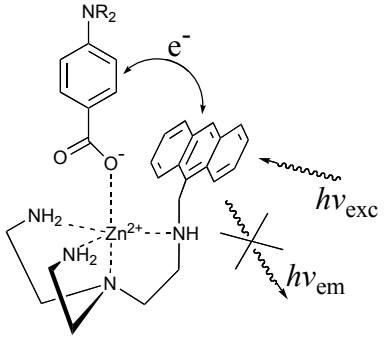


Figure 5.1. A representation of the electron transfer mechanism responsible for fluorescence quenching (**process 3**) of an excited anthracene unit, which signals the binding of a strongly electron accepting or donating substituted benzoate anions by the anion by the Zn(II) centre. Modified from reference 165.

Process 4 is **hydrogen bonding to the fluorophore.**[265] This involves fluorescence **quenching** in cases where the guest species forms, for example, O-H...π hydrogen bonds to the aromatic group of the excited fluorophore.

Process 5 is **collisional quenching**, which can include solvent quenching (already discussed under **Process 1**) and oxygen quenching. This will result in a **decrease in fluorescence**, as the excited state energy is lost through collisions of the excited fluorophore with other molecules. Since all experiments in this work were conducted in deoxygenated solutions, quenching by oxygen is not an issue here.

Process 6 is the **electronic energy transfer** quenching pathway, where the guest has excited-singlet states lower in energy than the first excited singlet of the fluorophore, allowing the excited state fluorophore to donate its electronic energy to a ground-state species[264] of the guest, in a singlet-singlet energy transfer. This process **quenches** the fluorescence of the fluorophore.[265]

Process 7 is the **formation of excimers or exciplexes**. In some circumstances there can be the initial formation of a complex between the excited-state fluorophore and a ground-state quencher.[264] These complexes are known as exciplexes,[268] from ***exci***ted com***plexes***, where the species are different, or as excimers,[23,26,157,159,160,269] from ***exci***ted di***mers***, where the species are the same.[149] These are emitting charge-transfer complexes, which are held together by favourable

orbital interactions or coulombic binding forces and may be stabilised by solvent interactions. The fluorescence spectra of excimers and exciplexes are notable in that the observed fluorescence is almost always at **longer wavelengths**, than the fluorescence of the excited-state fluorophore alone,[264,268] and that **loss of vibrational fine structure** occurs. Neither excimers nor exciplexes were seen in this work.

In addition to these processes, photodecomposition could also cause a decrease in fluorescence intensity.

At the outset it was not known which of these processes, if any, would be involved in generating fluorescence perturbations upon guest inclusion within the receptor complexes. To investigate this, a series of titration experiments in which fluorescence perturbation was monitored was conducted.

5.3. Photophysical guest inclusion titrations

All titrations were conducted in 20% aqueous 1,4-dioxane, at the same pH as the metal ion complexation experiments, to allow direct comparisons to be made. The solution was maintained at pH 7.0 (0.02 mol dm^{-3} lutidine (with the metal ions already strongly complexed in these experiments, buffers that are potential ligands no longer had to be avoided)), with constant ionic strength I = 0.1 mol dm^{-3} (NEt_4ClO_4), at 25°C. Host concentrations of 10^{-4} or 10^{-6} mol dm^{-3} were used. One limitation of the use of this solvent at pH 7.0 is that phenolate guests are unable to be investigated, since because of their weak acidity they would mostly be in the neutral phenol form, rather than the anionic phenolate. For this reason fluorescence perturbation by only the benzoate, acetate, amino acid and sulfonate classes of guest was investigated.

In some instances guests were used which absorb light in the regions of interest for the absorption and fluorescence studies. When guests absorb at either the excitation wavelength (350 nm) or in the region that the fluorophore emits (370-550 nm) corrections are required for the reduced intensity of the excitation beam and/or the absorbance of the emitted light, respectively. If not corrected, then the fluorescence perturbation could not be taken to be indicative of molecular inclusion. The absorbance spectra for all potential guests were examined before any fluorescence measurements were conducted. Of the guests that were studied only *p*-nitrobenzoate, showed any absorption in these regions, and for it the appropriate corrections, based on its molar extinction coefficients at the relevant wavelengths, were made.

In any discussion of fluorescence measurements the determination of quantum yields is desirable. The method for the determination of quantum yields is detailed in **Chapter 6**, and requires knowledge of the absorbance of the fluorophore at the excitation wavelength. Accordingly, before titrations in which fluorescence changes were monitored could begin, titrations in which the absorbance of the host complex were monitored had to be undertaken.

5.4. UV-Visible absorption titration studies for guest inclusion with fluorescent receptors 4-7

The titration of receptor **4** using sodium *p*-nitrobenzoate, **14**, in 20% aqueous 1,4-dioxane, under the conditions given in **5.3**, generated the series of UV-visible spectra shown in **Figure 5.2**. The absorption of **4** showed a moderate increase in the four bands at *ca* 390, 368, 350 and 334 nm, but no hypso or bathochromic shifts were observed**.**

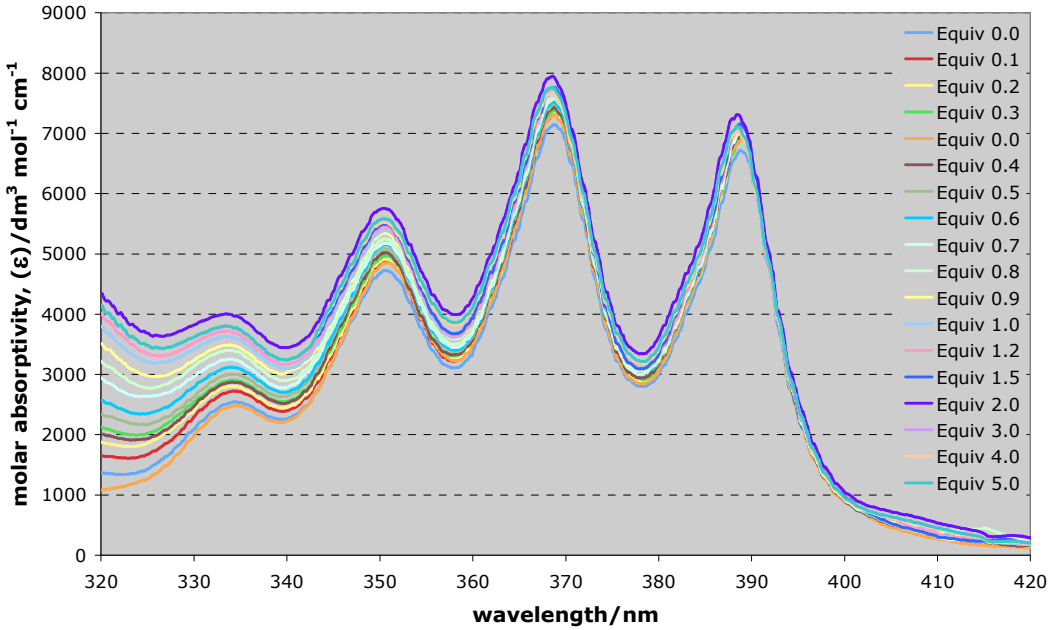


Figure 5.2. Absorption spectra of receptor complex **4** (1 x 10^{-4} mol dm^{-3}) with increasing molar equivalents of *p*-nitrobenzoate, **14**.

The inclusion of other guests showed similar changes, as did inclusions within the other hosts, **5**-**7**. The results are tabulated in **Table 5.1.** Interestingly there appears to be chiral discrimination between the *D* and *L* amino acids, most dramatically between (*D*)-tryptophanate, which showed *ca* 15% increase in absorbance, and (*L*)-tryptophanate, which showed *ca* 5% diminution in absorbance.

The UV-visible spectra provided the absorbance values necessary for the calculation of quantum yields. In addition the associated titration curves provided a means for determining the value of the guest binding constants, which gave the opportunity to confirm and expand upon the host-guest binding studies described in **Chapter 3**. This was considered a crucial part of the overall project as it is only by surveying a wide range of potential guests and measuring their binding constants with the different hosts that a true picture of the host selectivity can be established.

Table 5.1. Changes in absorbance of the receptor complexes **4**-**7** at 350 nm in response to guest inclusion.

Guest	Maximum observed changes in Absorption[a,b]			
	4	**5**	**6**	**7**
p-nitrobenzoate, **14**	19.1%	16.1%	24.5%	22.7%
p-aminobenzoate, **15**	32.5%	11.4%	28.7%	4.7%
p-dimethylaminobenzoate, **16**	6.6%	5.9%	12.3%	18.8%
benzoate, **18**	51.7%	-	25%	-
p-hydroxybenzoate, **19**	6.8%	3.1%	7.8%	7.7%
m-hydroxybenzoate, **20**	-0.6%	-	-	-
3,5-dihydroxybenzoate, **21**	18.7%	-	-	-
gallate, **22**	4.1%	-	4.1%	4.4%
o-hydroxybenzoate, **23**	5.5%	-	-	-
2,6-dihydroxybenzoate, **24**	8.1%	-	-	-
phenoxyacetate, **25**	4%	0%	0%	0%
(*D*)-histidinate, **26**	2.8%	0%	-10.4%	-8.9%
(*L*)-histidinate, **27**	-3.4%	-7.3%	-6.8%	-1.1%
(*D*)-tryptophanate, **28**	15.1%	11.0%	0%	0%
(*L*)-tryptophanate, **29**	-4.7%	0%	0%	0%
p-toluenesulfonate, **30**	2.2%	6.5%	3.2%	6.2%
benzenesulfonate, **31**	2.7%	1.2%	4.8%	4.2%

[a]Measured at pH 7.0 (0.02 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4). [b]The maximum observed change generally corresponded to the addition of 5-10 molar equivalents of the guest anion.

Some guests that showed no ^{1}H NMR chemical shift perturbation may induce UV-visible absorbance perturbations in the host that could be monitored, thereby expanding the range of binding constant measurements possible. Examples of this are *p*-hydroxybenzoate and the sulfonates, **30** and **31**. Interestingly, it was also observed that some guests that did show ^{1}H NMR chemical shift perturbation induced no UV-visible absorbance perturbation, such as the inclusion of phenoxyacetate in receptors **5**-**7**.

5.5. Strategy for obtaining binding constants determined from spectrophotometric measurements

From the UV-visible absorption spectra obtained in the titrations of the guest molecules with the receptor complexes, wavelengths were selected that show a change of absorption on addition of the guest species. A plot of the molar extinction coefficient against equivalents of guest could then be produced at the wavelength monitored. The log*K* values could then be determined through use of non-linear regression analysis, as described in **Appendix A3**.

5.6. Binding constants determined from absorption measurements

5.6.1. Binding constants for anionic guests with the fluorescent receptor having four hydrogen bond donor groups at the base of the cavity, 4.

The titration of [Cd((*S*)-athppc)]$(ClO_4)_2$, **4**, with *p*-nitrobenzoate, **14**, gave rise to the series of absorbance spectra as shown in **Figure 5.2** and expanded in **Figure 5.3.** The titration curve obtained from monitoring the change in the molar extinction coefficient of the system (at 350.5 nm) upon addition of **14** is shown in **Figure 5.4.**

The binding constant (to 2 SD) was calculated from the curve, with the value for the inclusion of *p*-nitrobenzoate, **14**, within receptor **4** determined as log*K* = 4.6 ± 0.3. This is within the range for the value of the binding constant determined from the ^{1}H NMR binding constant determination of log*K* (4.4 ± 0.3). The two methods, NMR and UV-visible, are not totally comparable in that the titration experiments are performed in different solvents, and the difference in solvents should have an effect on the association of the guest molecules. The NMR studies were performed using

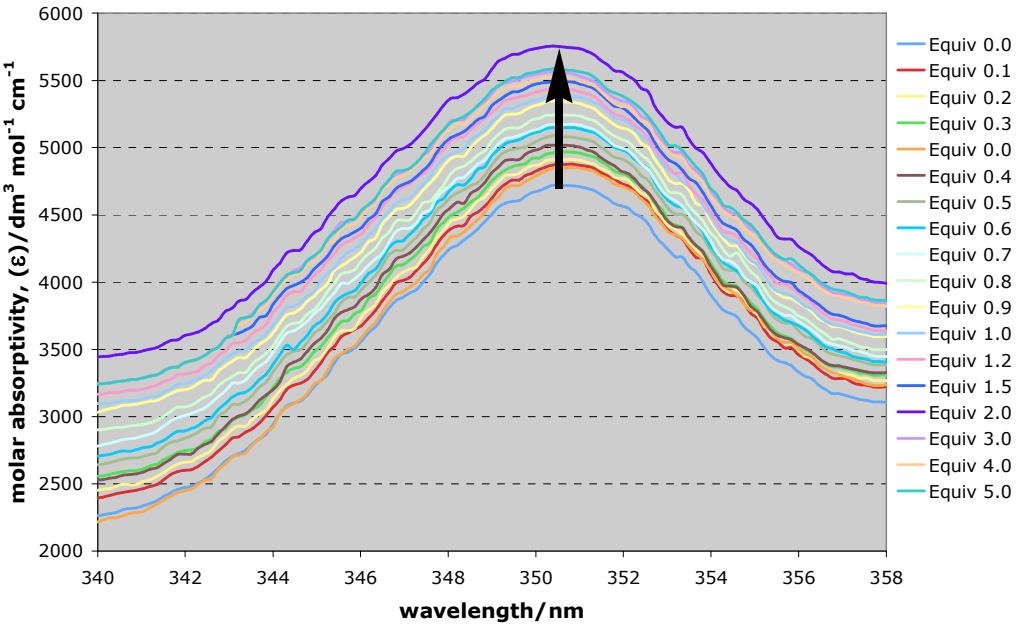


Figure 5.3. An expansion (from 340 nm to 358 nm) of the **Figure 5.2** UV-visible absorption spectra of receptor **4** alone [10^{-4} mol dm^{-3}] (bottom spectrum), and in the presence of increasing amounts of *p*-nitrobenzoate, **14**, from 0.1 molar equivalent to 5.0 molar equivalents, at pH 7.0 (0.02 mol dm^{-3} lutidine buffer) in 20% aqueous 1,4-dioxane (I = 0.1 mol dm^{-3}, NEt_4ClO_4) at 298 K.

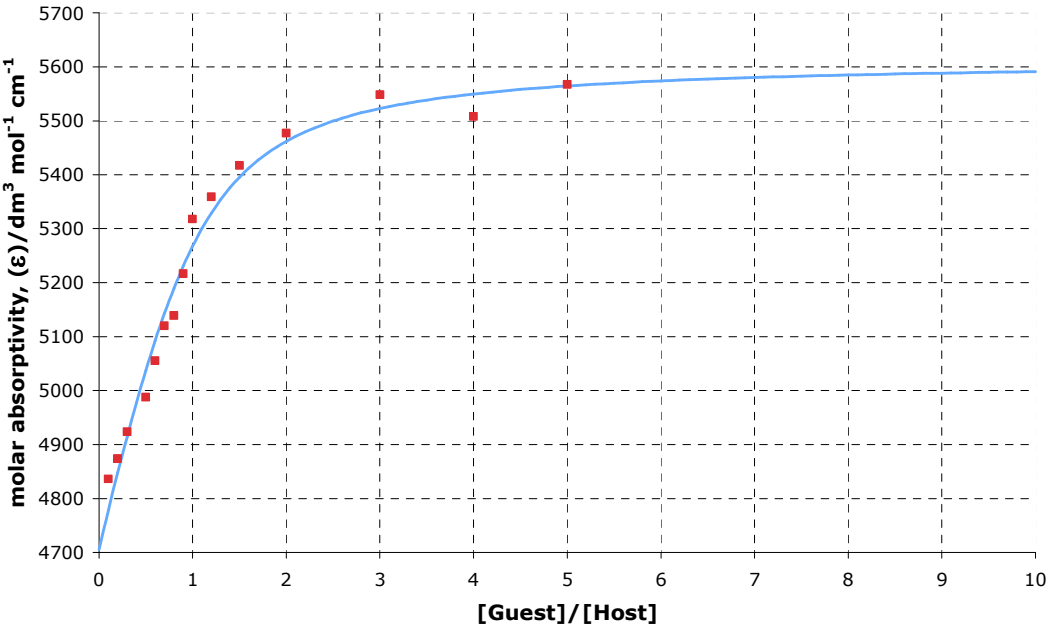


Figure 5.4. Titration curve obtained by monitoring the molar absorptivity of **4** (at 350.5 nm) on variation of guest **14**: host **4**, ratio, [**4**] = 10^{-4} mol dm^{-3}. Squares indicate the experimental data points and the curve indicates the theoretical ε values for the calculated values of K and ε_{HG}.

d_6-DMSO. DMSO is a viscous, highly polar aprotic solvent (7.2 on the polarity index[270]) which is known to be an efficient hydrogen bond acceptor[271] and has a

dielectric constant of 46.68 at 20°C, and a dipole moment of 4.1 D at 25°C. The spectrophotometric titration studies were conducted using 20% aqueous 1,4-dioxane. Dioxane is a polar aprotic solvent (4.8 on the polarity index[270]) which can also act as a hydrogen bond acceptor and has a dielectric constant of 2.25 at 20°C, and a dipole moment of 0.45 D at 25°C. Water is a polar protic solvent (10.2 on the polarity index), which can act as both a hydrogen bond donor and acceptor, with a dielectric constant of 80.1 at 20°C, and a dipole moment of 1.87 D at 25°C. The weighted (by mole fraction) mean value of the dielectric constant of the 20% aqueous 1,4-dioxane was calculated to be 17.82. The relative ordering of the log*K* values for a given host-guest combination measured in the two different solvents can be established by considering Coulomb's law:

$$F = Z_1 Z_2 / 4\pi\epsilon_0 r^2 \qquad (\mathbf{5.1})$$

where: F = magnitude of the attractive force acting on either species due to the other
$Z_{1,2}$ = charges of each of the two interacting species, 1 and 2.
r = distance between the two charges
ϵ_0 = permittivity (dielectric) constant

Since the only significant change between the NMR and spectrophotometric methods is a dielectric constant change of 46.68 to 17.82 and since the attractive force is inversely proportional to the dielectric constant of the solvent, the attractive force in 20% aqueous 1,4-dioxane will be 2.62 times greater than it is in DMSO. Hence it was expected that the log*K* values would be greater when determined from the spectrophotometric titrations (in dioxane-water) than those determined from the NMR (DMSO) studies.

The log*K* values determined from UV-visible absorption experiments, and the ^{1}H NMR derived values, for suitable guests with receptor **4** are shown in **Table 5.2**.

Table 5.2: Binding constants (log*K*) for the binding of guest anions with receptor **4**, determined by UV-visible absorption titration experiments and compared to the values determined through ^{1}H NMR.

	log*K* with receptor 4	
Guest anion	Absorption[a]	^{1}H NMR[b]
p-nitrobenzoate, **14**	4.6 ± 0.3	4.4 ± 0.3
p-aminobenzoate, **15**	>5.5	4.3 ± 0.2
p-dimethylaminobenzoate, **16**	4.2 ± 0.4	4.6 ± 0.4
m-hydroxybenzoate, **20**	5.3 ± 0.6	**c**
phenoxyacetate, **25**	>5.5	4.8 ± 0.2
(*L*)-histidinate, **27**	>5.5	>4.8
(*L*)-tryptophanate, **29**	5.1 ± 0.7	3.5 ± 0.1
p-toluenesulfonate, **30**	4.8 ± 0.7	**c**

[a]Measured at pH 7.0 (0.02 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4). Uncertainties are taken as two SD. [b]Measured in DMSO-d_6 at 295 K. Uncertainties are taken as two SD. [c]No significant changes in proton chemical shift occurred.

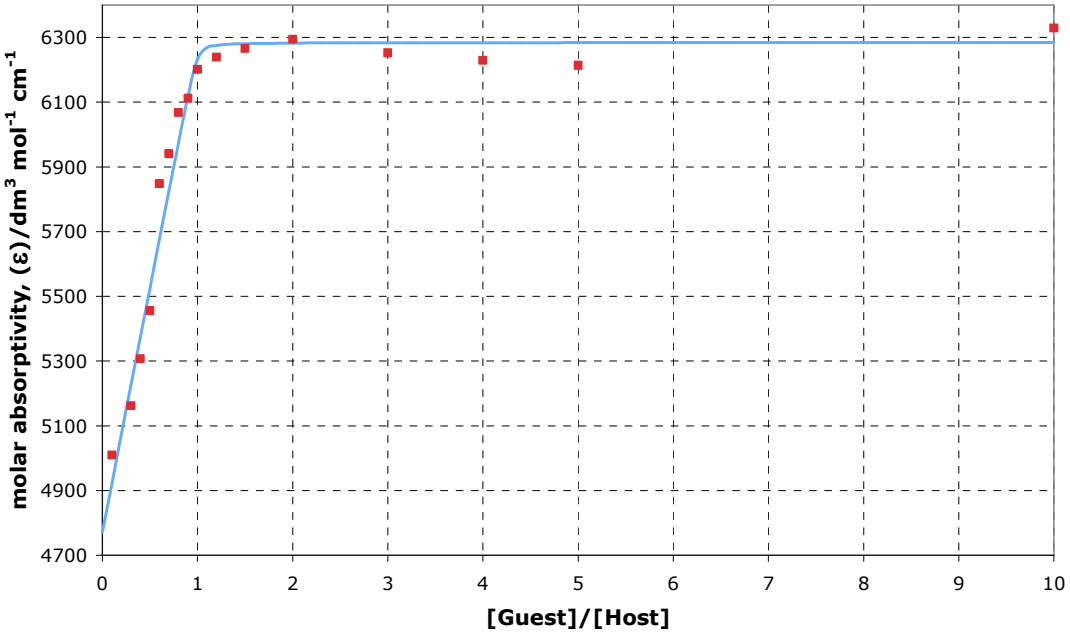


Figure 5.5. Titration curve obtained for molar absorptivity of **4** (at 350.5 nm) on variation of guest **15**: host **4**, ratio, [**4**] = 10^{-4} mol dm^{-3}. Squares indicate the experimental data points and the curve indicates the theoretical ε values for the calculated values of K and ε_{HG}.

The titration curve obtained from monitoring the change in the molar extinction coefficient of receptor **4** at *ca* 350.5 nm upon addition of the guest *p*-aminobenzoate, **15**, is shown in **Figure 5.5.** The binding constant was calculated as log$K$ = 6.9 ± 3.14, with the large error due to the extreme steepness of the curve, (this and other such values are reported as >5.5 in the Tables). To obtain a more accurate value for

the binding constant a more sensitive sensing technique (fluorescence) and a 10^{-6} mol dm^{-3} solution was subsequently used, as will be described later.

During the course of the NMR studies it was observed that the binding strengths for the inclusion of various guests generally followed the trend of the pK_a values for the parent acids of the various types of guests, in that the log$K$ value for inclusion of *p*-aminobenzoate, **15**, (pK_a 4.7) in **4** was 4.3 ± 0.2, whilst that for the inclusion of the *p*-dimethylaminobenzoate, **16**, (pK_a 5.03) in **4** was 4.6 ± 0.4, although both values for log$K$ could be the same when the error is considered. This trend is partially continued in the findings of the UV-visible results. The log$K$ value for inclusion of the *p*-nitrobenzoate, **14**, (pK_a 3.44) in **4** was 4.6 ± 0.3, whilst that for the inclusion of the *p*-aminobenzoate, **15**, (pK_a 4.7) in **4** was >5.5. However, the *p*-dimethylaminobenzoate, **16**, with a pK_a value of 5.03 has a log$K$ value of only 4.2 ± 0.4, hence the trend breaks down. This suggests that the high binding constant for *p*-aminobenzoate may be associated with its hydrogen bond donor capability towards one or two of the aromatic rings that define the walls of the cavity, in addition to the hydrogen bonds that occur at the base of the cavity.

5.6.2. Binding constants for anionic guests with fluorescent receptor 5, having a methylated phenoxy derived cavity and four hydrogen bond donor groups at the base of the cavity.

Titrations of [Cd((*S*)-athmppc)]$(ClO_4)_2$, **5**, to investigate the inclusion of aromatic anionic guests gave rise to changing series of absorbance spectra. As with inclusion in receptor **4**, the change in absorbance at 350.5 nm was monitored. The log$K$ values determined from UV-visible absorption experiments, and the ^{1}H NMR derived values, for the guests with receptor **5** are shown in **Table 5.3**.

Table 5.3: Binding constants (log*K*) for the binding of guest anions with receptor **5**, determined by UV-visible absorption titration experiments and compared to the values determined through ^{1}H NMR.

Guest anion	log*K* with receptor 5	
	Absorption[a]	^{1}H NMR[b]
p-nitrobenzoate, **14**	4.1 ± 0.2	4.0 ± 0.2
p-aminobenzoate, **15**	3.6 ± 0.4	**c**
p-dimethylaminobenzoate, **16**	3.1 ± 0.4	**c**
p-hydroxybenzoate, **19**	>5.5	**d**

[a]Measured at pH 7.0 (0.02 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4). Uncertainties are taken as two SD. [b]Measured in DMSO-d_6 at 295 K. Uncertainties are taken as two SD. [c]Not measured. [d]No significant changes in proton chemical shift occurred.

As with receptor **4**, from the absorption spectra for the inclusion of *p*-nitrobenzoate in the cavity of **5**, a curve was derived and the binding constant was calculated (log$K$ = 4.1 ± 0.2). The binding constants for inclusion of *p*-aminobenzoate, **15**. *p*-dimethylaminobenzoate, **16**, and *p*-hydroxybenzoate, **19**, within **5**, which were not determined during the ^{1}H NMR experiments, were able to be determined from the UV-visible absorption measurements. The strength of binding for these guests in receptor **5** does not fit the trend of the pK_a values.

5.6.3. Binding constants for anionic guests with the fluorescent receptor 6, having three hydrogen bond donor groups at the base of the cavity.

Titrations of [Cd((*S*)-apthppc)]$(ClO_4)_2$, **6**, to investigate the inclusion of aromatic anionic guests gave rise to a series of absorbance spectra. As with inclusion in receptor **4**, the largest change in absorbance centred on the absorbance maximum at 350.5 nm. The log$K$ values determined from UV-visible absorption experiments, and the ^{1}H NMR derived values, for the guests with receptor **6** are shown in **Table 5.4**.

As with receptor **5**, *p*-hydroxybenzoate, **19**, binds strongly, and *p*-dimethylaminobenzoate, **16**, has a low binding constant. The binding strengths

determined from the UV-visible studies for the inclusion of **14** and **15** in **6** are greater by more than an order of magnitude than those of the NMR studies, whereas the difference in the log*K* values of **14** in **4** between the two methods was only 0.3, which is less than experimental error. The presence of the extra pendant arm on the receptor seems to increase the effect that the change of solvent has on the binding of **14** and **15**.

Table 5.4: Binding constants (log*K*) for the binding of guest anions with receptor **6**, as determined by UV-visible absorption titration experiments and compared to the values determined through ^{1}H NMR.

	log*K* with receptor 6	
Guest anion	Absorption[a]	^{1}H NMR[b]
p-nitrobenzoate. **14**	4.1 ± 0.2	3.2 ± 0.2
p-aminobenzoate. **15**	>5.5	3.8 ± 0.4
p-dimethylaminobenzoate. **16**	3.9 ± 0.2	4.2 ± 0.2
p-hydroxybenzoate. **19**	>5.5	**c**
p-toluenesulfonate. **30**	4.0 ± 1.0	**c**

[a]Measured at pH 7.0 (0.02 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4). Uncertainties are taken as two SD. [b]Measured in DMSO-d_6 at 295 K. Uncertainties are taken as two SD. [c]No significant changes in proton chemical shift occurred.

When ordered in terms of increasing pK_a values of the parent acid, the guests are ordered **30**, **14**, **19**, **15** and **16**, with pK_a values of -0.43, 3.44, 4.58, 4.7 and 5.03, respectively, with log*K* values of 4.0 ± 1.0, 4.1 ± 0.2, >5.5, >5.5, and 3.9 ± 0.2, respectively. For inclusion in receptor **6**, binding strength does appear to increase with increasing pK_a, except for the *p*-dimethylaminobenzoate guest, **16**. This guest, consistently for receptors **4-6**, shows the smallest log*K* values, despite having the highest pK_a value of 5.03.

5.6.4. Binding constants for anionic guests with fluorescent receptor 7, having a methylated phenoxy derived cavity and three hydrogen bond donor groups at the base of the cavity.

Titrations of [Cd((*S*)-amthmppc)]$(ClO_4)_2$, **7**, to investigate the inclusion of aromatic anionic guests gave rise to a series of absorbance spectra. As with the inclusions in receptor **4**, the absorbance maximum at 350.5 nm was monitored. The log*K* values determined from UV-visible absorption experiments, and the ^{1}H NMR derived values, for the guests with receptor **7** are shown in **Table 5.5**.

Table 5.5: Binding constants (log*K*) for the binding of guest anions with receptor **7**, as determined by UV-visible absorption titration experiments and compared to the values determined through ^{1}H NMR.

	log*K* with receptor 7	
Guest anion	Absorption[a]	^{1}H NMR[b]
p-nitrobenzoate, **14**	4.8 ± 0.4	3.3 ± 0.2
p-aminobenzoate, **15**	5.0 ± 0.4	4.1 ± 0.2
p-dimethylaminobenzoate, **16**	3.0 ± 0.2	4.0 ± 0.4
p-hydroxybenzoate, **19**	>5.5	c
p-toluenesulfonate, **30**	4.0 ± 0.6	c

[a]Measured at pH 7.0 (0.0198 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4). Uncertainties are taken as two SD. [b]Measured in DMSO-d_6 at 295 K. Uncertainties are taken as two SD. [c]No significant changes in proton chemical shift occurred.

The log*K* values for inclusion of **19** and **30** in receptor **7** were able to be determined from the absorption spectra, whereas they had not been able to be determined during the ^{1}H NMR experiments. The large error for the inclusion of **30** is the result of the small size of the change in absorbance. As with receptor **5** and **6**, *p*-hydroxybenzoate, **19**, binds strongly with **7**, while *p*-dimethylaminobenzoate, **16**, has a low binding constant, in apparent contradiction of their relative pK_a values. It is apparent that the log*K* value derived from the UV-visible method for **16** inclusion in **7** is significantly lower than that from the NMR method. This is the reverse of what would be expected from the differences in dielectric constants of the solvents and provides another illustration of the unusual behaviour of this guest.

With the absorption properties of the hosts, the guests, and the host-guest complexes known, and a greater understanding of the binding strengths of the different host-guest combinations, the investigation of the fluorescence perturbations of the hosts upon guest inclusion was undertaken.

5.7. Fluorescence titration studies for guest inclusion with fluorescent receptors 4-7

The influence of guest inclusion on the fluorescence emission spectra of receptors **4-7** was investigated using a series of titration experiments. The detailed experimental procedure utilised in the fluorescence titration of the receptors **4-7** with solutions of guest anions is outlined in **Chapter 6**. Generally speaking it involved the addition of aliquots of a solution of guest compound to a series of dilute deoxygenated solution of the host (with the concentration of the host either 1 x 10^{-6} mol dm^{-3} or 1 x 10^{-4} mol dm^{-3}), buffered at pH 7.0 (0.02 mol dm^{-3} lutidine). The titrations were conducted in 20% aqueous 1,4-dioxane, at constant ionic strength I = 0.1 mol dm^{-3} (NEt_4ClO_4), at 25°C, and the measurement of the emission spectra (over the range 370-550 nm) was recorded upon each addition of the guest, at an excitation wavelength of 350 nm.

An initial investigation of the effect of the inclusion of *p*-nitrobenzoate, **14**, on the fluorescence emission intensity of receptor **4** was conducted at a 1 x 10^{-6} mol dm^{-3} concentration of the host. However, no significant change in fluorescence emission intensity was observed due to the very low absolute intensity at this concentration. The concentration was increased until changes of fluorescence emission intensity were observed (at 1 x 10^{-4} mol dm^{-3}). The series of emission spectra are shown in **Figure 5.6.** This process would be repeated for all host-guest

combinations. Only when no significant fluorescence emission intensity changes were observed for potential guest inclusion for solutions of host with concentrations ranging from 10^{-6} mol dm^{-3} to 10^{-4} mol dm^{-3} would the experiment be reported as showing no change.

The inclusion of *p*-nitrobenzoate, **14**, induced a maximum of a 10% diminution of the fluorescence intensity of **4**. Investigation into the inclusion of other guest molecules with receptor **4** also showed changes of fluorescence intensity with the majority of the guest anions studied, as did the inclusion of these guest anions with the other receptor complexes **5**-**7**.

With the receptor complexes showing a change of fluorescence emission intensity upon guest inclusion, and thus acting as fluorescent sensors, it was of importance to investigate whether the uncomplexed ligand **146** would itself act as a molecular sensor (in addition to being able to act as a pH and metal ion sensor),

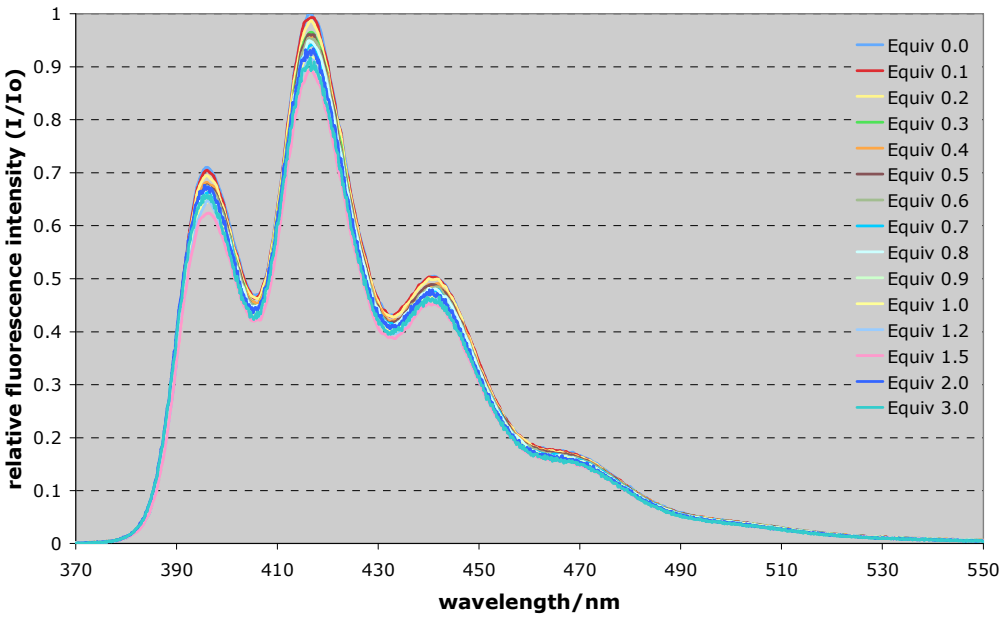


Figure 5.6. The fluorescence emission spectra of **4** (10^{-4} mol dm^{-3}) alone and with increasing equivalents of **14** in 20% aqueous 1,4-dioxane, I = 0.1 (NEt_4ClO_4), at pH 7.0 (0.02 mol dm^{-3} lutidine). I_o has been referenced as the fluorescence intensity of **4** at pH 7, and has been set to 1.

without being activated by complexation to Cd(II). Investigation of a 10^{-6} mol dm^{-3} solution of free ligand **146** at pH 13.0 in 20% aqueous 1,4-dioxane alone, and with 10 equivalents of guest (benzoate) showed absolutely no change in fluorescence intensity, whereas a 10^{-6} mol dm^{-3} solution of the receptor complex **4** showed a 107% increase of fluorescence at 10 equivalents of benzoate. This indicates that the free ligand, **146**, cannot itself act as a sensor for the inclusion of small aromatic molecules, but requires pre-organisation by metal complexation to produce a suitable receptor complex with the appropriate binding cavity. The other ligands, **170-172**, likewise showed no changes of fluorescence emission intensity when exposed to the guest anions.

Before these changes in fluorescence emission intensity can be understood it was necessary to look at the strength of binding of the guest that these changes have signalled. Just as with the absorption spectra where there was a wavelength at which the change in molar absorptivity could be monitored, so too can the emission peaks in the fluorescence spectra be monitored to determine binding constants.

5.8. Binding constants determined from fluorescence measurements

Monitoring the changes of the fluorescence emission intensities at *ca* 416 nm upon exposure to a potential guest enables binding strengths to be determined by analysing the curve derived from the changing molar fluorescence values plotted against equivalents of guest. However, there is a potential issue with determining the binding constants from fluorescence measurements. This is that fluorescence studies examine the species in the excited states, whereas absorption spectroscopy examines the ground state population. In the determination of log*K* by the fluorescence

method both the host and the host-guest complex undergo excitation by absorbing the exciting light at the excitation wavelength. The fluorescence intensity shown by each would then normally be in proportion to the concentration of each in the ground electronic state, after due allowance for the differing quantum yields of each. However, because the conformation of both the host and the host-guest complex may be different in the excited state it is possible that during the excited state lifetime (the S_1 state typically has a lifetime $>10^{-9}$ s, with anthracene having a natural S_1 excited state lifetime of 12.9 ns [188]), either host-guest dissociation or host-guest association may occur. In the system under study here this would merely involve the breaking or forming of hydrogen bonds. Any such association or dissociation would then cause the relative concentration of the host and host-guest within the population of excited state molecules to differ from that existing within the ground state population. Since it is the ratio of the excited state host and host-guest species that forms the basis for determining log*K*, in the fluorescence method, it may be found in some instances that the log*K* determined in this way differs from the log*K* determined by the UV-visible method, even though the experimental conditions for each remain the same. However, having said all this, it appears to be the case that only when the receptor is conjugated to the fluorophore is the binding strength in the excited state obtained.[149g] Since this is not the case with any of the receptors used in this work significant differences between the log*K* measurements made using the fluorescence method and those obtained by using NMR or UV-vis spectroscopy are not expected.

5.8.1. Binding constants of anionic guests with fluorescent receptor 4, having four hydrogen bond donor groups at the base of the cavity.

The titration of [Cd((*S*)-athppc)](ClO_4)$_2$, **4**, with *p*-nitrobenzoate, **14**, gave rise to a series of fluorescence spectra, with the peak of maximum intensity at 416 nm. An expansion of the spectra is shown in **Figure 5.7.**

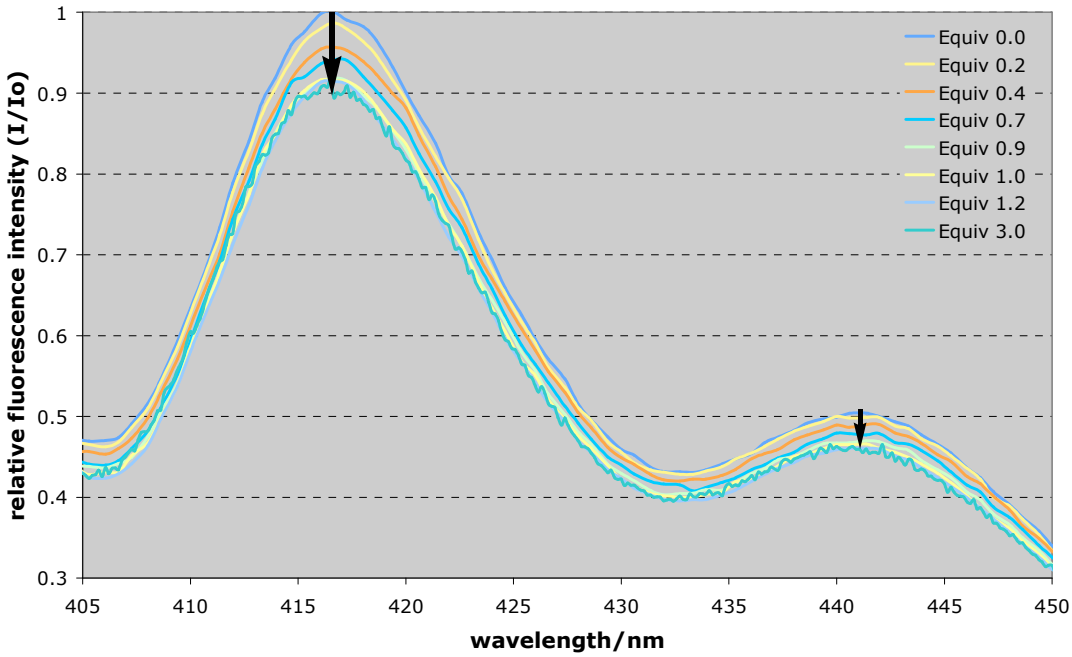


Figure 5.7. An expansion (from 405 nm to 450 nm) of the fluorescence emission spectra of receptor **4** alone [10^{-4} mol dm^{-3}] (top curve), and in the presence of increasing amounts of *p*-nitrobenzoate, **14**, at pH 7.0 (0.02 mol dm^{-3} lutidine buffer) in 20% aqueous 1,4-dioxane (I = 0.1 mol dm^{-3}, NEt_4ClO_4) at 298 K. The maximum intensity peak is at 416 nm. Some intermediate curves have been removed for greater clarity.

The wavelength of maximum intensity is also the wavelength at which the greatest change in fluorescence intensity upon titration with the guest occurs. Thus, it is the most appropriate wavelength to be monitored to obtain the binding constant. The change in fluorescence intensity can be related to the binding constant by means of the molar fluorescence, ε', of the species of interest in the solution. The basic equation defining the relationship of fluorescence to concentration[265] is:

$$F = \Phi I_0(1-e^{-\varepsilon bc}) \quad (\mathbf{5.2})$$

where: F = observed fluorescence
Φ = quantum yield
I_0 = the incident radiant power
ε = is the molar absorptivity
b = path length
c = molar concentration of the fluorophore.

For dilute solutions, where A < 0.05, the equation reduces to one comparable to Beer's law in spectrophotometry:

$$F = k\Phi I_0 \varepsilon bc \quad (\mathbf{5.3})$$

Thus at dilute concentrations, a plot of fluorescence versus concentration is linear.[265] The observed fluorescence is proportional to the quantum yield of the fluorescent species, the concentration of the species, and the molar absorptivity of the species, while k, I_0 and b are constants during the experiment. For dilute solutions molar fluorescence, ε', can be expressed as:

$$\varepsilon' = F/c = k\Phi I_0 \varepsilon b \quad (\mathbf{5.4})$$

It is the molar fluorescence values that are used to determine the binding constants, as described in **Appendix A.2**. By convention fluorescence measurements, such as ε' are expressed as dimensionless quantities on an arbitrary scale.[188]

The titration curve obtained from monitoring the change in the molar fluorescence of the system (at 416.5 nm) upon addition of the guest, **14**, is shown in **Figure 5.8.**

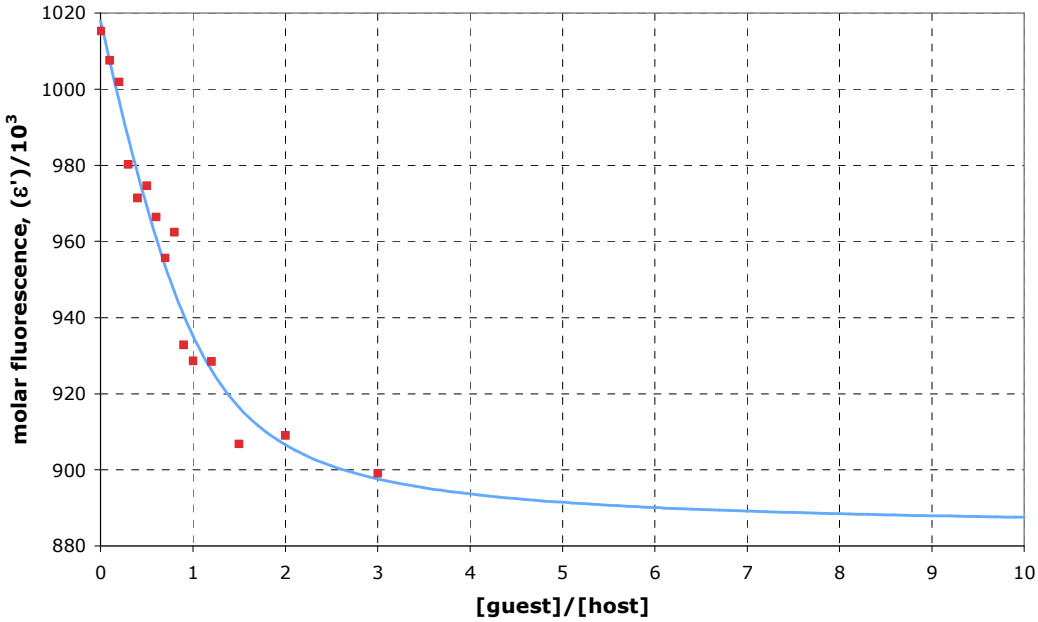


Figure 5.8. Titration curve obtained for molar fluorescence (at 416.5 nm) of a 10^{-4} mol dm^{-3} solution of **4** upon variation of guest **14**: host **4**, ratio. Squares indicate the experimental data points and the curve indicates the theoretical ε' values for the calculated values of K and ε'_{HG}.

The binding constant (to 2 SD) was calculated from the curve, with the value for the inclusion of *p*-nitrobenzoate, **14**, within receptor **4** determined as log$K$ = 4.6 ± 0.5. As a reproducibility check the experiment was repeated using a 10^{-6} mol dm^{-3} concentration of **4**, which gave a log$K$ value of 4.9 ± 0.4. Both these values are within the experimental error for the value of the binding constant (to 2 SD) determined by both the ^{1}H NMR (log$K$ = 4.4 ± 0.3) and UV-vis (log$K$ = 4.6 ± 0.3) methods. The log$K$ values determined from fluorescence titrations, and the UV-visible derived values, for investigated guests with receptor **4**, are shown in **Table 5.7**. Meaningful comparisons can be drawn between the entries since they were determined in the same solvent at the same temperature, except that the fluorescence data relates to the excited state binding constant, while the absorption data relates to the ground state binding constant.

Table 5.7. Binding constants (log*K*) for the binding of guest anions with receptor **4** determined by fluorescence titration experiments and compared to the values determined through the UV-visible absorption studies.

Guest anion	log*K* with receptor 4	
	Fluorescence[a]	Absorption[a]
p-nitrobenzoate, **14**	4.9 ± 0.4[b]	4.6 ± 0.3
p-aminobenzoate, **15**	6.5 ± 0.2[b]	>5.5
p-dimethylaminobenzoate, **16**	4.1 ± 0.8	4.2 ± 0.4
benzoate, **18**	2.3 ± 0.1[c]	-
p-hydroxybenzoate, **19**	4.5 ± 0.3	-
m-hydroxybenzoate, **20**	5.3 ± 0.5 [b]	5.3 ± 0.6
o-hydroxybenzoate, **23**	7.1 ± 0.5[b]	-
3,5-dihydroxybenzoate, **21**	6.1 ± 0.3 [b]	-
2,6-dihydroxybenzoate, **24**	7.5 ± 0.9 [b]	-
gallate, **22** (3,4,5-trihydroxybenzoate)	7.1 ± 0.5[b]	-
phenoxyacetate, **25**	5.5 ± 0.2 [b]	>5.5
(*L*)-histidinate, **27**	6.9 ± 1.3 [b]	>5.5
p-toluenesulfonate, **30**	4.6 ± 0.7	4.8 ± 0.7
benzenesulfonate, **31**	3.4 ± 0.3	-

[a][**4**] = 10^{-4} mol dm^{-3}, Measured at pH 7.0 (0.02 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4). Uncertainties are taken as two SD. [b][**4**] = 10^{-6} mol dm^{-3}. [c][**4**] = 10^{-3} mol dm^{-3}.

The binding constant for the inclusion of *p*-aminobenzoate, **15**, within receptor **4**, at 10^{-4} mol dm^{-3} concentrations, was first calculated as log$K$ = 5.7 ± 2.1, which is within the error for the value of the binding constant determined from both the UV-visible (**Figure 5.5**) and the ^{1}H NMR binding constant determinations. However, the titration experiment was subsequently conducted at 10^{-6} mol dm^{-3} concentrations of **4** so as to lower the error. The titration curve obtained in this way is shown in **Figure 5.9**, and gave a better defined log$K$ value of 6.5 ± 0.2. This was also accompanied by a change in molar fluorescence enhancement from a 32% increase to a 58% increase indicating a lowering of intermolecular collisional quenching at the greater dilution, which is more pronounced for host-guest molecules than for host molecules.

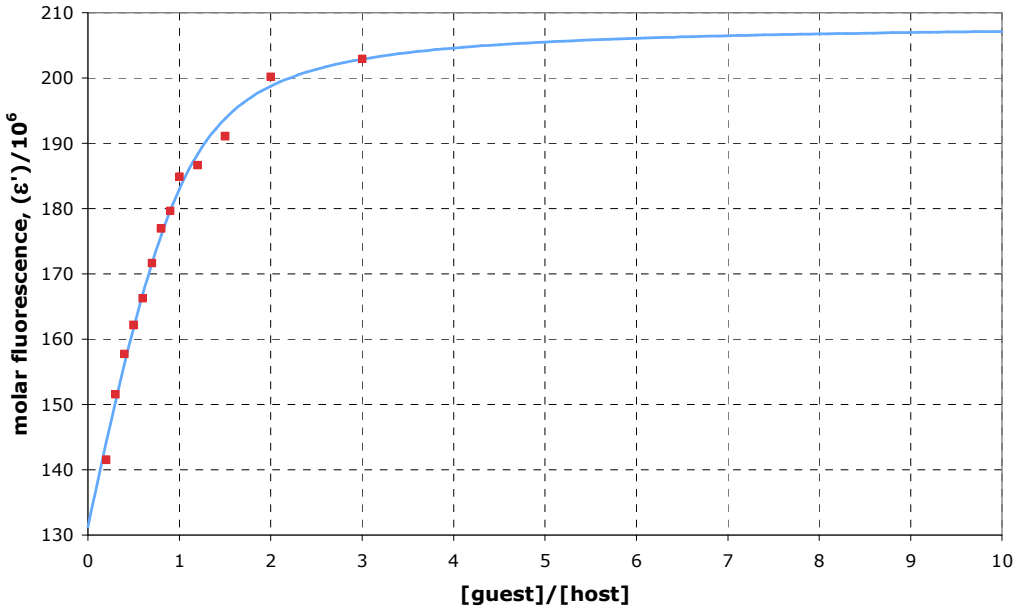


Figure 5.9. Titration curve obtained for molar fluorescence (at 416.5 nm) of the 10^{-6} mol dm^{-3} receptor **4** system, on variation of guest **15**: host **4**, ratio. Squares indicate the experimental data points and the curve indicates the theoretical ε' values for the calculated values of *K* and ε'_{HG}.

The titration curve obtained from monitoring the change in the molar fluorescence of receptor **4** upon addition of the guest *p*-dimethylaminobenzoate, **16**, is shown in **Figure 5.10.**

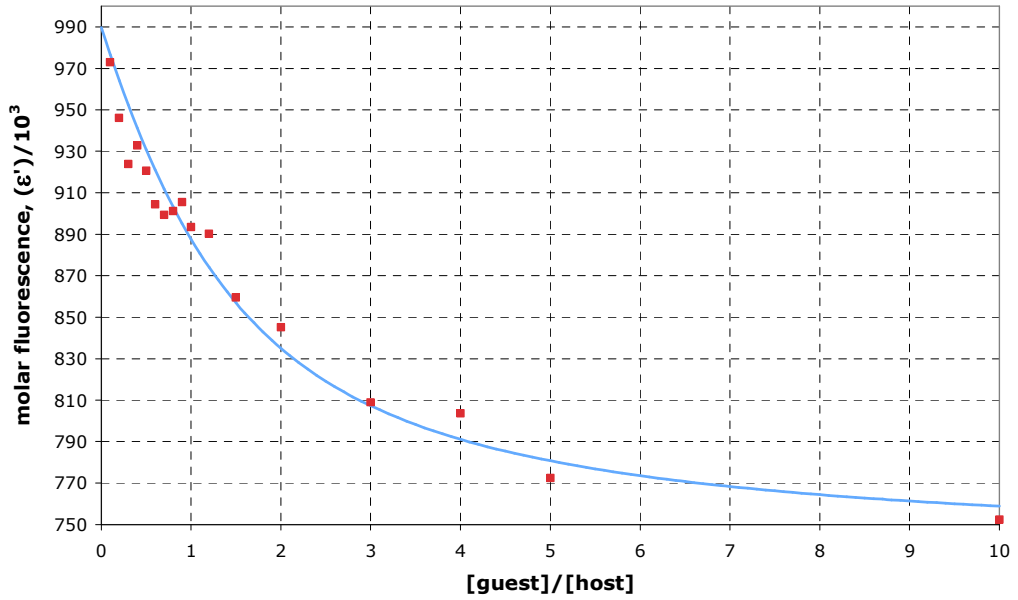


Figure 5.10. Titration curve obtained for molar fluorescence (at 416.5 nm) of the 10^{-4} mol dm^{-3} receptor **4** system, on variation of guest **16**: host **4**, ratio. Squares indicate the experimental data points and the curve indicates the theoretical ε' values for the calculated values of *K* and ε'_{HG}.

The binding constant was calculated for the inclusion of *p*-dimethylaminobenzoate, **16**, within receptor **4** as log*K* = 4.1 ± 0.8, which, within experimental error, is the same as the value for the UV-vis and the ^{1}H NMR derived binding constant. The titration curve obtained from monitoring the change in the molar fluorescence of the receptor **4** system upon addition of the guest *p*-hydroxybenzoate, **19**, is shown in **Figure 5.11.** The binding constant was calculated for the for the inclusion of **19** within receptor **4** as log*K* = 4.5 ± 0.3. There were no ^{1}H NMR or UV-visible derived log*K* values with which to compare the log*K*.

There were no significant changes in either the NMR or absorption spectra for the inclusion of gallate (3,4,5-trihydroxybenzoate), **22**, in receptor **4**, yet there was a small change in the fluorescence spectra. The titration curve obtained from monitoring the change in the molar fluorescence of the receptor **4** system upon addition of gallate is shown in **Figure 5.12.** The binding constant was calculated as

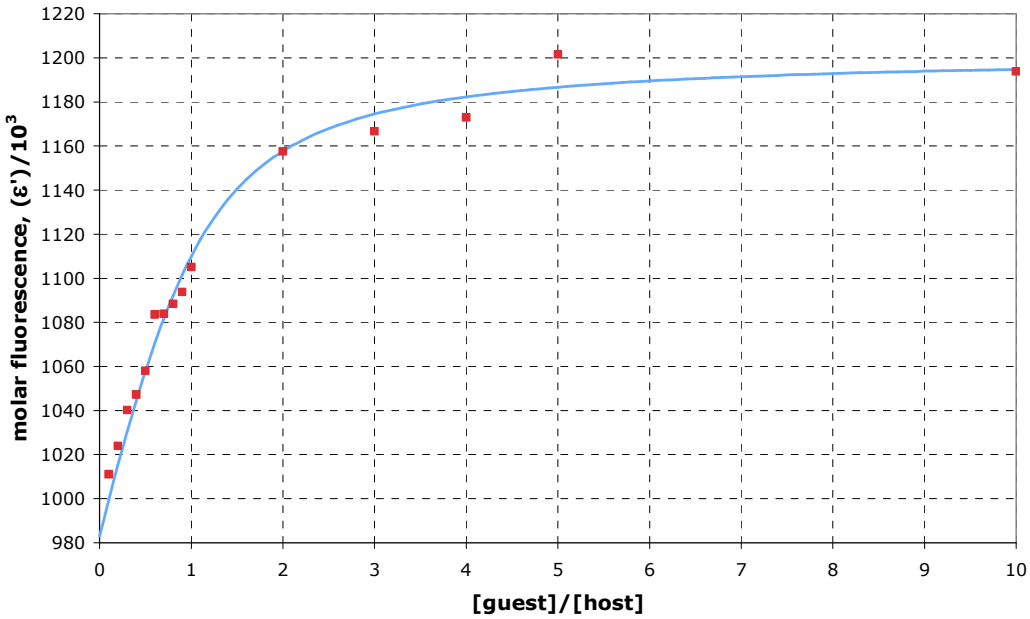


Figure 5.11. Titration curve obtained for molar fluorescence (at 416 nm) of the 10^{-4} mol dm^{-3} receptor **4** system, on variation of guest **19**: host **4**, ratio. Squares indicate the experimental data points and the curve indicates the theoretical ε' values for the calculated values of *K* and ε'_{HG}.

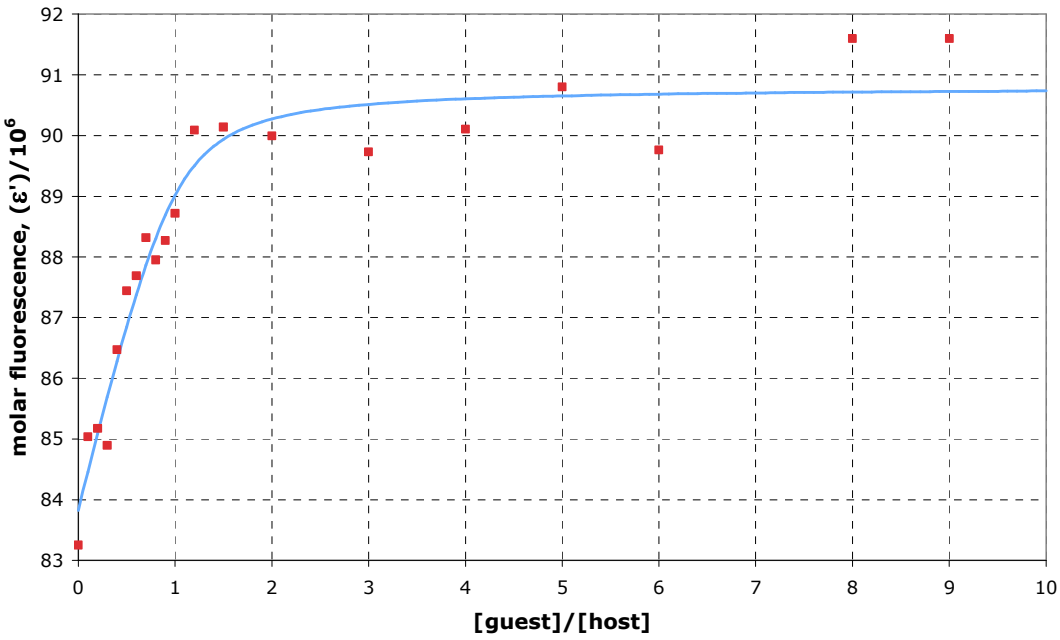


Figure 5.12. Titration curve obtained for molar fluorescence (at 416 nm) of the 10^{-6} mol dm^{-3} receptor **4** system, on variation of guest **22**: host **4**, ratio. Squares indicate the experimental data points and the curve indicates the theoretical ε' values for the calculated values of K and ε'_{HG}.

log$K$ = 7.1 ± 0.5, which is amongst the largest measured to date with this class of receptor. This large binding strength is derived from a total change in fluorescence intensity of only *ca* 9%, which unfortunately compromises the certainty with which it is determined. Since the log$K$ determination has been made at pH 7.0 only the carboxylate group is deprotonated and so this is the most likely site for bonding to the hydrogen bond donor groups of the host. With the hydroxy groups protonated it seemed possible that at either the 3 or 5 position O-H...π hydrogen bonding to the face of one of the host's aromatic rings,[272] in the manner shown in **Figure 5.13**, was augmenting the hydrogen bonding at the cavity base and was responsible for the heightened stability compared to that seen for *p*-hydroxybenzoate.

The large increase of the strength of binding with receptor **4** between **19** (4.5 ± 0.3) and **22** (7.1 ± 0.5) raised the question of whether the number and location of the hydroxy groups on the ring of the guest anion had any significant effect on the

strength of guest inclusion.

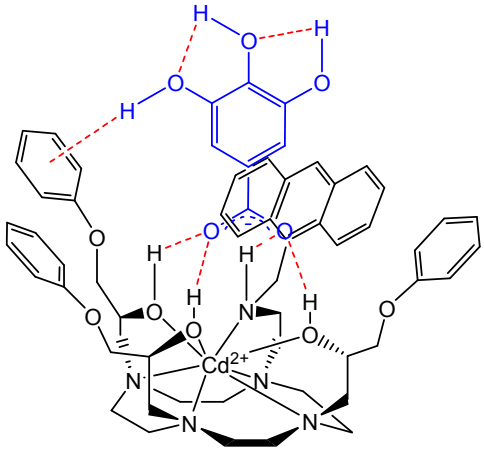


Figure 5.13. The possible O-H...π interaction of gallate in **4** which may be responsible for the high binding constant. The diagram is broadly representative of the conformation of a related *p*-aminobenzoate inclusion complex whose structure has been determined by X-ray crystallography.[125]

To this end a series of hydroxybenzoates was studied, ranging from benzoate, with no hydroxy groups to act as a reference point for both binding strength and fluorescence intensity, to *o-, m-* and *p*-hydroxybenzoate, which were investigated to observe whether the position of the substitution was important, and then 3,5-dihydroxybenzoate, which has two *meta*-hydroxy groups, and 2,6-dihydroxybenzoate. The series was augmented by gallate as already seen. The log*K* values, in increasing order, for the entire series are shown in **Table 5.8**.

Table 5.8 Binding strengths, obtained from the fluorescence measurements, for the hydroxybenzoate guests in receptor complex **4**, in increasing order.

Hydroxybenzoate series of guests	-COOH pK_a values	Log *K* values (fluorescence) [a]
benzoate, **18**[c]	4.20	2.3 ± 0.1
p-hydroxybenzoate, **19**[b]	4.58	4.5 ± 0.3
m-hydroxybenzoate, **20**	4.08	5.3 ± 0.5
3,5-dihydroxybenzoate, **21**	4.04	6.1 ± 0.3
3,4,5-trihydroxybenzoate, **22**, (gallate)	4.41	7.1 ± 0.5
o-hydroxybenzoate, **23**	2.98	7.1 ± 0.5
2,6-dihydroxybenzoate, **24**	1.05	7.5 ± 0.9

[a]Measured at pH 7.0 (0.02 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4), [**4**] = 10^{-6} mol dm^{-3}. [b][**4**] = 10^{-4} mol dm^{-3}, [c][**4**] = 10^{-3} mol dm^{-3}.

Benzoate, **18**, has a pK_a value of 4.20. As has been mentioned previously, anions with low pK_a values tend to have lower binding constants as the oxoanions have less electron density and form weaker hydrogen bonds with the hydroxy-groups at the base of the receptor's cavity. Benzoate has the lowest log$K$ value (2.3) of the hydroxybenzoate series with **4**. With *para*-hydroxy-substitution, **19** has a higher pK_a value (4.58) than benzoate, as the *para*-substitution pushes electron density down to the oxygens, and a higher binding constant (log$K$ = 4.5).

However, unlike gallate, the para-hydroxy-group is incorrectly oriented for O-H...π hydrogen bonding, and so may not have any significant further hydrogen bonding to strengthen inclusion. The *meta*-OH group of **20**, on the other hand, is in a position to form an O-H...π bond with the host, (**Figure 5.14**) which more than compensates for its lower pK_a of 4.08 and gives a higher log$K$ of 5.3. In support of this theory it was found that inclusion of **21**, which has a similar pK_a to **20**, but two *meta* –OH groups, in **4** is even stronger, with a log$K$ value of 6.1. Gallate, **22**, has an even higher log$K$ value (7.1 ± 0.5) than **21** for inclusion within **4**. This increase can be attributed to the addition of the *para* hydroxy-substituent, which increases the electron density on the oxoanions, as shown by the increased pK_a value of the parent acid of 4.41. Gallate has a high binding strength due to both the –O-H...π bonding of the *meta*-hydroxy substitution on the ring of the anion with the pendant arms of the host, as well as strong -O-H...O^- hydrogen bonds.

Following the reasoning developed above, the high log$K$ value of the *o*-hydroxybenzoate (salicylate) may be explained by even stronger –O-H...π bonding of the *ortho*-hydroxy group due to its more favourable alignment as shown in **Figure**

5.14. This more than compensates for the weaker -O-H...O^- hydrogen bonds at the base of the cavity expected because of the lower pK_a (2.98).

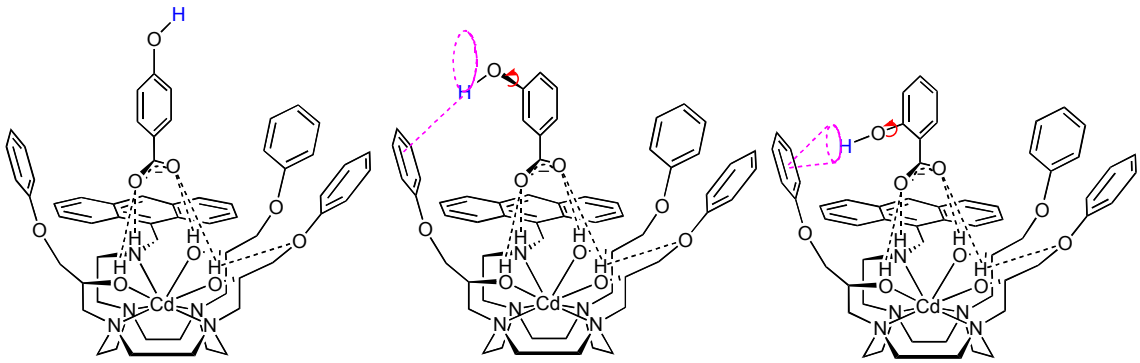


Figure 5.14. The position of the hydroxy-substituent on the guest changes the potential for -O-H...π hydrogen bonding. The *para*- hydroxy group is unable to interact with the aromatic groups of **4**, *meta*-substitution allows partial interaction, whilst all the potential locations of the hydrogen of an *ortho*- hydroxy group allow for strong hydrogen bond interaction. Although interaction is shown with a phenyl ring, it could equally well be with the anthracene, thereby quenching its fluorescence.

Having the hydroxy group in the *ortho*-position appears to lead to much more effective -O-H...π alignment than when the hydroxy group is in the *meta*-position. It can be seen in **Figure 5.14** that rotation around the C-O bond of the C-O-H group carries the hydroxy group out of alignment when *meta*, but not when *ortho*. In keeping with this, 2,6-dihydroxybenzoate has an even higher log*K* value of 7.5, even though the pK_a value has dropped to 1.05, which would suggest very weak hydrogen bonding at the base of the cavity. The higher stability must then be due to the presence of two *ortho* hydroxy groups that are forming –O-H...π bonds with the cavity walls.

An initial attempt to model these –O-H...π bonds was made by Professor Sadegh Salehzadeh of Bu-Ali-Sina University, using ab initio methods.[273] This showed that the *ortho* hydroxy group is in a suitable position to engage in hydrogen bonding with one of the aromatic rings of the cavity (**Figure 5.15.**). However the hydroxy H…ring distance of 5 Å is quite long (**Table 5.9**), indicating only a weak interaction.[274-279] Since the fluorescence and binding constant measurements that led

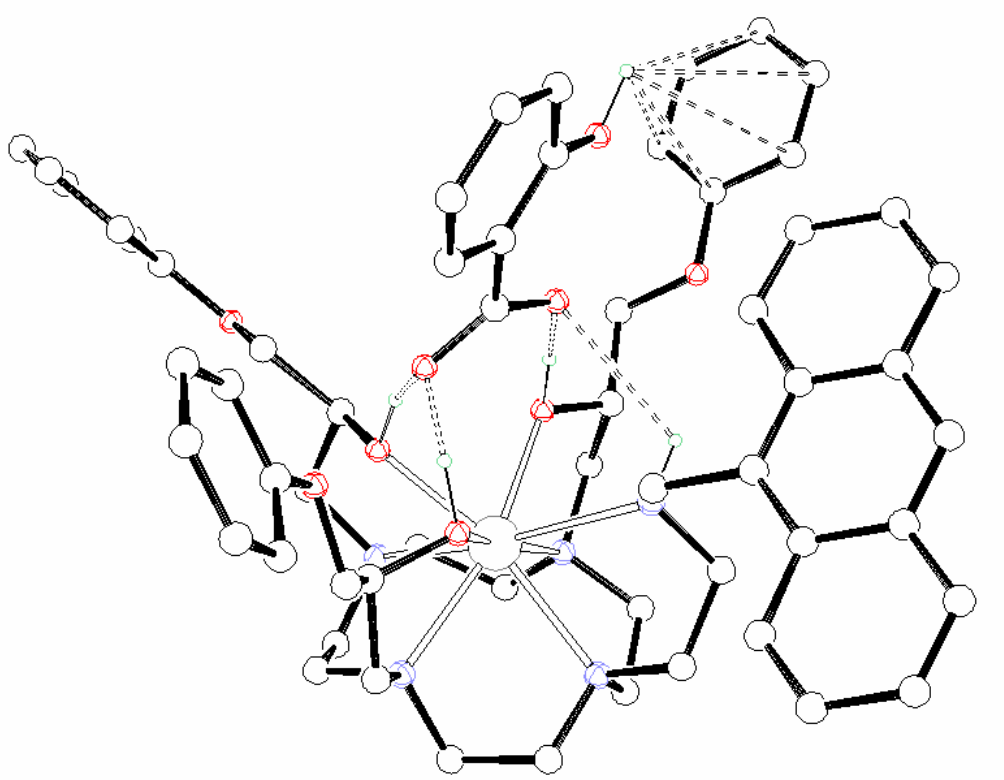


Fig 5.15. From B3LYP/LanL2MB calculations, showing that the H atom of hydroxyl group is in suitable direction with respect to aromatic ring, although the H to π-ring distance of approximately 5 Å indicates a weak interaction, and is similar to those found in some proteins.[274-279] Modeling was performed by Professor Sadegh Salehzadeh, Department of Chemistry, Bu-Ali-Sina University, Hamadan, Iran.[273]

Table 5.9. B3LYP/LANL2MB calculations.

Bond lengths	Å	*Bond angles*	°
Cd-N24	2.547	N24-Cd-N21	74.20
Cd-N21	2.511	N21-Cd-N47	70.07
Cd-N47	2.679	N47-Cd-N23	71.8
Cd-N23	2.474	N23-Cd-N24	73.2
Cd-N22	2.801	N24-Cd-N22	68.90
Cd-O16	2.242	N21-Cd-O16	72.54
Cd-O25	2.290	N47-Cd-O25	66.17
Cd-O26	2.354	N23-Cd-O26	73.65
N22-H86….O10	2.732		
O16-H80….O10	1.308	N22-Cd-O16	69.54
O25-H87….O9	1.345	O16-Cd-O25	73.65
O26-H88….O9	1.419	O25-Cd-O26	70.28
O-H……ring	4.73-5.64 (relative to the carbon atoms of ring)	O26-Cd-N22	70.83

to the suggestion of O-H...π hydrogen bonding were made in partially aqueous solution it is quite possible, in light of this modeling outcome, that a water molecule acts as a hydrogen bonding bridge between the O-H group of the guest and an aromatic ring and that it is in this way that the observed phenomena are accounted for.

5.8.2. Binding constants of anionic guests with fluorescent receptor 5, having a methylated phenoxy derived cavity and four hydrogen bond donor groups at the base of the cavity.

The fluorescence spectra for guest inclusion in receptor **5** also allowed binding constants to be determined, in the same fashion as for receptor **4**. These binding constants determined from the fluorescence measurements, along with those determined from UV-vis absorption, are shown in **Table 5.10.**

Table 5.10. Binding constants (log*K*) for the binding of guest anions with receptor **5**, determined by fluorescence titration experiments and compared to the values determined through UV-visible studies.

	log*K* with receptor 5	
Guest anion	Fluorescence[a]	Absorption[a]
p-nitrobenzoate, **14**	4.7 ± 0.8[b]	4.1 ± 0.2
p-aminobenzoate, **15**	4.3 ± 0.8[b]	3.6 ± 0.4
p-dimethylaminobenzoate, **16**	c	3.1 ± 0.4
p-hydroxybenzoate, **19**	3.0 ± 0.3	>5.5
p-toluenesulfonate, **30**	4.6 ± 0.4	-

[a]Measured at pH 7.0 (0.02 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4), [**5**] = 10^{-4} mol dm^{-3}. Uncertainties are taken as two SD. [b][**5**] = 10^{-6} mol dm^{-3}. [c]No significant changes in the fluorescence spectra.

The binding for *p*-nitrobenzoate, **14**, along with the uncharacteristically weak binding for *p*-aminobenzoate, **15**, in receptor **5** corresponds (within experimental error) to the values determined from the UV-visible absorption studies. The inclusion of **30** which was unable to be determined through the NMR or UV-vis

titrations, was determined from the fluorescence spectra as 4.6 ± 0.4, which is the same within experimental error to the values determined for the inclusion of these guests in receptor **4**.

A notable feature of inclusion of *p*-hydroxybenzoate within **5** is the observation that for the first time the log*K* value derived from the fluorescence study (3.0 ± 0.3) does not agree (within experimental error) with the value obtained from the absorption spectra. As foreshadowed earlier, observations of this type are always a possibility and in this case indicate some level of dissociation of the host-guest complex in the excited state.

The effect on binding constant values brought about by the methylating the upper rim of **4** can be seen in **Table 5.11.**

Table 5.11: Binding constants for the binding of guest anions with receptors **4** and **5** as determined from the fluorescence titration experiments.

	log*K* values[a]	
Guest anion	**4**	**5**
p-nitrobenzoate, **14**	4.9 ± 0.4[b]	4.7 ± 0.8
p-aminobenzoate, **15**	6.5 ± 0.2[b]	4.3 ± 0.8[b]
p-dimethylaminobenzoate, **16**	4.1 ± 0.4	c
p-hydroxybenzoate, **19**	4.5 ± 0.3	3.0 ± 0.3
p-toluenesulfonate, **30**	4.6 ± 0.7	4.6 ± 0.4

[a]Measured at pH 7.0 (0.02 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4). Uncertainties are taken as two SD. [b][Host] = 10^{-6} mol dm^{-3}. [c]No significant changes in the fluorescence spectra.

Only with *p*-aminobenzoate and *p*-hydroxybenzoate is there a significant alteration, this being a destabilisation of *ca* one order of magnitude. This is similar to the effect seen with the longer guests phenoxyacetate and histidine in **Chapter 3** for their inclusion in **5** compared to **4**. Unfortunately, the investigation of these two guests could be not be continued into the fluorescence studies as they produced no significant changes to the fluorescence intensities of any of the receptor complexes.

5.8.3. Binding constants for anionic guests with the fluorescent receptor, 6, having three hydrogen bond donor groups at the base of the cavity due to the presence of an extra pendant arm.

The fluorescence studies of guest inclusion with receptor **6** produced binding constants in the usual manner, as detailed in **Table 5.12.**

Table 5.12: Binding constants (log*K*) for the binding of guest anions with receptor **6**, as determined by fluorescence titration experiments and compared to the values determined through UV-visible absorption.

Guest anion	log*K* with receptor 6	
	Fluorescence[a]	Absorption[a]
p-nitrobenzoate, **14**	3.4 ± 0.3	4.1 ± 0.2
p-aminobenzoate, **15**	6.4 ± 0.3[b]	>5.5
p-dimethylaminobenzoate, **16**	3.2 ± 0.2	3.9 ± 0.2
benzoate, **18**	5.2 ± 0.2[b]	-
p-hydroxybenzoate, **19**	3.2 ± 0.5	>5.5
m-hydroxybenzoate, **20**	5.2 ± 0.2[b]	-
gallate, **22**	7.3 ± 1.1[b]	-
p-toluenesulfonate, **30**	3.3 ± 0.5	4.0 ± 1.0
benzenesulfonate, **31**	5.6 ± 0.4	-

[a]Measured at pH 7.0 (0.02 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4). [**6**] = 10^{-4} mol dm^{-3}. Uncertainties are taken as two SD. [b][**6**] = 10^{-6} mol dm^{-3}.

Within receptor **6** the fluorescence derived log*K* values for the inclusion of both **14** and **16** as well as **19**, are less than that determined from the UV-visible absorption titrations. This is different to what was found for receptor **4**, where the log*K* values for **14** and **16** derived for both methods were the same (within experimental error) and the difference for **19** was somewhat smaller. This would indicate that the change in conformation of receptor **6** on excitation is much more significant than any change that occurs in receptor **4**. This is understandable as receptor **6** has the extra pendant arm adjacent to the excited anthracene moiety, which receptor **4** does not. Interestingly benzoate binds in **6** with a log*K* *ca* 3 orders of magnitude higher than in **4**. This may be a consequence of O-H**...**π hydrogen

bonding originating from the non-coordinating hydroxy group on the 'fifth' arm directed towards the aromatic ring of the benzoate.

5.8.4. Binding constants for anionic guests with fluorescent receptor 7, having a methylated phenoxy derived cavity and three hydrogen bond donor groups at the base of the cavity due to the presence of an extra pendant arm.

The fluorescence titrations of [Cd((*S*)-amthmppc)]$(ClO_4)_2$, **7**, produced binding constants in the usual manner, as detailed in **Table 5.13.**

Table 5.13: Binding constants for the binding of guest anions with receptor **7**, as determined by fluorescence titration experiments and compared to the values determined through UV-vis studies.

	log*K* with receptor 7	
Guest anion	Fluorescence[a]	Absorption[a]
p-nitrobenzoate, **14**	4.7 ± 0.7	4.8 ± 0.4
p-aminobenzoate, **15**	c	5.0 ± 0.4
p-dimethylaminobenzoate, **16**	c	3.0 ± 0.2
p-hydroxybenzoate, **19**	3.3 ± 0.6	>5.5
gallate, **22**	6.9 ± 0.6[b]	c
p-toluenesulfonate, **30**	4.2 ± 0.4	4.0 ± 0.6
benzenesulfonate, **31**	3.2 ± 0.6	-

[a]Measured at pH 7.0 (0.0198 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4). [**7**] = 10^{-4} mol dm^{-3}. Uncertainties are taken as two SD. [b][**7**] = 10^{-6} mol dm^{-3}. [c]No significant change in the spectra.

Whilst the log*K* values derived from both methods were the same within the experimental error, the values determined from the fluorescence titrations were the lower of the two for the inclusion of **14**, **19** and **31** within receptor **7**.

The effect of methylation of the upper rim of the cavity (changing from receptor **6** to **7**) was shown to have little effect on the log*K* values determined from the fluorescence data. The binding constants for guest inclusion in both **6** and **7**

appear in **Table 5.14**. The only guest that shows a difference of binding strengths between receptors **6** and **7** is benzenesulfonate, **31**, which shows a lower log*K* value in the substituted receptor **7** (3.2 ± 0.6) than in receptor **6** (5.6 ± 0.4).

Table 5.14: Binding constants for the binding of guest anions with receptors **6** and **7** as determined from the fluorescence titration experiments.

	log*K* values[a]	
Guest anion	**6**	**7**
p-nitrobenzoate, **14**	3.4 ± 0.3	4.7 ± 0.7
p-aminobenzoate, **15**	6.4 ± 0.3[b]	c
p-dimethylaminobenzoate, **16**	3.2 ± 0.2	c
benzoate, **18**	5.2 ± 0.2[b]	-
p-hydroxybenzoate, **19**	3.2 ± 0.5	3.3 ± 0.6
m-hydroxybenzoate, **20**	5.2 ± 0.2[b]	-
gallate, **22**	7.3 ± 1.1[b]	6.9 ± 0.6[b]
p-toluenesulfonate, **30**	3.3 ± 0.5	4.2 ± 0.4
benzenesulfonate, **31**	5.6 ± 0.4	3.2 ± 0.6

[a]Measured at pH 7.0 (0.02 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4). Uncertainties are taken as two SD. [b][Host] = 10^{-6} mol dm^{-3}. [c]No significant changes in the fluorescence spectra.

5.9. Fluorescence changes upon guest inclusion with fluorescent receptors 4-7

With some understanding of the stability of inclusion of guest species within the receptor complexes **4**-**7**, the changes in fluorescence emission intensities that result from these guest inclusions can now be discussed. From the seven processes identified for fluorescence perturbation associated with guest molecule inclusion that were mentioned earlier, six were identified as causing quenching or diminution of the observed fluorescence emission intensity. It might then be expected that the majority of observed fluorescence changes would be due to a diminution of fluorescence emission intensity. However this was not the case. With two notable exceptions, namely *p*-nitrobenzoate and *p*-dimethylaminobenzoate, most other cases

of guest inclusion resulted in an increase of fluorescence emission intensity. This points to the elimination of water from the guest anion binding cavity, as the guest enters, as being a universal source of fluorescence enhancement in these receptors. It is possible that the OH groups in the sensors hydrogen bond to solvent water within the cavity. The bound water may then in turn hydrogen bond to the π-system of the anthracene moiety pseudointramolecularly.[149f] The quenching ability of water towards the fluorophore of **4** was quite evident when its fluorescence in 20% aqueous 1,4-dioxane was compared with 55% aqueous 1,4-dioxane. On making this change the fluorescence of **4** dropped by 80%. The enhanced fluorescence may then be attenuated by any quenching process which will be of a magnitude and nature specific to each individual guest.

5.9.1. Fluorescence changes in 4 upon guest inclusion.

The results of the investigations into the perturbation of the fluorescence of **4** upon guest inclusion are tabulated in **Table 5.15.** The relative fluorescence emission intensities are shown in **Figure 5.16**., which shows that the most common result of guest inclusion within receptor **4** is a weak increase in fluorescence emission intensity. In other cases there is no observable change and with just a few guests there is a diminution of fluorescence emission intensity. As was mentioned at the beginning of this chapter, **process 1**, solvent displacement, can be called upon to explain an increase in observed fluorescence emission intensity.

Process 1 involves displacement of a quenching solvent (water) by the included guest species, causing a revival of fluorescence. As all guest species examined are of a similar size, it would have been expected that the number of water

molecules displaced would be similar, as would the revival of the fluorescence. As there are large differences in the fluorescence emission intensities of the different host-guest inclusion complexes, more than one process must be involved, with processes more dependent on the properties of each guest either adding or

Table 5.15. Changes in fluorescence intensity (%) of receptor **4** due to inclusion of guests **14**-**31**, measured at the maximum observed change (usually 10 equivalents guest (with Φ)) and at the calculated change for 100% host-guest complex formation (determined during the evaluation of the binding constant).

Guest vs 4	ΔI^{a} max_{obs}	Φ at max_{obs} change	$\mathbf{HG}_{calc}$
p-nitrobenzoate, **14**[b]	-10.0%	0.463	-12.9%
p-aminobenzoate, **15**[b]	58.0%	0.846	58.8%
p-dimethylaminobenzoate, **16**	-28.0%	0.471	-29.6%
benzoate, **18**[c]	90.6%	0.859	116.7%
p-hydroxybenzoate, **19**	25.0%	0.830	26.9%
m-hydroxybenzoate **20**[b]	14.0%	0.901	21.4%
3,5-dihydroxybenzoate, **21**[b]	-8.0%	0.575	-8.0%
gallate, **22**[b]	9.0%	0.718	10.3%
o-hydroxybenzoate, **23**[b]	19.1%	0.895	19.5%
2,6-dihydroxybenzoate, **24**	-4%	0.647	-4.2%
phenoxyacetate, **25**[b]	1.8%	0.671	2.0%
(*D*)-histidinate, **26**[b]	0%	0.665	0%
(*L*)-histidinate, **27**[b]	7.5%	0.715	7.6%
(*D*)-tryptophanate, **28**[b]	0%	0.592	0%
(*L*)-tryptophanate, **29**[b]	0%	0.718	0%
p-toluenesulfonate, **30**	6.0%	0.716	7.6%
benzenesulfonate, **31**	25.0%	0.885	38.6%

[a]Measured at pH 7.0 (0.02 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4). [**4**] = 10^{-4} mol dm^{-3}. Φ of **4** = 0.684. [b][**4**] = 10^{-6} mol dm^{-3}. [c][**4**] = 10^{-3} mol dm^{-3}.

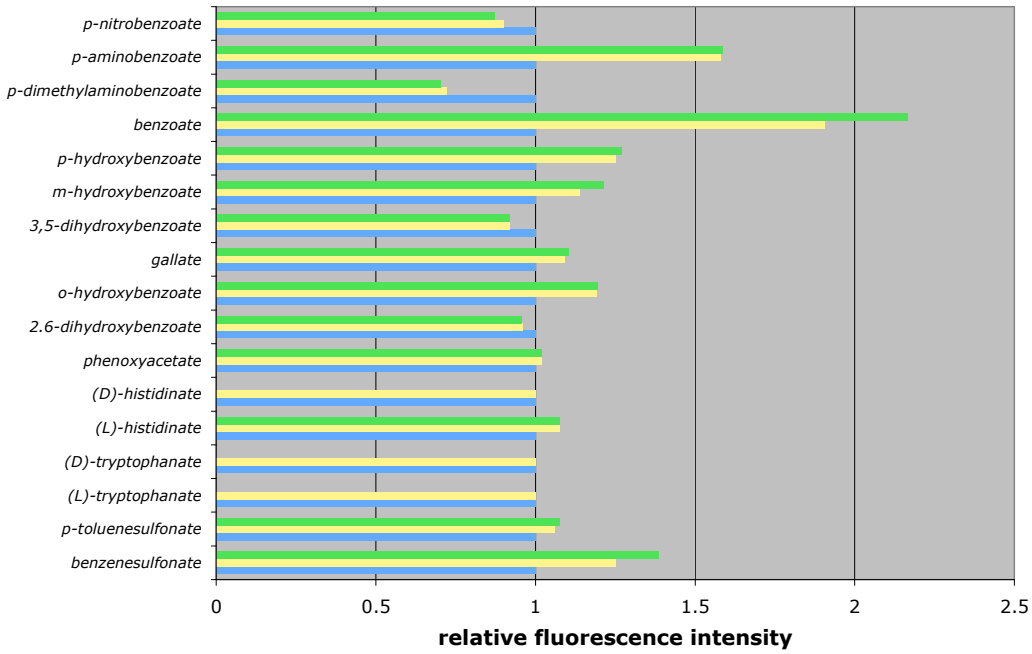


Figure 5.16. The relative fluorescence intensities of **4** upon inclusion of guests **14**–**31**, showing the fluorescence emission intensity of the host alone (blue bar), the fluorescence emission intensity after the greatest observed change (yellow bar), and the calculated fluorescence emission intensity for 100% formation of host-guest inclusion complex (green bar). All intensities have been set relative to that of receptor **4**, which has been arbitrarily given a fluorescence intensity of 1.

subtracting from the general increase caused by solvent displacement. The maximum observed fluorescence change of the weak binder benzoate (107% increase at 10^{-6} mol dm^{-3} concentrations of **4**, 90.6% increase at 10^{-3} mol dm^{-3} concentrations), which has no obvious additional quenching attributes, may represent the maximum increase of fluorescence emission intensity due to solvent displacement achievable. The calculated quantum yield for full formation of this particular host-guest complex is $\Phi = 0.889$ at 10^{-3} mol dm^{-3} concentrations of **4**.

If solvent displacement should generally cause a doubling of the observed fluorescence emission intensity, then the actual range of observed fluorescence emission intensities for the guest inclusions must involve one or more concomitant quenching processes. **Process 2** (as described in **section 5.2**), which is PeT interference due to anthryl N-H hydrogen bond donation, is the most obvious and universal of these. Here the formation of hydrogen bonds between the acceptors of

the guest and the donor hydrogen of the anthrylamine of the host results in the pushing back of electron density onto the amine, giving rise to quenching. The quenching of fluorescence due to **process 2** is dependent on the strength of the hydrogen bonding between host and guest. These hydrogen bond strengths are related to the ability of the guest anion to act as a hydrogen bond acceptor, and are gauged by its pK_a value. Hence if **process 2** were involved then guests with higher pK_a values would show more quenching, and have a lower net fluorescence increase, or even a diminution of fluorescence emission intensity, than a similar guest with a lower pK_a value. Correlations between binding constants and pK_a values have not always been good suggesting that the binding constants are not only a function of hydrogen bond strength. So the correlation between binding constant and **process 2** quenching is not likely to be good either, but some cases are apparent. For example *m*-hydroxybenzoate (pK_a 4.08, log$K$ = 5.3) shows an overall maximum increase in fluorescence emission intensity of 14%. This overall increase can be considered as an enhancement of ca 100% due to **process 1**, and a concurrent quenching of fluorescence due to **process 2**, which brings the net fluorescence change down to only a 14% increase. Gallate, on the other hand, should form stronger hydrogen bonds (pK_a 4.41, log$K$ = 7.1), pushing more electron density back onto the anthrylamine, and increasing the quenching, which is perhaps why the net fluorescence increase is only 9%.

For two of the guests that show a reduction of fluorescence, *p*-nitrobenzoate (-10%), and *p*-dimethylaminobenzoate, (-28%), **process 3**, PeT interference through space, is quite likely operating alongside **process 2**. This is because these two anions have strong electron accepting or electron donating groups, respectively.[165] The work of Fabbrizzi and co-workers on a zinc(II) complex of a 9-anthracenyl appended

tren ligand[165] (**Figure 5.1**), demonstrated this nicely when they showed that inclusion of either *p*-nitrobenzoate or *p*-dimethylaminobenzoate brought about a *ca* 90% reduction of its fluorescence due to through space PeT quenching, whereas inclusion of benzoate had no effect.

For the guests with further hydrogen bonding groups, such as the hydroxybenzoates, **19-24**, aminoacids, **26-29**, *p*-aminobenzoate, and *p*-dimethylaminobenzoate, there is the potential for **process 4** to be involved. In this process X-H...π hydrogen bonding to the aromatic ring of the fluorophore will quench fluorescence by vibrational deactivation of the excited fluorophore.

A good subset of the entire range of host-guest complexes for comparing fluorescence perturbation, via **processes 2 and 4** in particular, is that of the hydroxybenzoate series, tabulated in **Table 5.16.**

Table 5.16. Maximum fluorescence changes obtained from the fluorescence measurements for the inclusion of the hydroxybenzoate guests in **4**, ranked by log*K*.

Hydroxybenzoate series of guests[a]	**Δ I max$_{obs}$**	**-COOH pK_a values**	**log*K* values**
benzoate, **18**	107%, 90.6%[b]	4.20	2.3 ± 0.1
p-hydroxybenzoate, **19**[c]	25 %	4.58	4.5 ± 0.3
m-hydroxybenzoate, **20**	14 %	4.08	5.3 ± 0.5
3,5-dihydroxybenzoate, **21**	-8 %	4.04	6.1 ± 0.3
3,4,5-trihydroxybenzoate, **22** (gallate)	9 %	4.41	7.1 ± 0.5
o-hydroxybenzoate, **23**	19 %	2.98	7.1 ± 0.5
2,6-dihydroxybenzoate, **24**	-4%	1.05	7.5 ± 0.9

[a]Measured at pH 7.0 (0.02 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4). [**4**] = 10^{-6} mol dm^{-3}. [b][**4**] = 10^{-3} mol dm^{-3}. [c][**4**] = 10^{-4} mol dm^{-3}.

In this series benzoate, **18**, is the weakest binder, (log*K* = 2.3), but it is seen to induce the largest change in fluorescence. This suggests an inverse relationship between binding strength and fluorescence enhancement, indicative of a dominance of enhancement **process 1**, accompanied by progressively greater quenching through **processes 2 and 4** as the binding strength increases. This trend is followed for the

first four entries in **Table 5.16**, but the pattern shows partial breakdown thereafter, which warrants closer examination.

The second largest change in fluorescence (25% increase) was observed for *p*-hydroxybenzoate. Its higher pK_a value, compared to **18**, would enable stronger hydrogen bonding, allowing **process 2** to cause the diminution in fluorescence observed. The single *para*- hydroxy-substituent is pointing out of the cavity, and is incorrectly aligned for additional hydrogen bonding to the cavity walls. **Figure 5.14.(a)** shows the inclusion of **19**.

The third entry, *m*-hydroxybenzoate, has a lower pK_a value for the -CO_2H group but shows a higher binding constant, (log$K$ = 5.3), which has been explained by the additional O-H...π bonding. The further lowering of the fluorescence enhancement is consistent with **process 4** becoming operative as well as **processes 1 and 2**. The hydroxy substituent is in a position to interact with the aromatic group of the fluorophore, as shown in **Figure 5.14(b)**.

3,5-dihydroxybenzoate, **21**, has a lower pK_a value again, but is bound more strongly. This is consistent with the formation of two O-H...π hydrogen bonds offsetting weaker hydrogen bonding at the base of the cavity. This is supported by further reduction of the fluorescence, which arises because the probability of the O-H...π interaction involving the aromatic rings of the anthracene has been doubled.

Gallate fits between the above two. Effectively it has only one *meta* O-H...π binder/quencher (due to internal hydrogen bonding between the 3- and 4- hydroxy groups, as shown in **Figure 5.13**) but, on the other hand it is more basic (pK_a = 4.41, due to the *para*-hydroxy group) strengthening the binding at the base of the cavity and giving an overall log$K$ of 7.1. The quenching is not as high as with 3,5-

dihydroxybenzoate showing that **process 4** quenching in these systems is more effective than **process 2**.

The data for the *ortho*-hydroxy benzoates is slightly puzzling. The low pK_a values for the two guests suggest that their binding constants should be low, yet for *o*-hydroxybenzoate it is $10^{7.1}$ and it is $10^{7.5}$ for 2,6-dihydroxybenzoate. The increase with increasing *ortho*-substitution and diminishing pK_a must mean O-H...π hydrogen bonding is the source of the stability. This in turn should give rise to progressively greater quenching, which it does (+19% to -4%) which is similar to what was seen with the corresponding *meta* compounds (+14% to -8%). The surprising thing is that one might expect the stronger O-H...π binding to cause the size of the fluorescence decrease of the *ortho* compounds to be greater than those of the *meta* compounds.

5.9.2. Fluorescence changes upon guest inclusion within 5.

Whether having *p*-methyl substituents on the upper rim of the cavity would have any effect on the fluorescence emission intensity of the host was investigated by titration of receptor **5** with the same guest anions as was used with receptor **4**. The results of the inclusion of guest anions in receptor **5** are shown in **Table 5.17.**

The observed changes in fluorescence for the inclusion of guests within the *p*-methylated receptor **5** are similar to those with **4**, in that some guests caused an increase in fluorescence (guests **15**, **19** and **31**), others showed no change, whilst two showed a diminution of fluorescence intensity. Benzoate was not examined with this receptor. Interestingly the inclusion of **30** within receptor **5** showed a diminution of fluorescence intensity, whilst in receptor **4** there had been an increase in fluorescence

Table 5.17. Changes in fluorescence emission intensity (%) of receptor **5**, due to guest inclusion measured at the maximum observed change and at the calculated expected change for 100% host-guest (**HG**) complex formation.

Guest vs 5[a]	ΔI max_{obs}	Φ at max_{obs} change	$\mathbf{HG}_{calc}$
p-nitrobenzoate, **14**	-6.00%	0.466	-6.30%
p-aminobenzoate, **15**[b]	11.00%	0.596	12.00%
p-dimethylaminobenzoate, **16**	0%	0.517	0%
p-hydroxybenzoate, **19**	23.10%	0.685	47.30%
phenoxyacetate, **25**[b]	0%	0.546	0%
(*D*)-histidinate, **26**[b]	0%	0.546	0%
(*L*)-histidinate, **27**[b]	0%	0.589	0%
(*D*)-tryptophanate, **28**[b]	0%	0.492	0%
(*L*)-tryptophanate, **29**[b]	0%	0.546	0%
p-toluenesulfonate, **30**	-9.40%	0.448	-11.10%
benzenesulfonate, **31**	8.80%	0.717	19.90%

[a]Measured at pH 7.0 (0.02 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4). [**5**] = 10^{-4} mol dm^{-3}. Φ of **5** = 0.546. [b][**5**] = 10^{-6} mol dm^{-3}.

intensity. Also the inclusion of **16** showed no net change in fluorescence, indicating that **process 2** has been weakened (quenching is reduced to an extent that there is no net diminution of fluorescence) in accordance with the weaker binding (smaller log$K$). It is still unclear why the addition of *p*-methyl groups to the upper rim of the cavity affects the binding strength, but the fluorescence perturbation is consistent with this. The relative fluorescence emission intensities for guest inclusion within receptor **5** are shown in **Figure 5.17**.

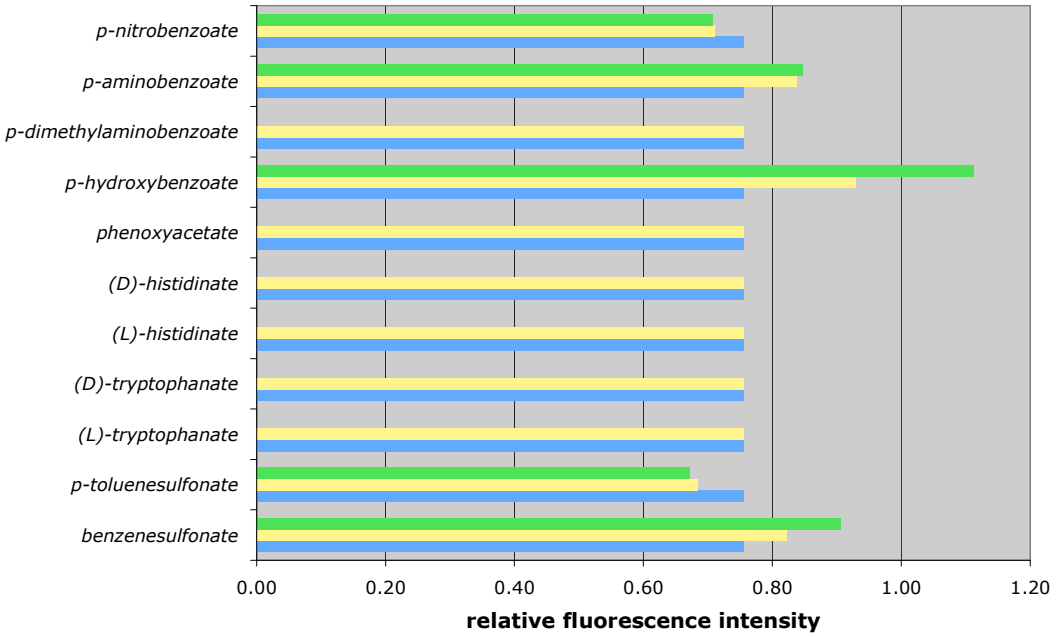


Figure 5.17. The relative fluorescence intensities of **5** upon guest inclusion, showing the fluorescence emission intensity of the host alone (blue bar), the fluorescence emission intensity after the greatest observed change (10 equivalents, yellow bar), and the calculated fluorescence emission intensity for 100% formation of host-guest inclusion complex (green bar). All intensities have been set relative to that of receptor **4**, which has been arbitrarily given a fluorescence intensity of 1.

5.9.3. Fluorescence changes upon guest inclusion within 6 and 7.

The effect of *N*-alkylation of the anthrylamine (conversion from a secondary to a tertiary amine) on the fluorescence emission intensities of the host was investigated using receptors **6** and **7**. The results of the inclusion of guest anions in receptor **6** are shown in **Table 5.18.**

Inclusion in **6** showed the usual diminution of fluorescence emission intensity for the electron acceptor and donor guests *p*-nitrobenzoate and *p*-dimethylaminobenzoate.

Table 5.18. Changes in fluorescence emission intensity (%) of **6** due to guest inclusion measured at the maximum observed change and at the calculated expected change for 100% host-guest complex formation.

Guest vs 6[a]	ΔI max_{obs}	Φ at max_{obs} change	HG_{calc}
p-nitrobenzoate, **14**	-32.20%	0.187	-47.90%
p-aminobenzoate, **15**[b]	168.10%	0.508	174.30%
p-dimethylaminobenzoate, **16**	-38.20%	0.142	-65.70%
benzoate, **18**[b]	119.20%	0.594	191.60%
p-hydroxybenzoate, **19**	43.60%	0.376	74.90%
m-hydroxybenzoate, **20**[b]	142.80%	0.500	250.40%
gallate, **22**[b]	7.90%	0.280	8.00%
phenoxyacetate, **25**[b]	0%	0.251	0%
(*D*)-histidinate, **26**[b]	0%	0.280	0%
(*L*)-histidinate, **27**[b]	0%	0.269	0%
(*D*)-tryptophanate, **28**[b]	0%	0.251	0%
(*L*)-tryptophanate, **29**[b]	0%	0.251	0%
p-toluenesulfonate, **30**	42.60%	0.377	91.40%
benzenesulfonate, **31**	12.00%	0.312	16.80%

[a]Measured at pH 7.0 (0.02 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4). [**6**] = 10^{-4} mol dm^{-3}. Φ of **6** = 0.251. [b][**6**] = 10^{-6} mol dm^{-3}.

All other guests showed an increase in fluorescence emission intensity, which were quite large for benzoate (119%), *p*-aminobenzoate (168%) and *m*-hydroxybenzoate (143%). The introduction of the fifth pendant arm should totally eliminate quenching *via* **process 2** and because of the non-coordinating hydroxy group associated with the fifth arm the initial solvation of the cavity should be higher, leading to greater fluorescence enhancement on desolvation by the guest. Thus, greater fluorescence enhancements using **6**, compared to **4**, were expected and this is generally found to be the case. The relative fluorescence emission intensities are shown in **Figure 5.18**.

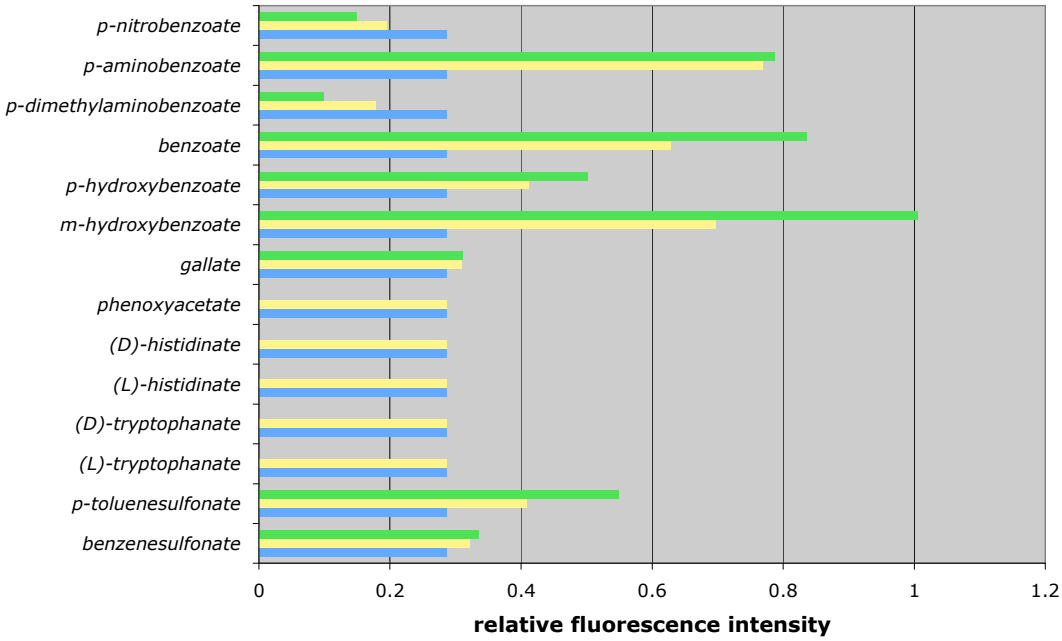


Figure 5.18. The relative fluorescence intensities of **6** upon guest inclusion, showing the fluorescence emission intensity of the host alone (blue bar), the fluorescence emission intensity after the greatest observed change (10 equivalents, yellow bar), and the calculated fluorescence emission intensity for 100% formation of host-guest inclusion complex (green bar). All intensities have been set relative to that of receptor **4**, which has arbitrarily been given a fluorescence intensity of 1.

The results of the inclusion of guest anions in receptor **7** are shown in **Table 5.19**, with the relative fluorescence emission intensities are shown in **Figure 5.19**.

Table 5.19. Changes in fluorescence emission intensity (%) of **7** due to guest inclusion measured at the maximum observed change and at the calculated expected change for 100% host-guest complex formation.

Guest vs 7	ΔI^{a} max_{obs}	Φ at max_{obs} change	$\mathbf{HG}_{calc}$
p-nitrobenzoate, **14**	-8.20%	0.170	-8.60%
p-aminobenzoate, **15**	4.90%	0.258	5.10%
p-dimethylaminobenzoate, **16**	0%	0.198	0%
p-hydroxybenzoate, **19**	18.20%	0.291	35.30%
gallate, **22**[b]	36.70%	0.370	36.80%
phenoxyacetate, **25**[b]	0%	0.244	0%
(*D*)-histidinate, **26**[b]	0%	0.268	0%
(*L*)-histidinate, **27**[b]	5.00%	0.302	6.20%
(*D*)-tryptophanate, **28**[b]	0%	0.244	0%
(*L*)-tryptophanate, **29**[b]	0%	0.244	0%
p-toluenesulfonate, **30**	11.20%	0.264	12.90%
benzenesulfonate, **31**	6.70%	0.312	24.70%

[a]Measured at pH 7.0 (0.02 mol dm^{-3} lutidine) in 20% aqueous 1,4-dioxane at 298 K, I = 0.1 mol dm^{-3} (NEt_4ClO_4). [**7**] = 10^{-4} mol dm^{-3}. Φ of **7** = 0.244. [b][**7**] = 10^{-6} mol dm^{-3}.

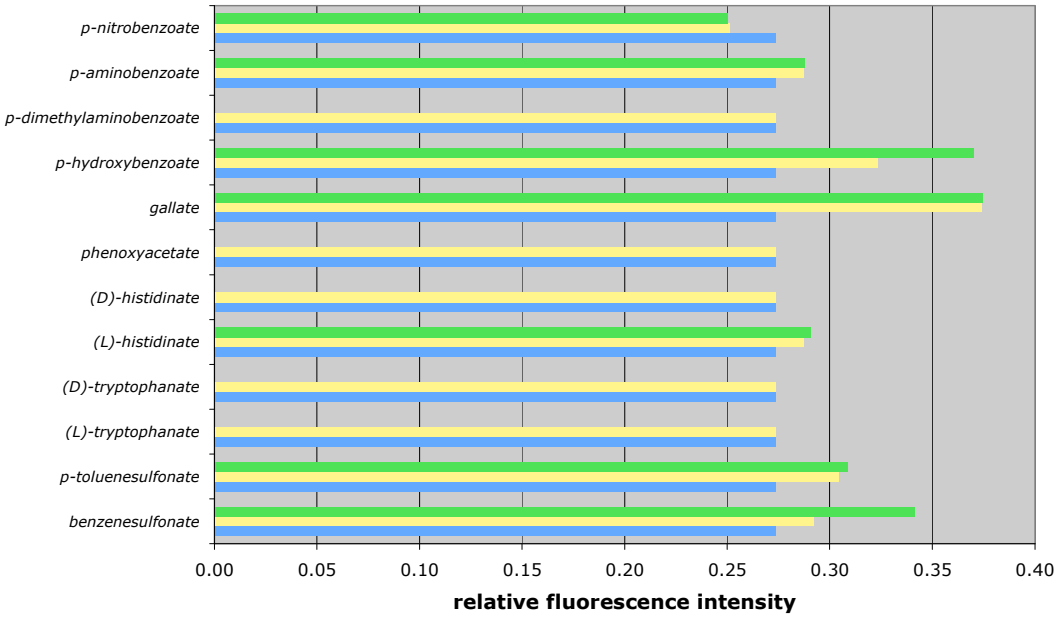


Figure 5.19. The relative fluorescence intensities of **7** upon guest inclusion, showing the fluorescence emission intensity of the host alone (blue bar), the fluorescence emission intensity after the greatest observed change (10 equivalents, yellow bar), and the calculated fluorescence emission intensity for 100% formation of host-guest inclusion complex (green bar). All intensities have been set relative to that of receptor **4**, which has arbitrarily been given a fluorescence intensity of 1.

Inclusion of the strong electron acceptor guest *p*-nitrobenzoate within the *N*-alkylated, *p*-methyl substituted cavity of receptor **7** caused it to show the usual diminution of fluorescence emission intensity, however this change was smaller than that seen for receptor **6**. Unusually there was no change in the fluorescence intensity upon inclusion of *p*-dimethylaminobenzoate within the cavity of **7**, which differs from the quenching observed with receptor **6**. All other guests showed either no change, in the case of *p*-dimethylaminobenzoate, phenoxyacetate, *D*-histidinate and tryptophanate, or an increase in fluorescence emission intensity, which was large only for the inclusion of gallate (37%).

5.10. Concluding remarks

This wide ranging survey of the perturbations of host fluorescence caused by the various potential guest molecules, and their binding constants, establishes the level and nature of the fluorescence signalled selectivity amongst different aromatic anionic guests. Measured binding constants span five orders of magnitude from $10^{2.5}$ to $10^{7.5}$ and measured fluorescence perturbations extend from 38.2% diminution to 168.1% enhancement.

Very strong sequestration selectivity within receptor **4** was noted for benzoates having hydrogen bonding groups in the *para* position such as *p*-aminobenzoate ($10^{6.5}$) and, to a lower extent, *p*-hydroxybenzoate ($10^{4.5}$). This selectivity was heightened when additional hydroxy groups, were introduced, most notably in the *ortho*-positions. It is quite plausible to suggest, in the light of related crystal structures,[115,123] that the hydroxy groups *ortho*, and to a lesser extent *meta*, to the benzoate are suitably positioned to locate the guest in the cavity through two O-H...π interactions with a trans-related pair of aromatic moieties, in addition to the O-H...O^- and in some cases N-H...O^-, hydrogen bonding occurring at the base of the cavity.

Signalling selectivity was determined by the observation of fluorescence perturbations upon guest inclusion. Generally this was an increase in fluorescence emission intensity, although many guests showed no change. Only *p*-nitrobenzoate consistently showed a diminution of fluorescence emission intensity, which was attributed to a significant through space electron transfer process. The largest fluorescence change observed for the inclusion of a guest in receptor **4** was a 107% increase for the inclusion of benzoate (which showed a 119% increase in **6**). The

largest fluorescence change observed for receptor **5** was a *ca* 23% increase for the inclusion of *p*-hydroxybenzoate, for receptor **6** was a *ca* 168% increase for the inclusion of *p*-aminobenzoate (which showed a 58% increase in receptor **4**), and for receptor **7** was a *ca* 37% increase for the inclusion of gallate. The larger fluorescence emission intensity changes were observed for inclusion within receptors **4** and **6**, with the methylated sensors **5** and **7** generally showing much smaller perturbations. Receptor **6** consistently showed larger fluorescence perturbations (% change) than receptor **4**, with the inclusion of *p*-aminobenzoate, benzoate and *m*-hydroxybenzoate all showing more than doubling of the fluorescence intensity.

A summary of movement of receptor ligand **146** along the full extent of the fluorescence quantum yield range in response to pH, complexation with Cd(II) and introduction of guests to the Cd(II) complex, is shown in **Figure 5.20**.

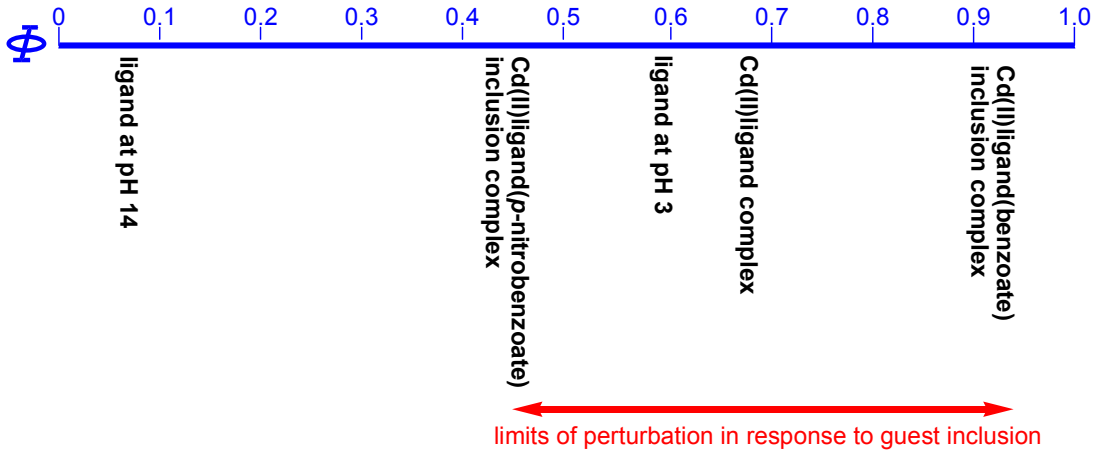


Figure 5.20. A representation of the quantum yields (Φ) for receptor ligand **146** (10^{-6} mol dm^{-3}) in response to pH change, formation of the Cd(II) complexes, and introduction of benzoate and *p*-nitrobenzoate to the Cd(II) complex, which define the limits of Φ movement in response to anion inclusion within $[Cd(\mathbf{146})]^{2+}$.

Chapter 6

Experimental

6. Experimental

6.1. General Experimental

All reactions were carried out under a nitrogen atmosphere, unless otherwise indicated. Cyclen was purchased from Strem chemicals, in 98% purity, and was used as such. Solvent and reagent purification was performed according to established methods.[280] The (2*S*)-(+)-3-[4'-(*tert*-butyl)phenoxy]-1,2-epoxypropane was generously donated by Professor Xu Xingyou.

Silica flash chromatography was carried out using the methods described by Zubrick.[281] Merck Kieselgel 60 (230-400 mesh) silica gel was utilized. Thin layer silica chromatography (tlc) was performed using Merck no. 5554 aluminium backed plates with silica gel 60 PF_{254}. For alumina flash chromatography, Fluka basic alumina oxide, pH 10 ± 0.5, Brockman II (100-290 mesh) was utilized. Thin layer chromatography was performed on Merck no. 5551 aluminium backed neutral (type T) aluminium oxide 150 F_{254} plates.

6.2. Physical Methods

Elemental analyses were conducted at the University of Otago, New Zealand. Melting points were recorded on a Reichert hot-stage apparatus and are uncorrected. ^{1}H NMR (200 MHz) and $^{13}C\{^{1}H\}$ NMR (50.291 MHz) spectra were recorded on a Varian Oxford 200 spectrophotometer. ^{1}H NMR (300.075 MHz) and $^{13}C\{^{1}H\}$ NMR (75.462 MHz) spectra were recorded on a Varian Gemini 300 spectrophotometer. Chemical shifts of the $^{13}C\{^{1}H\}$ NMR spectra were referenced to the central

resonance of the multiplets of the following solvents which were taken as: δ 77.00 for $CDCl_3$, δ 39.52 for DMSO-d_6, δ 128.00 for benzene-d_6, δ 29.80 for acetone-d_6, δ 49.00 for CD_3OD and to the –*C*N peak at δ 118.10 for CD_3CN. In the case of D_2O, 1,4-dioxane was added as a reference, δ 67.19. Chemical shifts of the ^1H NMR spectra were referenced to the central resonance of the residual solvent peak at δ 7.26 in $CDCl_3$, δ 2.50 for DMSO-d_6, δ 7.16 for benzene-d_6, δ 2.05 for acetone-d_6, δ 3.31 for CD_3OD and δ 1.94 for CD_3CN. In the case of D_2O, 1,4-dioxane was added as a reference, δ 3.75. Conductivity measurements (Λ_M) were made on 10^{-3} mol dm^{-3} solutions in DMF at 298 K using a Model Aqua-C Conductivity-TDS-Temp. Meter. Infrared spectra were recorded on a BioRad FTS-40A spectrophotometer. Optical Rotations were measured at ambient temperature using a PolAAr automatic polarimeter.

6.3. Host-guest binding constant determinations by ^1H NMR

Guest anions used in the guest binding experiments were generally employed in the form of their sodium salts, which were, in most cases, prepared by reacting stoichiometric quantities of the acidic component (carboxylic acids, amino acids or phenols) with sodium hydroxide in water or ethanol. The salt either precipitated or the solvent was removed and the solid residue recrystallised from ethanol or a similar solvent.

The general procedure for the titration of the guest by the host involved the preparation of separate (0.7 cm^3) NMR samples in DMSO-d_6. The guest concentration in each tube was maintained at 1mM, whilst the concentration of the host was varied for each sample, generally from 0 mM up to 10 mM. All samples

were prepared from stock solutions of each of the different receptor complexes (14 mM in DMSO-d_6) and the guest (50 μL, 14 mM in DMSO-d_6). A further host stock solution (1.4 mM) was made through the dilution of the 14 mM host stock solution, such that lower concentrations of the host (< 1 mM) could be achieved with precision.

All titrations were performed in 5 mm NMR tubes, and the stock solutions of host and guest were added separately using a 250 μL micropipette. The volume of solution in each tube was kept constant at 0.7 cm^3 by the topping up of the tube using more DMSO-d_6 with the micropipette.

All titration measurements were recorded at 294 ± 0.5 K. All stock solutions were made in DMSO-d_6, apart from those of the histidinate guest salts, which required 10% D_2O in DMSO-d_6 (v/v) to aid solubility.

^{1}H NMR titration curves were generated using the IGOR data analysis software,[282] and the binding constants (log*K* values) were obtained through analysis of the chemical shift data using a non-linear regression procedure written by Dr A. K. W. Stephens, the Flinders University of South Australia, 1999.

6.4. Ultraviolet-visible spectroscopy

UV-visible absorbance spectra were measured on a Varian Cary 50 SCAN UV-Visible spectrophotometer using quartz cells (1.0 cm path length) over a wavelength range of 300-500 nm at 0.15 nm intervals, with a scan rate of 50 nm/min and a slit width of 5.0 nm. The blank used contained all species present in the solutions of interest except for the ligand, complex, and guest, where applicable. Baseline corrections measurements were used for all spectra. All solutions were

equilibrated at 25°C. Concentrations of all solutions were 10^{-4} M, in 20% aqueous 1,4-dioxane. Solutions were prepared freshly prior to measurement.

6.4.1. pH titrations.

To observe the influence of pH on the uv/vis absorption properties of the ligands **131**, **146** and **170-173**, a series of titration experiments was conducted, in which the molar absorbances of the ligands at different pH values were investigated.

Solutions of each of the protonated (with 0.005 mol dm^{-3} $HClO_4$) ligands (at 10^{-4} mol dm^{-3} for UV-visible titrations) in 20% aqueous 1,4-dioxane, at a constant ionic strength of I = 0.1 mol dm^{-3} (NEt_4ClO_4), were titrated with aliquots of 0.100 mol dm^{-3} carbon dioxide free tetraethylammonium hydroxide solution. The absorption spectrum (over the range 300-500 nm) was recorded at each of the resulting pH values, which ranged from *ca* 2 to 14, as indicated by use of a combination glass electrode calibrated against aqueous buffer solutions (for pH values 2-12) or by indicator paper (for pH > 12). The dilution effects are overcome by the comparison of the molar absorbance values, rather than simply considering the absorption spectra.

6.4.2. Metal complexation absorption studies.

The influence of metal complexation on the absorption properties of the ligands, **146** and **170-173**, was investigated by a series of titration experiments, in which the change of the molar absorbances of the ligands, upon addition of the metal ions, were investigated.

Solutions of each of the ligands (at 10^{-4} mol dm^{-3}) buffered at pH 7.0 (HEPES) in 20% aqueous 1,4-dioxane, at a constant ionic strength of I = 0.1 mol dm^{-3} (NEt_4ClO_4), were treated with aliquots (initially 0.1 cm^3) of 10^{-3} mol dm^{-3} metal(II) perchlorate solution. The absorption spectrum (over the range 300-500 nm) was recorded after each addition. The dilution affects are overcome by the comparison of the molar absorbance values, rather than simply considering the absorption spectra. The molar absorbance values determined through the titration of the ligands with 1 equivalent of cadmium(II) perchlorate solution, were identical (within experimental error) to the molar absorbances of a reference solution of the corresponding cadmium(II) complex.

6.4.3. Host-guest binding constant determinations from UV-visible spectroscopy.

To observe the influence of guest inclusion on the absorbance properties of the receptor complexes **4-7**, a series of titration experiments was conducted, in which the change of the molar absorbances of the receptors were monitored at increasing concentrations of the guest. This was conducted by either of the two following methods.

A series of 5 cm^3 solutions containing the receptor alone (10^{-4} mol dm^{-3}) and in the presence of 0.1-10 equivalents of guest, were made in 20% aqueous 1,4-dioxane, buffered at pH 7.0, and at a constant ionic strength of I = 0.1 mol dm^{-3} (NEt_4ClO_4). Measurements of the absorption spectra (over the range 300-500 nm) were recorded on each solution, and the molar absorbance values determined.

Alternatively, solutions of each of the receptors (10 cm^3) (10^{-4} mol dm^{-3} concentrations) in 20% aqueous 1,4-dioxane, buffered at pH 7.0, and at a constant

ionic strength of I = 0.1 mol dm^{-3} (NEt_4ClO_4), were titrated with aliquots (initially of 0.1 cm^3) of a 10^{-3} mol dm^{-3} solution of the guest species, following the method of Fabbrizzi.[283] Measurements of the absorption spectra (over the range 300-500 nm) of the solutions after each addition (i.e. at 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.2, 1.5, 2, 3, 4, 5, and 10 equivalents of guest) were recorded. The dilution effects are overcome by the comparison of the molar absorbance values, rather than simply considering the absorption spectra.

Investigation found that the molar absorbance values determined by either method were identical (within experimental error).

From the molar absorbance data the inclusion complex stability constants of complexes **4-7** with various guests were also determined as described in Appendix A.

6.5. Fluorescence Spectroscopy

Fluorescence emission spectra were recorded on a Varian Cary Eclipse Fluorescence spectrophotometer, using quartz cells (1.0 cm path length) over a wavelength range of 370-550 nm at 0.15 nm intervals, with a scan rate of 40 nm/min. Both the excitation and emission monochromator slit widths were set at 5 nm, and due to the highly fluorescent nature of these compounds, a 1.5 absorbance attenuator was used for the 10^{-3} and 10^{-4} mol dm^{-3} solutions, while the 10^{-6} mol dm^{-3} solutions required no attenuation. Baseline correction measurements were used for all spectra; solutions containing the solvent, supporting electrolyte and buffer (where applicable) were used. All solutions were equilibrated at 25°C for all measurements. When the concentrations of the compounds investigated were the same for that used for the

UV-visible absorbance measurements, the same solutions were used, and the experiments run concurrently (see **Section 6.4.**). Excitation wavelengths were determined from the absorption spectra, with an excitation wavelength of 350 nm used for solutions in 20% aqueous 1,4-dioxane. This maximised the emission intensity at 416 ± 2 nm. These excitation wavelengths coincide with isosbestic points as seen in the studies of the ligands against varying pH, near the maximum of the third longest wavelength absorbance band for all complexes. All solvents were purged with N_2 prior to dissolution of the solute, and all solutions were subsequently purged for another 2 minutes prior to all titration experiments.

6.5.1 pH titrations.

To observe the influence of pH on the fluorescence properties of the ligands **131**, **146** and **170-173**, a series of titration experiments was conducted, in which the molar fluorescence emission values of the ligands at different pH values were investigated. Solutions of each of the protonated (with 0.005 mol dm^{-3} $HClO_4$) ligands (at 10^{-6} mol dm^{-3}) ligands in 20% aqueous 1,4-dioxane, at a constant ionic strength of I = 0.1 mol dm^{-3} (NEt_4ClO_4), were treated with aliquots of a 0.1 mol dm^{-3} solution tetraethylammonium hydroxide, with the measurement of the fluorescence spectra (over the range 370-550 nm) at the different resulting pH values, which ranged from *ca* 2 to 14, as indicated by use of a combination glass electrode calibrated against aqueous buffer solutions. The dilution effects are overcome by the comparison of the molar fluorescence values, rather than simply considering the emission spectra.

6.5.2. Metal complexation fluorescence studies.

The influence of metal complexation on the fluorescence properties of the ligands, **146** and **170-173**, was investigated by a series of titration experiments, in which the change of the molar fluorescence emission values of the ligands, upon addition of the metal ions, were investigated, following the method of Kimura.[151] Solutions of each of the ligands (at 10^{-4} mol dm^{-3}) buffered at pH 7.0 (HEPES) in 20% aqueous 1,4-dioxane, at a constant ionic strength of I = 0.1 mol dm^{-3} (NEt_4ClO_4), were treated with aliquots (initially 0.1 cm^3) of a 10^{-3} mol dm^{-3} metal(II) perchlorate solution. The measurement of the fluorescence emission spectra (over the range 370-550 nm) after each addition was recorded. The dilution effects are overcome by the comparison of the molar fluorescence values, rather than simply considering the emission spectra.

The molar fluorescence values determined through the titration of the ligand **146** with 1 equivalent of cadmium(II) perchlorate solution, was identical (within experimental error) to the molar fluorescence (I_o) of the reference solution of the corresponding cadmium(II) complex, **4**.

6.5.3. Host-guest binding constant determinations from fluorescence.

To observe the influence of guest inclusion on the fluorescence properties of the receptor complexes **4-7**, a series of titration experiments was conducted, in which the change of the molar fluorescence emission values of the receptors were monitored at increasing concentrations of the guest, following the method of Fabbrizzi.[283,284] Solutions of each of the receptors (10 cm^3) (at 10^{-4} or 10^{-6} mol dm^{-3}

concentrations) in 20% aqueous 1,4-dioxane, buffered at pH 7.0, and at a constant ionic strength of I = 0.1 mol dm^{-3} (NEt_4ClO_4), were treated with by the addition of aliquots (initially of 0.1 cm^3) of a 10^{-3} or 10^{-5} mol dm^{-3}, respectively, solution of the guest species. Measurements of the fluorescence spectra (over the range 370-550 nm) of the solutions after each addition (i.e. at 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.2, 1.5, 2, 3, 4, 5, and 10 equivalents of guest) were recorded. The dilution effects were overcome by the comparison of the molar fluorescence values, rather than simply considering the emission spectra.

From the molar fluorescence data the inclusion complex stability constants of complexes **4**-**7** with various guests were also determined with fluorescence measurements following the procedure described in Appendix A.

6.6. Determinations of relative quantum yields.

The use of the optically dilute method[285] was employed for the determination of the quantum yields (Φ_F). Equation **6.1** relates the quantum yield of an unknown to that of a reference standard.

$$\Phi_x = \Phi_r \bullet A_r/A_x \bullet F_x/F_r \bullet (n_x)^2/(n_r)^2 \qquad (\mathbf{6.1})$$

where x refers to the unknown
r refers to the reference
Φ is the quantum yield
A is the absorbance of the solution at the excitation wavelength
F is the integrated area under the emission spectrum
n is the refractive index of the solvent

The reference standard used was quinine sulfate (10^{-6} mol dm^{-3}, Φ_r = 0.55 in 0.1 N (0.05 mol dm^{-3}) sulfuric acid).[286,287] Analytical reagent grade quinine sulfate was dried to constant weight before being used to prepare the standard solutions.

The refractive indices used were, n = 1.422 for 1,4-dioxane,[288] n = 1.354 for 20% aqueous 1,4-dioxane,[289] n = 1.333 for water.[288]

UV-visible absorbance spectra and fluorescence emission spectra of the standard were recorded as described in the above sections. The excitation wavelength for quinine sulfate was matched to that used for the unknown (350 nm) to ensure that the intensity of the exciting light was identical for both reference and unknown. Care must be taken when selecting the excitation wavelength, as the relative quantum yield of quinine sulfate changes with excitation wavelength, as shown in **Table 6.1**, and this must be taken into account.[265]

Computerised integration was used to calculate the area under each emission spectra curve, between 370 and 550 nm. Errors in quantum yield values obtained are approximately 10%.[285]

Table 6.1 Change of Φ of Quinine with excitation wavelength

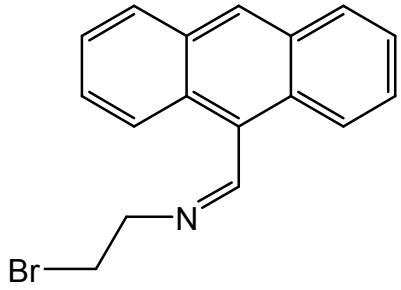
λ_{ex}/nm)	Relative Φ
250	1.02
313	1.00
345	0.98
348	0.99
350*	1.00*
366	1.09
380	1.2
390	1.23

Table modified from that in Chen[290]. Measurements in 0.1 N (0.05 mol dm^{-3}) H_2SO_4 at 25°C. Quantum yield at 313 nm (Φ = 0.55) taken as 1.00. *This work.

6.7. Synthesis of Compounds

6.7.1. Synthesis of pendant arms.

9-(2-bromoethyliminomethyl)anthracene, (149).

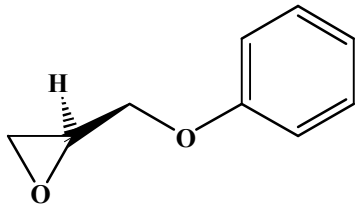


149

The title compound was prepared using a modification of the published method of Fabbrizzi and co-workers.[108] 2-bromoethylamine hydrobromide (5.96 g, 29.0 mmol) was dissolved in 1.0 mol dm^{-3} NaOH (30 cm^3) and extracted into CH_2Cl_2 (5 x 30 cm^3). The organic extracts were combined, and the volume reduced to *ca* 30 cm^3. This concentrated solution was then added dropwise to a stirred solution of 9-anthraldehyde (5.00 g, 24.0 mmol) in CH_2Cl_2 (30 cm^3) at RT. The mixture was stirred over molecular sieves (3.00 g) for 1 h, after which time additional 2-bromoethylamine hydrobromide (5.13 g, 25 mmol) and NaOH (1.01 g, 25.0 mmol) were added. The reaction mixture was stirred overnight at a gentle reflux, after which time the reaction was cooled to RT, filtered, and the solvent reduced to dryness. The residue was recrystallised from ether/hexane (1:1) (140 cm^3) to yield the pure product, as crystalline yellow needles (5.40 g, 72%), mp 84-86°C, after drying it under N_2. (Found: C, 65.65; H, 4.48; N, 4.52. Calc. for $C_{17}H_{14}BrN$: C, 65.40; H, 4.52; N, 4.49%); ν_{max}/cm^{-1}: 1635 (C=N), 1560, 1450, 885, 745 cm^{-1} (KBr); λ_{max}/nm (CH_3CN/H_2O, 4:1): 383.8 nm ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 8 951), 364.7 (9 301), 348.0

(6 318), 333.4 (sh), 253.9 (156 460), 222.0 (10 098); $\delta_H(CDCl_3)$ 9.45 (1 H, br s, -C*H*=N-), 8.59-8.55 (2 H, m, Anth*H*), 8.52 (1 H, s, Anth*H*), 8.06-8.01 (2 H, m, Anth*H*), 7.6-7.4 (4 H, m, Anth*H*), 4.37 (2 H, dt, *J* 5.55, 1.4 Hz, -CH_2-N=), 3.92 (2 H, t, *J* 5.55 Hz, -CH_2Br); $\delta_C(CDCl_3)$ 163.0 (1 C, -C=N-, APT↓), 131.3 (2 C, Anth, APT↑ *ipso*), 130.0 (2 C, Anth, APT↑ *ipso*), 129.7 (1 C, Anth, APT↓), 128.9 (2 C, Anth, APT↓), 127.8 (1 C, Anth, APT↑ *ipso*), 126.8 (2 C, Anth, APT↓), 125.3 (2 C, Anth, APT↓), 124.9 (2 C, Anth, APT↓), 63.9 (1 C, -C=N-*C*H_2-, APT↑), 33.1 (1 C, -*C*H_2-Br, APT↑).

(2*S*)-(+)-3-Phenoxy-1,2-epoxypropane, (160).



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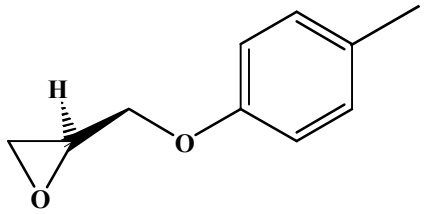
The procedure described by Smith[114] was followed. To a stirred suspension of oil-free sodium hydride (1.00 g, 21.4 mmol) in dry DMF (15 cm^3) a solution of phenol (1.61 g, 17.1 mmol) dissolved in dry DMF (10 cm^3) was added dropwise and stirred for 1 h at RT. A solution of (2*S*)-(+)-glycidyl tosylate (3.39 g, 13.9 mmol) dissolved in dry DMF (12 cm^3) was then added and the reaction was stirred for 1 h and as the reaction mixture thickened dry DMF (10 cm^3) was added. The reaction was then stirred for 18 h after which it was quenched with saturated NH_4Cl, (10 cm^3), diluted with water (150 cm^3) and extracted into ether (5 x 150 cm^3). Combined ether extracts were washed with ice-cold NaOH (0.1 M, 4 x 100 cm^3), distilled water (200 cm^3), brine (100 cm^3), then dried over Na_2SO_4, filtered through a layer (1 cm)

of celite and concentrated under vacuum to yield a pale yellow oil. Purification by flash chromatography (TLC on silica, R_f = 0.39, silica gel, CH_2Cl_2/Hexane 9:1) yielded **160** as a colourless oil (1.55 g 74%), $[\alpha]_D^{298}$ = +11.3 (c 2.57, CH_3OH); $\delta_H(CDCl_3)$ 7.34-7.24, (2 H, m, Ph*H*); 7.00-6.90, (3 H, m, Ph*H*); 4.22 (1 H, dd, *J* 2.9, 11 Hz, -*H*CH-); 3.96, (1H, dd, *J* 5.2, 11 Hz, -HC*H*-); 3.29, (1 H, m, CH(O)); 2.91, (1 H, t, *J* 4.2 Hz, -HC*H*(O)); 2.76, (1 H, dd, *J* 2.9, 5.2 Hz, -*H*CH(O)); $\delta_c(CDCl_3)$ 159.4 (1 C, Ph, *ipso*), 129.8 (2 C, Ph), 121.5 (1 C, Ph), 114.8 (2 C, Ph), 68.9 (1 C, -*C*H_2-), 50.4 (1 C, -*C*H(O)-), 45.0 (1 C, -*C*H_2(O)-).

(2*S*)-(+)-3-[4'-(methyl)phenoxy]-1,2-epoxy propane, (161).



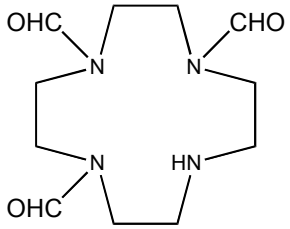
161

p-Cresol (1.62 g, 15.0 mmol) in dry DMF (10 cm^3) was added dropwise over 10 min to a stirring oil-free suspension of sodium hydride (0.360 g, 15.0 mmol) in dry DMF (10 cm^3) at RT. The solution was kept stirring for 1 h, then followed by the addition of (2*S*)-(+) glycidyl tosylate (3.42 g, 15.0 mmol) also in dry DMF (10 cm^3) within 15 min. The reaction mixture was stirred for 24 h. The completion of the reaction was monitored using TLC and indicated by the absence of the glycidyl tosylate. At the end of the reaction, the DMF was evaporated, and water (25 cm^3) was added to dissolve the sodium tosylate. The product was isolated as pale yellow oil by diethyl ether extraction (4 x 50 cm^3). To purify the oil, it was passed through a silica column (60 g, 15 cm) to afford colourless oil, **161** (1.68 g, 70%), $[\alpha]_{589}^{298}$ =

+2.24 (*c* 1.9, $CHCl_3$); $\delta_H(CDCl_3)$ 7.10, (2 H, dd, J=8.8, 0.6 Hz, Ph*H*), 6.83, (2 H, dt, J=2.8, 8.8Hz, Ph*H*), 4.22 (1 H, dd, *J* 3.2, 11.1 Hz, -(O)*H*CH-), 3.93, (1 H, dd, 5.6, 11.1 Hz, -(O)HC*H*-), 3.34-3.37 (1 H, m, CH_2-C*H*(O)-CH_2), 2.90 (1 H, dd, *J* 4.1, 4.9 Hz, CH-HC*H*(O)), 2.76 (1 H, dd, *J* 2.8, 4.9 Hz, CH-*H*CH(O)), 2.30 (3 H, s, -CH_3); $\delta_C(CDCl_3)$ 156.4 (1 C, Ph, *ipso*), 130.4 (1 C, Ph, *ipso*), 129.9 (2 C, Ph), 114.5 (2 C, Ph), 68.8 (1 C, -CH_2-), 50.1 (1 C, -CH-), 44.6 (1 C, -CH-), 20.4 (1 C, -*C*H_3).

6.7.2. Protection and deprotection steps.

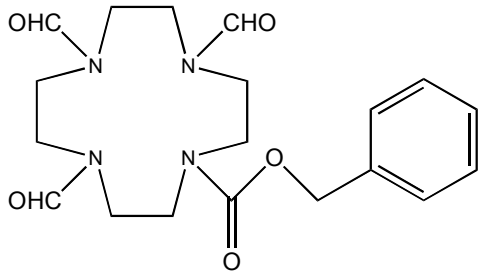
1,4,7-Triformyl-1,4,7,10-tetraazacyclododecane, (151).



151

Using a procedure originally devised by Boldrini[225] and modified by Yoo,[202] chloral hydrate (3.84 g, 23.0 mmol) was added to a stirred solution of cyclen (1.00 g, 5.8 mmol) dissolved in anhydrous ethanol (30 cm^3). The mixture was stirred at 60°C for 4 h under nitrogen and concentrated *in vacuo* to dryness to yield the product, **151**, as a yellow oil (1.46 g, quantitative), $\delta_H(CDCl_3)$ 8.3-7.8 (3 H, br), 3.90-2.65 (17 H, br); $\delta_C(CDCl_3)$ 164.4-162.2 (3 C, -H*C*=O), 53.1-40.0 (8 C, cyclen*C*H_2).

1,4,7-Triformyl-10-(Benzyloxycarbonyl)-1,4,7,10-tetraazacyclododecane, (153).

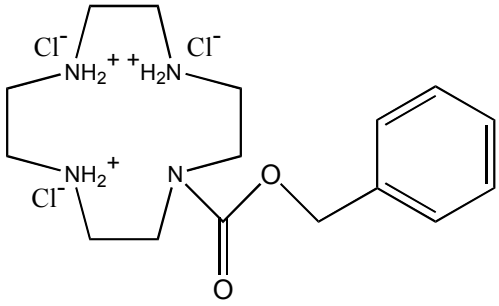


153

The synthesis of **153** was accomplished by employing a method described by Yoo.[202] Deionized water (30 cm^3) was added to the flask containing **151** (0.682 g, 2.7 mmol, natural pH 9) and upon complete dissolution, benzyl chloroformate, **152**, (0.710 g, 4.2 mmol) was added and the mixture was stirred for 1 h. After this time the pH was adjusted from 4 to 10 with saturated Na_2CO_3 solution and further benzyl chloroformate (0.710 g, 4.2 mmol) added. The solution was stirred for 1 h and the pH adjusted from 6 to 10 (saturated Na_2CO_3 solution) and benzyl chloroformate (0.710 g, 4.2 mmol) again added to the mixture, which was then stirred overnight under nitrogen. The product was extracted with dichloromethane (5 x 20 cm^3). The combined organic layers were then washed with saturated $NaHCO_3$ (10 cm^3), dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo* to give **153** as a yellow oil: (0.583 g, 55%) which could be used in the triformyl deprotection step without further purification. Purification of **153**, for the purposes of further analysis, was accomplished by a procedure devised by Yoo.[202] Diethyl ether (5 cm^3) was used to dissolve **153** (0.200 g, 0.5 mmol), which was then refrigerated overnight to give a thick oil. The ether was then decanted and the thick oil was dissolved in ethyl acetate (1 cm^3) and excess diethyl ether was added to precipitate the product. The solvent was then decanted and ether (0.5 cm^3) was added. The white oily substance was then triturated until resinous and then dried for 72 h under vacuum to give a hygroscopic white solid, **153** (0.180 g, 90%), $\delta_H(CDCl_3)$ 7.95-8.01 (3 H, m, *H*C=O), 7.28 (5 H, br

s, Bn), 5.05 (2 H, s, BnCH_2-), 3.0-3.6 (16 H, m, cyclenCH_2); δ_C($CDCl_3$) 166.3 (1 C, C=O), 165.5 (1 C, C=O), 164.8 (1 C, C=O), 164.3 (1 C, C=O), 163.8 (1 C, Bn), 157.8 (1 C, Bn), 136.1 (2 C, Bn), 129.0-128.3 (2 C, Bn), 68.0-67.9 (1 C, Bn$C$$H_2$-) 52.7-43.4 (8 C, cyclen$C$$H_2$).

1-(Benzyloxycarbonyl)-1,4,7,10-tetraazacyclododecane.3HCl.H_2O, (154).

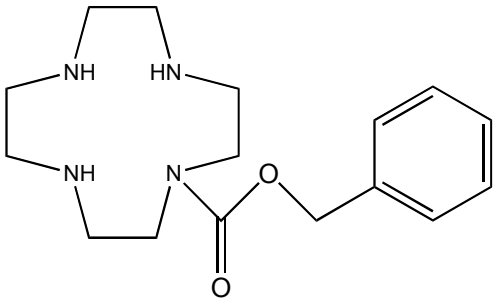


154

The named product was prepared according to the method described by Yoo.[202] A solution of **153** (0.504 g, 1.3 mmol) was dissolved in 1 M HCl (35 cm^3) and stirred at 50˚C for 5 h after which the solvent was removed *in vacuo* at 60˚C to yield a white solid. The crude product was then refluxed in ethanol (20 cm^3) for 1 h and allowed to cool to RT. The solid was filtered off, and washed with diethyl ether (5 cm^3) and then dried in air to yield the 1st crop of the pure product, **154** (64.0 mg, 12%). To the ethanol filtrate, excess ether, assessed by cloudiness of the solution, was added and the white precipitate was collected by filtration, washed with diethyl ether (5 cm^3), and dried in air: yield 2nd crop of **154** (0.450 g, 84%), (Found: C, 44.13; H, 7.41; N, 12.80. $C_{16}H_{31}Cl_3N_4O_3$ requires: C, 44.30; H, 7.20; N, 12.92%); δ_H(D_2O) 7.43 (5 H, br s, Bn), 5.17 (2 H, s, -BnCH_2-), 3.69 (4 H, br t, J 5.2 Hz, cyclenCH_2), 3.19 (12 H, br s, cyclenCH_2); δ_C(D_2O, 1,4-Dioxane) 159.0 (1 C, C=O), 136.3 (1 C, Bn), 129.5 (1 C, Bn), 129.4 (2 C, Bn), 129.0 (2 C, Bn), 69.2 (1 C,

Bn*C*H$_2$), 47.0 (2 C, cyclen*C*H$_2$), 45.8 (2 C, cyclen*C*H$_2$), 44.6 (2 C, cyclen*C*H$_2$), 43.4 (2 C, cyclen*C*H$_2$).

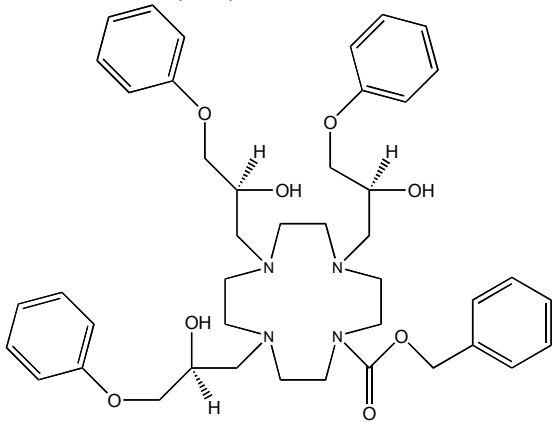
1-(Benzyloxycarbonyl)-1,4,7,10-tetraazacyclododecane, (155).



155

To a stirred solution of **154** (0.514 g, 1.2 mmol) in water (5 cm^3), chilled NaOH (5 M 10 cm^3) was added dropwise until a pH of 13 was attained. The solution was then stirred for 1 h at RT, extracted with $CHCl_3$ (4 x 10 cm^3) and the combined organic extracts were washed with chilled NaOH (1.25 M, 10 cm^3), $NaHCO_3$ (5 cm^3), and brine (5 cm^3), dried over Na_2SO_4, gravity filtered, and concentrated *in vacuo* to give the free amine **155** (0.350 g, 92%), $\delta_H(CDCl_3)$ 7.35 (5H, br s, Bn), 5.15 (2H, s, -C*H*$_2$-Bn), 3.63 (4H, br s, cyclenC*H*$_2$), 3.6-3.5 (3 H, br m, -N*H*-), 3.2-2.7 (12 H, br m, cyclenC*H*$_2$); $\delta_C(CDCl_3)$ 156.3 (1 C, C=O), 136.2 (1 C, Bn), 128.6 (1 C, Bn), 128.2 (2 C, Bn), 128.0 (2 C, Bn), 67.4 (1 C, Bn*C*H$_2$-), 50.3 (2 C, cyclen*C*H$_2$), 48.7 (2 C, cyclen*C*H$_2$), 47.6 (2 C, cyclen*C*H$_2$), 46.6 (2 C, cyclen*C*H$_2$).

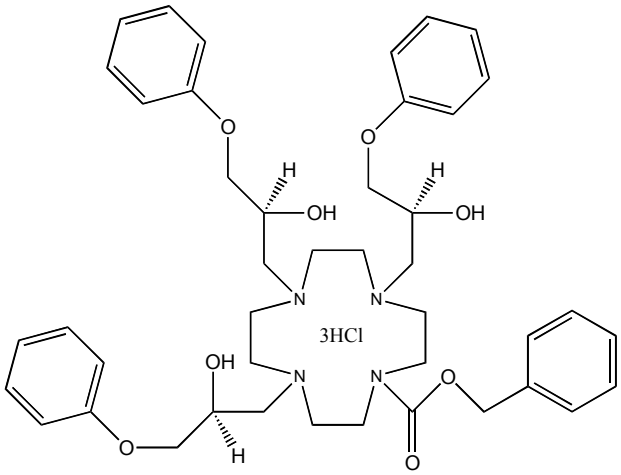
1-(Benzyloxycarbonyl)-4,7,10-tris((2*S*)-(-)-2-hydroxy-3-phenoxypropyl)-1,4,7,10-tetraazacyclododecane, (163).



163

Utilising a procedure outlined by Smith[114] a solution of (2*S*)-(+)-3-phenoxy-1,2-epoxypropane, **160**, (0.623 g, 4.2 mmol) was added to a refluxing solution of **155** (0.424 g, 1.4 mmol) in dry ethanol (10 cm^3). The reaction was monitored by TLC on silica, CH_2Cl_2/hexane 9:1) and upon complete disappearance of the epoxide after 5 d, the solvent was evaporated under vacuum to give a viscous yellow oil, **163** (1.00 g, quantitative), $[\alpha]_{589}^{298}$ = -57.5 (c 0.02, $CHCl_3$); δ_H($CDCl_3$) 7.29 (10 H, br m, Ar*H*), 6.94 (10 H, br m, Ar*H*), 5.13 (2 H, br s, -C*H*$_2$Bn), 4.3-2.0 (34 H, br m, -O*H*, -C*H*$_2$-); δ_C($CDCl_3$) 158.6 (3 C, Ph, *ipso*), 156.2 (1 C, C=O), 136.6 (1 C, Bn, *ipso*), 129.3 (6 C, Ph), 128.5 (1 C, Bn), 128.4 (2 C, Bn), 127.9 (2 C, Bn), 120.7 (3 C, Ph), 114.4 (6 C, Ph), 69.7 (2 C, O*C*H_2), 69.6 (1 C, O*C*H_2), 67.0 (1 C, -*C*H_2Bn), 66.0 (2 C, methine), 65.3 (1 C, methine), 59.5 (2 C, exo-*C*H_2N), 58.0 (1 C, exo-*C*H_2N), 55.1 (2 C, cyclen*C*H_2), 52.8 (2 C, cyclen*C*H_2), 49.8 (2 C, cyclen*C*H_2), 47.6 (2 C, cyclen*C*H_2).

1-(Benzyloxycarbonyl)-4,7,10-tris ((2*S*)-2-hydroxy-3-phenoxypropyl)-1,4,7,10-tetraazacyclododecane.3HCl.H_2O, (182).

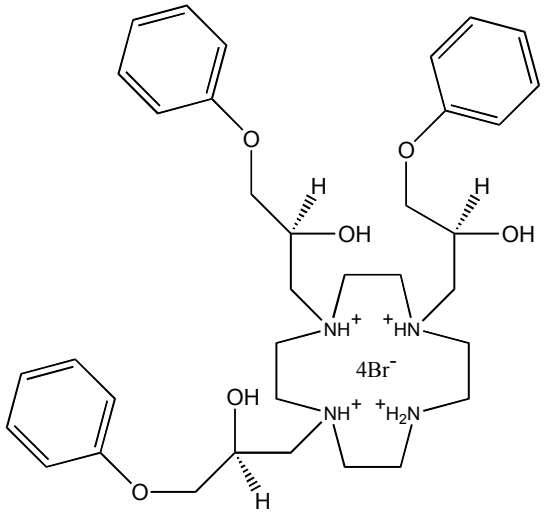


182

A stirred, ice-cold, solution of **163** (0.525 g, 0.7 mmol) dissolved in ethanol (10 cm^3) was treated with aqueous HCl (32 % w/v, 20 cm^3) and allowed to continue stirring for 1 h upon which a white precipitate formed. Precipitate was filtered, washed with ether (5 cm^3), cold ethanol (5 cm^3) and dried in air to give a white powder, **182** (0.604 g, 97 %), (Found: C, 58.53; H, 7.10; N, 6.37. $C_{43}H_{61}Cl_3N_4O_9$ requires: C, 58.40; H, 6.95; N, 6.34%); δ_H(DMSO-d_6) 7.37 (10 H, br m, Ar*H*); 7.07 (10 H, br m, Ar*H*); 5.13 (2 H, br s, -CH_2Bn); 4.3-2.6 (37 H, br m, -CH_2-, -O*H* & -N*H*); δ_C (CD_3OD) 159.9 (1 C, C=O), 159.7 (3 C, Ph, *ipso*), 136.7 (1 C, Bn, *ipso*), 130.5 (6 C, Ph), 129.9 (1 C, Bn), 129.7 (4 C, Bn), 122.3 (2 C, Ph), 122.2 (1 C, Ph), 115.7 (6 C, Ph), 70.9 (3 C, OCH_2), 70.0 (1 C, CH_2Bn), 67.9 (1 C, methine), 66.0 (2 C, methine), 58.3 (1 C, exo-CH_2N), 57.6 (2 C, exo-CH_2N), 53.8 (2 C, cyclenCH_2), 52.3 (2 C, cyclenCH_2), 50.7 (2 C, cyclenCH_2), 46.2 (2 C, cyclenCH_2).

Removal of the benzyloxycarbonyl protecting group was achieved by either acid hydrolysis or by catalytic transfer hydrogenation.

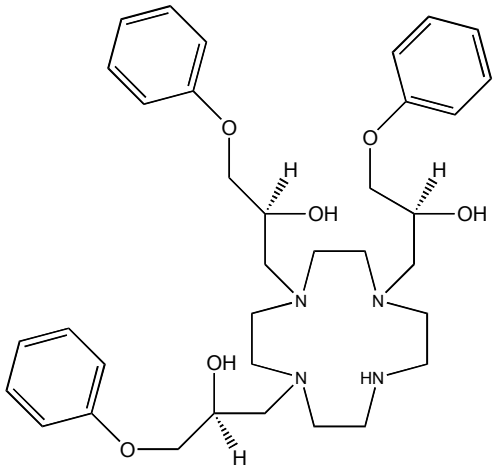
1,4,7, tris ((2*S*)-2-hydroxy-3-phenoxypropyl)-1,4,7,10-tetraazacyclodo-decane .4HBr, (166).



166

Hydrogen bromide (45 % in acetic acid, 0.700 g, 5.5 mmol) was added to a solution of **163** (0.427 g, 0.6 mmol) dissolved in acetic acid (10 cm^3) and stirred at RT for 5 h. The solution was then diluted with anhydrous diethyl ether until the hydrobromide precipitated. The suspension was then stirred for a further 3 h, filtered by vacuum and, triturated with methanol-ether (1:1) to give an off-white solid, **166** (0.175 g, 41%), (Found: C, 44.23; H, 5.93; N, 5.67. $C_{35}H_{54}Br_4N_4O_6$ requires: 44.42; H, 5.75; N, 5.92%); δ_H(CD_3OD) 7.27 (6 H, br m, Ph*H*), 6.92 (9 H, br m, Ph*H*), 4.8-2.0 (39 H, br m, -C*H*$_2$- , N*H* & -O*H*); δ_C(CD_3OD) 159.9 (2 C, Ph, *ipso*), 159.6 (1 C, Ph, *ipso*), 130.6 (4 C, Ph), 130.5 (2 C, Ph), 122.3 (1 C, Ph), 122.1 (2 C, Ph), 115.7 (6 C, Ph), 71.1 (1 C, O*C*H$_2$), 70.8 (1 C, O*C*H$_2$), 70.6 (1 C, O*C*H$_2$), 68.0 (1 C, methine), 67.8 (1 C, methine), 67.3 (1 C, methine), 64.9 (1 C, exo-*C*H$_2$N), 58.1, (1 C, exo-*C*H$_2$N), 57.6 (1 C, exo-*C*H$_2$N), 55.5 (2 C, cyclen*C*H$_2$), 53.4 (2 C, cyclen*C*H$_2$), 51.9 (2 C, cyclen*C*H$_2$), 43.8 (2 C, cyclen*C*H$_2$).

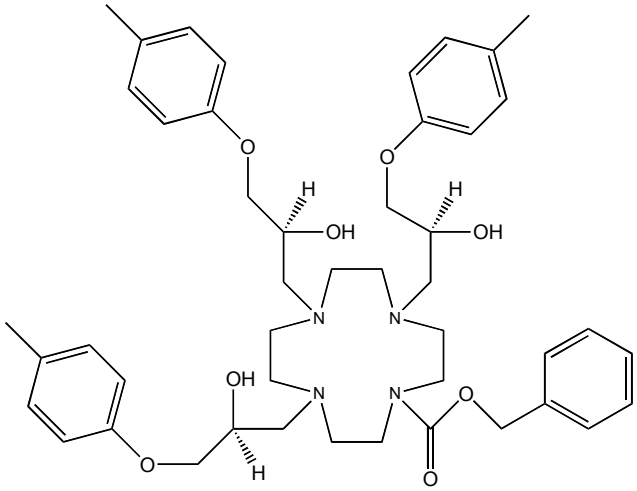
1,4,7, tris ((*S*)-(-)-2-hydroxy-3-phenoxypropyl)-1,4,7,10-tetraazacyclododecane, (168).



168

Cyclohexene (0.300 g, 3.7 mmol) was added to a solution of **163** (0.523 g, 0.7 mmol) dissolved in absolute ethanol (10 cm^3). The solution was stirred and then 10% Pd/C catalyst (500 mg) was added. The reaction mixture was refluxed at 80˚C for 5 h, filtered through a small celite column and the filter cake washed with absolute ethanol (5 cm^3). The filtrate was concentrated *in vacuo* to give deprotected **168** as a brown oil (0.507 g, 97%), $[\alpha]_{589}^{298}$ = -23.96 (c 0.04, CH_3OH); $\delta_H(CDCl_3)$ 7.27 (6 H, m, Ar*H*); 6.92 (9 H, m, Ar*H*); 4.8– 2.0 (35 H, br m, -CH_2-, N*H* & -O*H*); $\delta_C(CDCl_3)$ 158.6 (2 C, Ph, *ipso*), 158.6 (1 C, Ph, *ipso*), 129.3 (2 C, Ph), 129.2 (4 C, Ph), 120.7 (1 C, Ph), 120.6 (2 C, Ph), 114.5 (4 C, Ph),114.4 (2 C, Ph), 69.9 (2 C, O*C*H_2), 69.3 (1 C, O*C*H_2), 66.4 (1 C, methine), 65.5 (2 C, methine), 60.2 (3 C, exo-*C*H_2N), 51.4 (4 C, cyclen*C*H_2), 44.4 (4 C, cyclen*C*H_2).

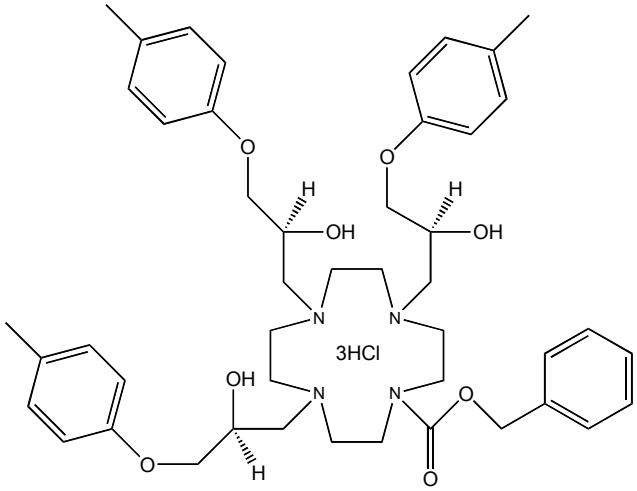
1-(Benzyloxycarbonyl)-4,7,10-tris((2*S*)-(-)-2-hydroxy-3-[4'-(methyl)phenoxy] propyl)-1,4,7,10-tetraazacyclododecane, (164).



164

A solution of **161** (2.05 g, 12.5 mmol) in dry EtOH (30 cm^3) was added to a refluxing solution of **155** (1.28 g, 4.2 mmol) in dry ethanol (30 cm^3), and was refluxed for 10 days. The reaction was monitored by TLC on silica, CH_2Cl_2/hexane 9:1) and upon complete disappearance of the starting material the reaction was cooled to RT and the solvent was evaporated off under vacuum to give the product, **164**, as a viscous yellow oil (3.33 g, quantitative), $[\alpha]_{589}^{298}$ = -18.02 (c 0.02, CH_3OH); $\delta_H(CDCl_3)$ 7.37 (5 H, m, Bn), 7.09 (6 H, m, Ar), 6.86 (6 H, m, Ar), 5.32 (2 H, s, -C*H*$_2$Bn), 5.12 (3 H, br s, -O*H*), 4.6-2.2 (31 H, br m, -C*H*$_2$-), 2.26 (9 H, s, -C*H*$_3$); $\delta_C(CDCl_3)$ 156.9 (2 C, Ar, *ipso*), 156.6 (1 C, Ar, *ipso*), 155.9 (1 C, *C*=O), 136.4 (1 C, Bn, *ipso*), 131.7 (3 C, Ar), 131.6 (6 C, Ar), 128.8 (2 C, Bn), 128.2 (3 C, Bn), 115.6 (6 C, Ar), 70.1 (1 C, O*C*H$_2$), 69.6 (2 C, O*C*H$_2$), 67.0 (1 C, Bn*C*H$_2$-), 66.2 (1 C, methine), 65.9 (2 C, methine), 60.9 (1 C, exo-*C*H$_2$N), 59.9 (1 C, exo-*C*H$_2$N), 58.1 (1 C, exo-*C*H$_2$N), 53.8 (2 C, cyclen*C*H$_2$), 51.3 (2 C, cyclen*C*H$_2$), 48.0 (2 C, cyclen*C*H$_2$), 46.0 (2 C, cyclen*C*H$_2$), 20.5 (3 C, -*C*H$_3$).

1-(Benzyloxycarbonyl)-4,7,10-tris((2*S*)-(-)-2-hydroxy-3-[4'-(methyl)phenoxy] propyl)-1,4,7,10-tetraazacyclododecane.3HCl, (183).

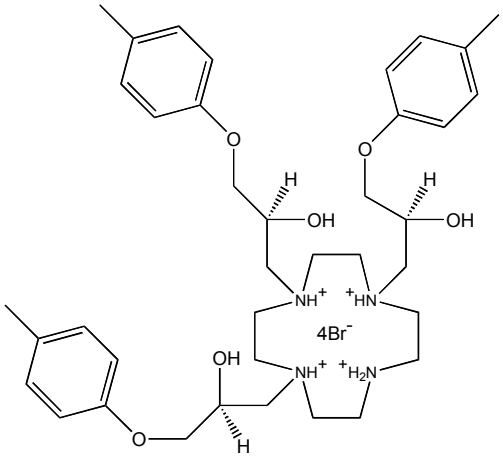


183

A stirred, ice-cold, solution of **164** (0.189 g, 0.2 mmol) dissolved in ethanol (4 cm^3) was treated with aqueous 32% HCl (7.2 cm^3) and allowed to continue stirring overnight. Upon addition of the acid a white precipitate formed. The precipitate was filtered off, washed with ether (5 cm^3), cold ethanol (5 cm^3) and dried in air to give a white powder, **183** (0.098 g, 45%), (Found: C, 60.66; H, 7.21; N, 5.99. $C_{46}H_{65}Cl_3N_4O_8$ requires: C, 60.82; H, 7.14; N, 6.17%); $\delta_H(CD_3OD)$ 7.26 (5 H, br d, Bn), 7.05 (6 H, br m, Ar*H*), 6.84 (6 H, m, Ar*H*), 5.20 (2 H, CH_2Bn), 4.6-2.4 (37 H, br m, -C*H*, -O*H*, N*H*, -CH_2-), 2.29 (9 H, s, -CH_3); $\delta_C(CD_3OD)$ 159.1 (1 C, *C*=O), 157.9 (2 C, Ar, *ipso*), 157.7 (1 C, Ar, *ipso*), 136.9 (1 C, Bn, *ipso*), 131.8 (2 C, Ar), 131.6 (1 C, Ar), 131.0 (2 C, Ar), 130.9 (4 C, Ar), 129.9 (1 C, Bn), 129.8 (2 C, Bn), 129.7 (2 C, Bn), 115.6 (6 C, Ar), 71.0 (2 C, ArO-*C*H_2-), 70.1 (1 C, ArO-*C*H_2-), 68.2 (1 C, -*C*H_2Bn), 66.0 (2 C, methine), 64.5 (1 C, methine), 57.5 (2 C, exo-*C*H_2N), 57.2 (1 C, exo-*C*H_2N), 56.0 (1 C, cyclen*C*H_2), 54.4 (1 C, cyclen*C*H_2), 54.1 (1 C, cyclen*C*H_2), 53.6 (1 C, cyclen*C*H_2), 52.6 (1 C, cyclen*C*H_2), 51.3 (1 C, cyclen*C*H_2), 46.3 (1 C, cyclen*C*H_2), 45.1 (1 C, cyclen*C*H_2), 20.5 (3 C, -*C*H_3).

Removal of the benzyloxycarbonyl protecting group was achieved firstly by acid hydrolysis and then by catalytic transfer hydrogenation.

1,4,7, tris ((2*S*)-2-hydroxy-3-[4'-(methyl)phenoxy]propyl)-1,4,7,10-tetraazacyclo-dodecane.4HBr.2EtOH, (167).

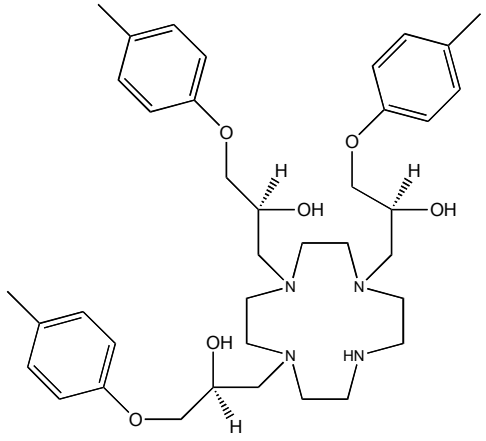


167

Hydrogen bromide (45% in acetic acid, 1.54 g, 1.3 cm^3) was added to a solution of **164** (1.00 g, 1.3 mmol) dissolved in acetic acid (22 cm^3) and stirred at RT overnight. The solution was then diluted with anhydrous diethyl ether until the hydrobromide precipitated. The suspension was then stirred for a further 3 h, filtered by vacuum and, triturated with ethanol-ether (1:1) to give an off-white solid, **167** (yield 0.790 g, 66%), (Found: C, 46.46; H, 6.43; N, 5.05. $C_{42}H_{72}Br_4N_4O_8$ requires: C, 46.68; H, 6.72; N, 5.18%); δ_H(DMSO-d_6) 7.30 (2 H, br s, Ar*H*), 7.08 (5 H, br m, Ar*H*), 6.86 (5 H, br m, Ar*H*), 5.2-2.6 (51 H, br m, -O*H*, -C*H*-, -N*H*-, -CH_2- & CH_2O*H* of EtOH), 2.22 (9 H, s, -CH_3), 1.08 (6 H, CH_3 of EtOH); δ_C(CD_3OD): δ 157.9 (2 C, Ar, *ipso*), 157.7 (1 C, Ar, *ipso*), 131.8 (2 C, Ar), 131.7 (1 C, Ar), 131.0 (4 C, Ar), 130.9 (2 C, Ar), 115.6 (6 C, Ar), 71.1 (1 C, O*C*H_2), 70.1 (2 C, O*C*H_2), 66.1 (2 C, methine), 64.5 (1 C, methine), 58.3 (2 C, *C*H_2 of EtOH), 57.5 (2 C, exo-*C*H_2N), 57.2 (1 C, exo-*C*H_2N), 56.0 (1 C, cyclen*C*H_2), 55.0 (1 C, cyclen*C*H_2), 54.1 (1 C,

cyclenCH_2), 53.6 (1 C, cyclenCH_2), 52.6 (1 C, cyclenCH_2), 51.0 (1 C, cyclenCH_2), 46.3 (1 C, cyclenCH_2), 45.1 (1 C, cyclenCH_2), 20.5 (3 C, -CH_3), 18.4 (2 C, CH_3 of EtOH).

1,4,7, tris ((2*S*)-(-)-2-hydroxy-3-[4'-(methyl)phenoxy]propyl)-1,4,7,10-tetraaza-cyclododecane, (169).

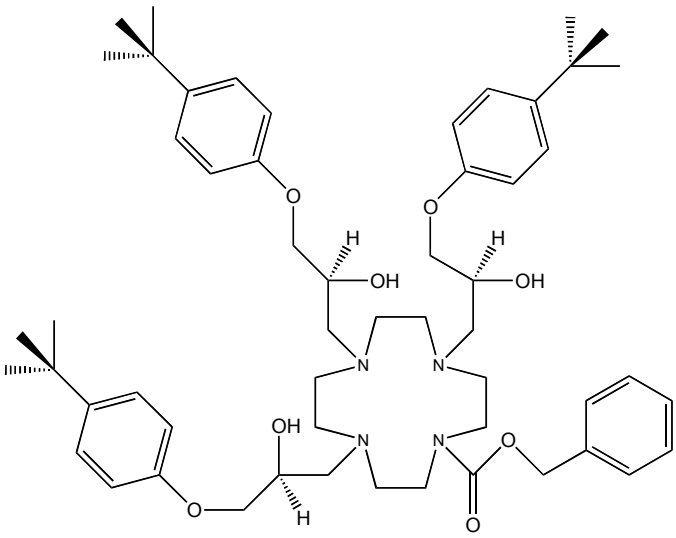


169

Cyclohexene (1.91 g, 3.7 mmol) was added to a solution of **164** (3.33 g, 4.2 mmol) dissolved in absolute ethanol (65 cm^3). The solution was stirred and then 10% Pd/C catalyst (3.20 g) was added. The reaction mixture was refluxed at 80˚C for 5 h, filtered through a small celite column and the filter cake washed with absolute ethanol (40 cm^3). The filtrate was concentrated *in vacuo* to give the deprotected product as a brown oil, **169** (1.66 g, 60%), $[\alpha]_D^{298}$ = -23.42 (c 0.08**,** CH_3OH); $\delta_H(CDCl_3)$ 7.35 (4 H, br s, ArH); 7.05 (4 H, d, *J* 4.2 Hz, ArH); 6.79 (4 H, d, *J* 7.2 Hz, ArH); 4.3-1.9 (35 H, br m, -O*H*, -N*H*, -C*H*- & -CH_2-); 2.27 (9 H, s, -CH_3); $\delta_C(CDCl_3)$ 156.6 (3 C, Ar, *ipso*), 130.0 (3 C, Ar), 129.5 (6 C, Ar), 114.4 (6 C, Ar), 70.3 (2 C, OCH_2), 70.0 (1 C, OCH_2), 67.1 (1 C, methine), 66.0 (2 C, methine), 61.1 (2 C, exo-CH_2N), 60.4 (1 C, exo-CH_2N), 59.7 (1 C, cyclenCH_2), 55.8 (1 C, cyclenCH_2), 54.6 (1 C, cyclenCH_2), 54.2 (1 C, cyclenCH_2), 52.9 (1 C, cyclenCH_2),

49.6 (1 C, cyclen*C*H_2), 47.8 (1 C, cyclen*C*H_2), 46.0 (1 C, cyclen*C*H_2), 20.4 (3 C, -*C*H_3)

1-(Benzyloxycarbonyl)-4,7,10-tris((2*S*)-(-)-2-hydroxy-3-[4'-(*tert*- butyl)phenoxy propyl)-1,4,7,10-tetraazacyclododecane, (165).

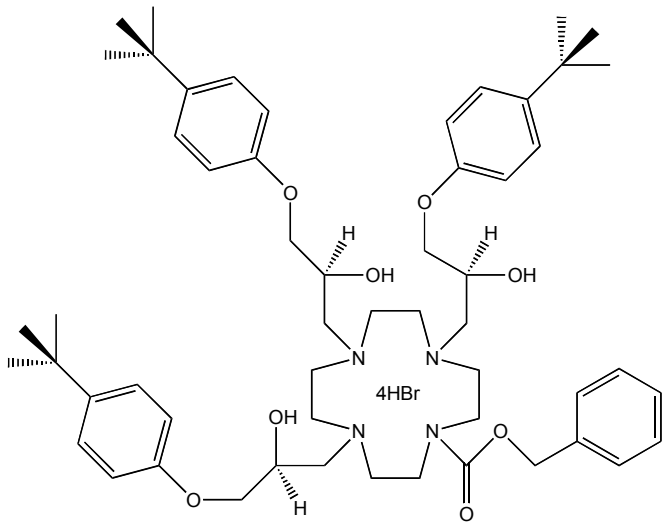


165

(2*S*)-(+)-3-[4'-(*tert*-butyl)phenoxy]-1,2-epoxy propane, **162**, (0.307 g, 1.5 mmol) was dissolved in dry EtOH (20 cm^3). **155** (0.199 g, 0.7 mmol) in dry EtOH (20 cm^3) was added and the combined mixture was refluxed for 6 days. The reaction was monitored by TLC (CH_2Cl_2/hexane, 9:1). The reaction was then cooled to RT, filtered and the filtrate was evaporated to leave a yellow oil, **165** (0.420 g, 83%), $[\alpha]_{589}^{298}$ = -20.9 (c 0.08, MeCN); δ_H(DMSO-d_6) 7.26 (9 H, d, Ar); 6.88 (8 H, d, Ar), 5.09 (2 H, br s, C*H*$_2$Bn), 4.8-2.2 (34 H, br m, -O*H*, -C*H*- & -C*H*$_2$-), 1.33 (27 H, s, -C*H*$_3$); δ_C(DMSO-d_6) 160.0 (1 C, *C*=O), 156.2 (2 C, Ar, *ipso*), 155.8 (1 C, Ar, *ipso*), 143.8 (2 C, Ar-C$(CH_3)_3$), 143.6 (1 C, Ar-C$(CH_3)_3$), 136.2 (1 C, Bn, *ipso*), 128.8 (2 C, Bn), 128.2 (1 C, Bn), 128.0 (2 C, Bn), 126.0 (6 C, Ar), 114.0 (6 C, Ar), 70.5 (1 C, O*C*H_2), 70.4 (1 C, O*C*H_2), 70.0 (1 C, O*C*H_2), 67.8 (1 C, -*C*H_2Bn), 65.8 (1 C, methine), 65.0 (1 C, methine), 64.0 (1 C, methine), 58.7 (1 C, exo-*C*H_2N), 56.1 (2 C,

exo-*C*H_2N), 54.9 (1 C, cyclen*C*H_2), 53.9 (1 C, cyclen*C*H_2), 51.6 (1 C, cyclen*C*H_2), 49.7 (1 C, cyclen*C*H_2), 46.4 (1 C, cyclen*C*H_2), 45.3 (1 C, cyclen*C*H_2), 42.0 (1 C, cyclen*C*H_2), 41.0 (1 C, cyclen*C*H_2), 34.6, (3 C, -*C*(CH_3)), 31.9 (9 C, C(*C*H_3)).

1-(Benzyloxycarbonyl)-4,7,10-tris((2*S*)-2-hydroxy-3-[4'-(*tert*- butyl)phenoxy] propyl)-1,4,7,10-tetraazacyclododecane.4HBr, (184).



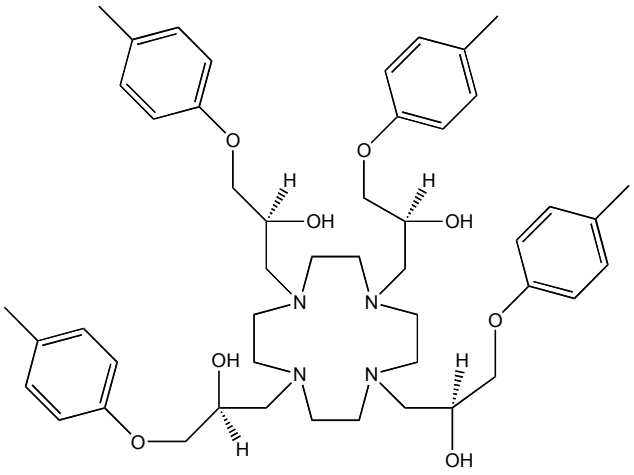
184

An ice-cold stirred solution of **165** (0.100 g, 0.1 mmol) in EtOH (5 cm^3) was treated with 48% HBr in acetic acid (100 μL) and allowed to continue stirring for 1h. The solvent was evaporated, and the residue was triturated with ether. The solid was collected by filtration, dried under high vacuum, resulting in the product, **184**, as an orange powder (0.039 g, 28%); δ_H(DMSO-d_6) 7.29 (9 H, distorted d, *J* 7.8 Hz, Ar*H*); 6.87 (8 H, d, *J* 7.8 Hz, Ar*H*); 5.12 (2 H, s, -CH_2Bn); 4.3-2.6 (38 H, br m, -O*H*, -CH_2-, -N*H* & -C*H*-); 1.24 (27 H, s, -C(CH_3)$_3$); δ_C(DMSO-d_6) 156.2 (1 C, C=O), 156.1 (1 C, Ar, *ipso*), 156.0 (2 C, Ar, *ipso*), 143.1 (2 C, Ar-C(CH_3)$_3$, *ipso*), 142.9 (1 C, Ar-C(CH_3)$_3$, *ipso*), 136.0 (1 C, Bn, *ipso*), 128.5 (2 C, Bn), 128.0 (1 C, Bn), 127.9 (2 C, Bn), 126.1 (6 C, Ar), 114.0 (6 C, Ar), 70.3 (1 C, O*C*H_2), 70.1 (2 C, O*C*H_2), 69.8 (1 C, -*C*H_2Bn), 65.2 (1 C, methine), 64.8 (2 C, methine), 58.4 (3 C, exo-

CH_2N), 55. 5 (2 C, cyclen*C*H_2), 54.1 (2 C, cyclen*C*H_2), 49.3 (2 C, cyclen*C*H_2), 45.0 (2 C, cyclen*C*H_2), 33.8 (3 C, -*C*(CH_3)$_3$, 31.3 (9 C, -C(*C*H_3)$_3$.

6.7.3. Synthesis of ligands.

1,4,7,10-tetrakis(2*S*)-(-)-2-hydroxy-3-([4'-(methyl)phenoxy]-propyl)-1,4,7,10-tetraazacyclododecane, (thmppc), (185).

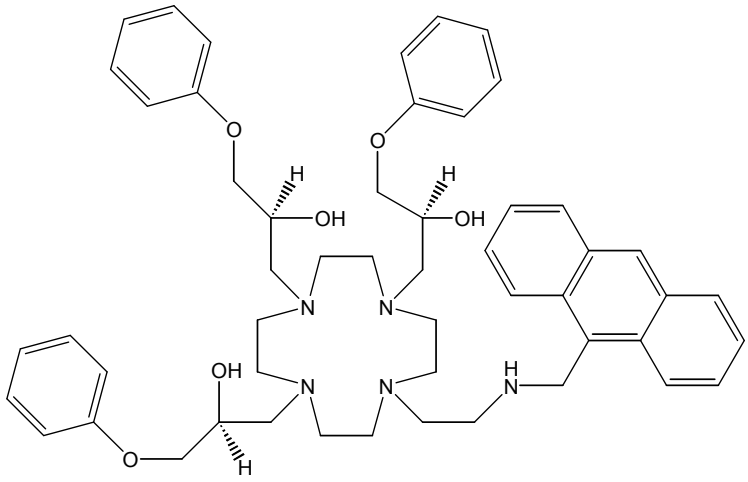


185

161 (1.19 g, 7.2 mmol) in dry ethanol (10 cm^3) was added dropwise over 10 minutes to a gently refluxing solution of cyclen (0.304 g, 1.8 mmol) in dry ethanol (10 cm^3). The reaction mixture was stirred overnight and the reaction progress was monitored by TLC. The reaction was cooled to RT and the product precipitated as a white solid, **185**, which was collected by filtration and dried under vacuum (1.40 g, 96%), $[\alpha]_{589}^{298}$ = -124 (*c* 0.2, $CHCl_3$); (Found C, 69.48; H, 8.48; N, 6.81. $C_{48}H_{68}N_4O_8$ requires C, 69.54; H, 8.27; N, 6.76%); δ_H(DMSO-d_6) 7.04 (8 H, m, *J* 8.2 Hz, Ar*H*), 6.81 (8 H, m, *J* 8.2 Hz, Ar*H*), 4.27 (4 H, br s, -O*H*), 4.0-2.3 (36 H, br m, -CH_2- & -(OH)C*H*-), 2.21 (12 H, s, -CH_3); δ_H($CDCl_3$) 7.04 (8 H, d, Ar), 6.80 (8 H, d, Ar), 4.18 (4 H, br m, -O*H*), 4.02-2.51 (36 H, br m, -CH_2- & -(OH)C*H*-), 2.26 (12 H,

s, -CH_3); δ_C($CDCl_3$) 156.8 (4 C, Ar *ipso*), 129.9 (8 C, Ar), 129.8 (4 C, Ar), 114.5 (8 C, Ar), 70.1 (4 C, ArO-CH_2-), 66.0 (4 C, -(OH)CH-), 59.0 (4 C, CH-CH_2-N), 51.6 (8 C, cyclenCH_2), 20.4 (4 C, –CH_3).

1-((*N*-(2-(-9-anthracenylmethyl)aminoethyl))-4,7,10-tris((2*S*)-(-)-2-hydroxy-3-phenoxypropyl)-1,4,7,10-tetraazacyclododecane, ((*S*)-athppc), (146).

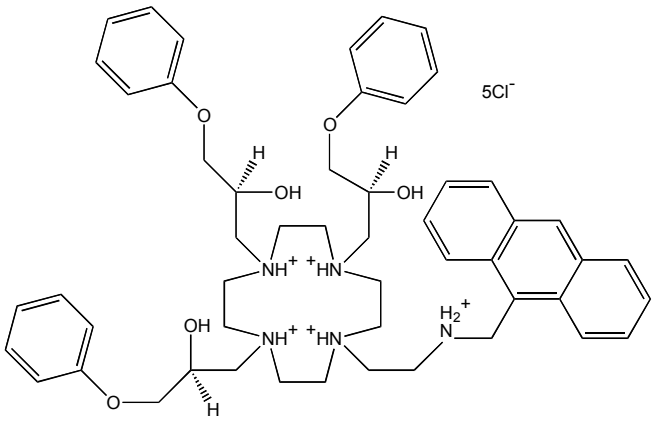


146

168 (2.71 g, 4.4 mmol) was dissolved in dry MeCN (200 cm^3) and excess **149** (1.36 g, 4.4 mmol) was added as a solid, as was $NaHCO_3$ (0.540 g) and molecular sieves. The reaction was refluxed for 10 days, in the dark, after which time the reaction mixture was cooled to RT, filtered and the solvent removed under reduced pressure leaving the imine intermediate as a red oil (3.23 g, 3.8 mmol, 87%). The sample was redissolved in EtOH (40 cm^3) and $NaBH_4$ (0.22 g, 4 mmol) was added. The reaction was stirred overnight, after which time the reaction was diluted with water (40 cm^3), and extracted with CH_2Cl_2 (4 x 30 cm^3). The combined organic layers were dried over Na_2SO_4, then filtered and evaporated to yield the crude product as a red oil, **146** (1.82 g, 76%). The product was purified either by column chromatography (basic alumina, 1% MeOH/CH_2Cl_2) yield (1.00 g, 41%) or by converting it to its penta HBr salt, **187** (1.09 g, 45%). The free ligand was recovered

from the salt by dissolving the pure acid salt, **187**, (0.570 g, 0.4 mmol) in water/ethanol (1:1) and basifying to pH 12 with 1 M NaOH. Extraction with CH_2Cl_2, drying with Na_2SO_4, filtration and evaporation of the solvent under reduced pressure gave the product, **146**, as a red/brown oil (0.377 g, quantitative recovery), $[\alpha]_{589}^{298}$ = -3.96 (c 0.004, EtOH), λ_{max}/nm (20% aqueous 1,4-dioxane) 388.5 nm (ε/dm^3 mol^{-1} cm^{-1} 6 896), 368.4 (7 347), 350.6 (4 647), 334.4 (2 170), 321.1 (sh) (805); λ_{max}/nm (CH_3CN/H_2O 4:1) 387.5 nm (ε/dm^3 mol^{-1} cm^{-1} 6 227), 367.5 (6 610), 349.3 (4 316), 333.1 (2 250), 319.0 (1 113); δ_H(DMSO-d_6) 8.60 (3 H, m, Anth*H*), 8.10 (2 H, m, Anth*H*), 7.60 (4 H, m, Anth*H*), 7.30 (6 H, m, Ph*H*), 6.95 (9 H, m, Ph*H*), 5.3-2.0 (41 H, br m, -O*H*, -C*H*-, -N*H* & -CH_2-); δ_C($CDCl_3$) 158.0 (3 C, Ph, *ipso*), 132.4 (2 C, Anth), 132.2 (2 C, Anth), 130.4 (6 C, Ph), 130.0 (1 C, Anth), 126.9 (2 C, Anth), 126.1 (1 C, Anth), 126.0 (2 C, Anth), 121.6 (2 C, Anth), 121.3 (2 C, Anth), 120.3 (3 C, Ph), 115.2 (6 C, Ph), 71.4 (1 C, O*C*H_2), 71.1 (1 C, O*C*H_2), 68.7 (1 C, O*C*H_2), 68.4 (1 C, methine), 67.5 (1 C, methine), 67.1 (1 C, methine), 61.4 (1 C, exo-*C*H_2N), 58.9 (1 C, exo-*C*H_2N), 58.3 (1 C, exo-*C*H_2N), 57.4 (1 C, exo-*C*H_2N), 56.4 (1 C, exo-*C*H_2NH), 53.1 (2 C, cyclen*C*H_2), 52.5 (2 C, cyclen*C*H_2), 51.9 (2 C, cyclen*C*H_2), 51.4 (2 C, cyclen*C*H_2), 50.4 (1 C, -*C*H_2-N), 46.0 (1 C, Anth*C*H_2).

1-((*N*-(2-(-9-anthracenylmethyl)aminoethyl))-4,7,10-tris((2*S*)-(-)-2-hydroxy-3-phenoxypropyl)-1,4,7,10-tetraazacyclododecane.5HCl.Et_2O.H_2O, ((*S*)-athppc.5HCl.Et_2O.H_2O), (186).

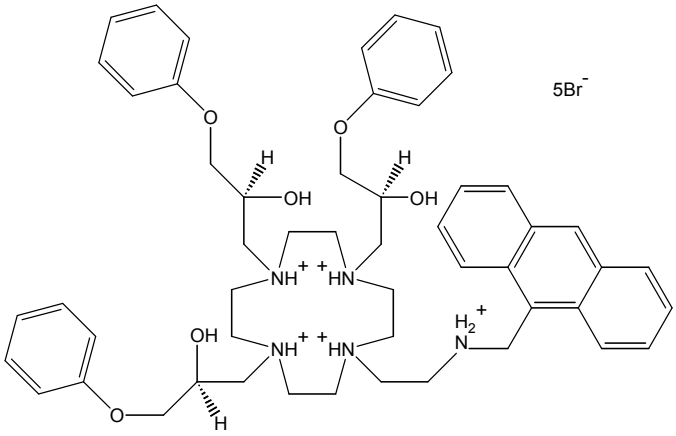


186

146 (2.95 g, 3.4 mmol) was dissolved in EtOH (40 cm^3) and cooled in ice, then treated with 32% HCl acid (10 cm^3) and allowed to stir overnight. The solvent was then concentrated by rotatory evaporation, and the residue was triturated with ether. The brown solid was collected by filtration and dried under vacuum to yield the product as a pale brown powder, **186** (1.25 g, 33%), $[\alpha]_{589}^{298}$ = -4.3 (c 0.009, EtOH); (Found: C, 59.30; H, 7.60; N, 6.50. $C_{56}H_{86}Cl_5N_5O_8$ requires C, 59.50; H, 7.30; N, 6.20%); λ_{max}/nm (20% aqueous 1,4-dioxane) 389 (ε/dm^3 mol^{-1} cm^{-1} 7 890), 368 (8 140), 350 (4 645), 334 (2 167), 321 (sh) (800); δ_H(CD_3OD) 8.56 (1 H, s, Anth*H*); 8.41 (2 H, m, Anth*H*); 7.98 (2 H, t, *J* 8 Hz, Anth*H*); 7.49 (4 H, m, Anth*H*); 7.12 (6 H, t, *J* 7.6 Hz, Ph*H*); 6.83 (9 H, m, Ph*H*); 5.2-2.5 (56 H, br m, -O*H*, -N*H*-, -C*H* & -CH_2-), 1.18 (6 H, t, *J* 7 Hz, CH_3 in Et_2O); δ_C(CD_3OD) 159.8 (1 C, Ph, *ipso*), 159.7 (2 C, Ph, *ipso*), 132.8 (2 C, Anth, *ipso*), 132.3 (1 C, Anth, *ipso*), 132.0 (2 C, Anth, *ipso*), 130.6 (6 C, Ph), 128.9 (2 C, Anth), 126.5 (2 C, Anth), 124.4 (1 C, Anth), 124.2 (2 C, Anth), 122.4 (3 C, Ph), 122.2 (2 C, Anth), 115.7 (6 C, Ph), 70.9 (2 C, O*C*H_2), 70.5 (1 C, O*C*H_2), 68.5 (1 C, methine), 68.0 (1 C, methine), 67.0 (1 C, methine), 66.9 (2 C, *C*H_2 in Et_2O), 66.0 (1 C, exo-C*H*$_2$N), 65.0 (1 C, exo-C*H*$_2$N),

60.2 (1 C, exo-C*H*$_2$N), 58.5 (2 C, exo-C*H*$_2$N), 58.0 (1 C, exo-C*H*$_2$NH), 56.1 (2 C, cyclen*C*H$_2$), 54.0 (2 C, cyclen*C*H$_2$), 52.3 (2 C, cyclen*C*H$_2$), 51.7 (2 C, cyclen*C*H$_2$), 44.8 (1 C, Anth*C*H$_2$), 15.5 (2 C, *C*H$_3$ in Et$_2$O).

1-((*N*-(2-(-9-anthracenylmethyl)aminoethyl))-4,7,10-tris((2*S*)-2-hydroxy-3-phenoxypropyl)-1,4,7,10-tetraazacyclododecane.5HBr.2H$_2$O, ((*S*)-athppc.5HBr.2H$_2$O), (187).

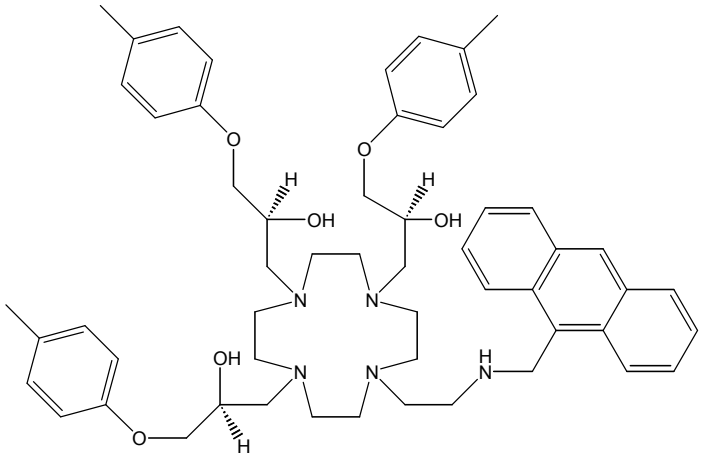


187

146 (1.82 g, 2.9 mmol) was dissolved in dry EtOH (5 cm^3) and cooled to 0°C. The ice-cold solution was treated with aqueous 48% HBr (1.82 cm^3) and allowed to stir for 1h. The solvent was evaporated and the residue triturated with ether. The solid was collected by filtration and dried under high vacuum. The product was a brown powder, **187** (0.575 g, 15%), (Found: C, 48.30; H, 5.53; N, 5.54. $C_{52}H_{74}Br_5N_5O_8$ requires: C, 48.17; H, 5.75; N, 5.40%); λ_{max}/nm (20% aqueous 1,4-dioxane) 388 (ε/dm^3 mol^{-1} cm^{-1} 7900), 369 (8350), 351 (4650), 335 (2165), 321 (sh)(800); δ_H(CD$_3$OD): 8.42 (3 H, m, Anth), 8.00 (2 H, t, *J* 8.8 Hz, Anth), 7.50 (4 H, m, Anth), 7.13 (6 H, t, *J* 7.6 Hz, Ph), 6.83 (9 H, m, Ph), 5.30 (13 H, br s, -O*H* & -N*H*-), 4.6-2.6 (37 H, br m, -C*H*- & -C*H*$_2$-); δ_C(CD$_3$OD): 160.0 (1 C, Ph, *ipso*), 159.8 (2 C, Ph, *ipso*), 132.8 (2 C, Anth), 132.3 (2 C, Anth), 131.8 (1 C, Anth), 130.6 (6 C,

Ph), 129.0 (2 C, Anth), 126.7 (2 C, Anth), 124.9 (1 C, Anth), 124.5 (2 C, Anth), 122.4 (3 C, Ph), 122.2 (2 C, Anth), 115.7 (6 C, Ph), 70.9 (2 C, O*C*H_2), 70.5 (1 C, O*C*H_2), 68.1 (1 C, methine), 67.5 (1 C, methine), 66.9 (1 C, methine), 65.5 (1 C, exo-*C*H_2N), 64.9 C, (1 C, exo-*C*H_2N), 60.1 (1 C, exo-*C*H_2N), 58.4 (1 C, exo-*C*H_2N), 57.9 (1 C, exo-*C*H_2NH), 55.5 (2 C, cyclen*C*H_2), 53.3 (2 C, cyclen*C*H_2), 52.1 (2 C, cyclen*C*H_2), 45.8 (2 C, cyclen*C*H_2), 44.0 (1 C, -Anth*C*H_2).

1-((*N*-(2-(-9-anthracenylmethyl)aminoethyl))-4,7,10-tris((2*S*)-2-hydroxy-3-[4'-(methyl)phenoxy]propyl)-1,4,7,10-tetraazacyclododecane, ((*S*)-athmppc), (170).

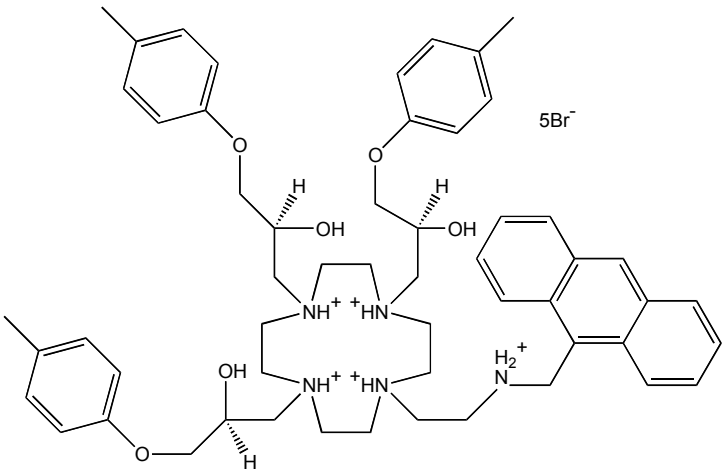


170

169 (0.871 g, 1.2 mmol) was dissolved in dry MeCN (60 cm^3). **149** (0.386 g, 1.2 mmol) was added as a solid, as was $NaHCO_3$ (0.133 g). Molecular sieves were added to absorb the produced water. The reaction was wrapped in foil to keep out light. The reaction was refluxed for 10 days after which time the reaction mixture was cooled to RT, filtered and the solvent removed under reduced pressure. The product formed as a red oil. This was redissolved in EtOH (25 cm^3) and $NaBH_4$ (0.10 g) was added as a solid. The solution was stirred overnight, then diluted with water (30cm^3), which turned it milky white. It was then extracted into CH_2Cl_2 (4 x 30cm^3), which was dried over Na_2SO_4. The drying agent was removed by filtration

and the solvent was evaporated, leaving a residue which was dried *in vacuo* to yield the crude product, **170**, as a red oil (0.740 g, 67%). Purification was achieved by making the acid salt of the ligand. Crude **170** (0.240 g, 0.3 mmol) was dissolved in dry EtOH (3 cm^3) and cooled in ice-water. 32% aqueous HCl (0.4 cm^3, 5.0 mmol) was then added dropwise. The solution was stirred overnight, and the solvent was then evaporated to leave an oily residue. Trituration with ether yielded a pale brown powder**, 188**, that was dried *in vacuo* (0.121 g, 42%). The free ligand was recovered by dissolving the pure acid salt, **188**, in water/ethanol (1:1) and basifying to pH 12 with 1 M NaOH. Extraction with CH_2Cl_2, drying with Na_2SO_4, filtration and evaporation of the solvent under reduced pressure gave the pure product, **170**, as a red/brown oil (0.102 g, quantitative recovery); λ_{max}/nm (20% aqueous 1,4-Dioxane) 386.4 (ε/dm^3 mol^{-1} cm^{-1} 6 226), 366.5 (6 673), 348.8 (4 345), 332.6 (2 141), 320.1 (sh) (920); δ_H($CDCl_3$) 8.44 (1 H, s, Anth*H*); 8.02 (2 H, d, *J* 8.0 Hz, Anth*H*); 7.46 (2 H, m, Anth*H*); 7.33 (4 H, m, Anth*H*); 7.07 (6 H, m, Ar*H*); 6.80 (6 H, br s, Ar*H*); 5.3-2.5 (41 H, br m, -N*H*-, -O*H*, C*H* & -CH_2-); 2.23 (9 H, s, -CH_3); δ_C($CDCl_3$) 156.5 (1 C, Ar, *ipso*), 156.3 (2 C, Ar, *ipso*), 131.4 (2 C, Anth), 130.0 (6 C, Ar), 129.2 (3 C, Ar), 129.0 (1 C, Anth), 128.7 (2 C, Anth), 128.4 (1 C, Anth), 128.1 (2 C, Anth), 128.1 (2 C, Anth), 126.3 (2 C, Anth), 125.3 (2 C, Anth), 115.3 (2 C, Ar), 114.3 (4 C, Ar), 70.3 (2 C, O*C*H_2), 69.2 (1 C, O*C*H_2), 66.4 (1 C, methine), 65.6 (2 C, methine), 62.9 (1 C, exo-CH_2N), 60.4 (2 C, exo-CH_2N), 59.7 (1 C, exo-CH_2N), 57.2 (1 C, exo-CH_2NH), 53.0-50.0 (8 C, m, cyclenCH_2), 45.5 (1 C, AnthCH_2), 20.4 (3 C, -*C*H_3).

1-((*N*-(2-(-9-anthracenylmethyl)aminoethyl))-4,7,10-tris((2*S*)-(-)-2-hydroxy-3-[(4-methyl)phenoxy]propyl)-1,4,7,10-tetraazacyclododecane.5HBr.EtOH, ((*S*)-athmppc.5HBr.EtOH), (189).

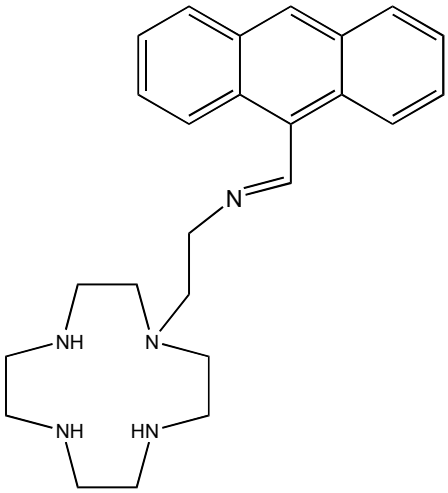


189

170 (0.440 g, 0.5 mmol) was dissolved in EtOH (7 cm^3) and cooled in ice, then treated dropwise with 48% HBr acid (0.3 cm^3) and allowed to stir overnight. The solvent was then concentrated by rotatory evaporation, and the residue was triturated with ether. The brown solid was collected by filtration and dried under vacuum to yield the product, **189**, as a pale brown powder (0.361 g, 68%), $[\alpha]_{589}^{298}$ = -9.9 (c 0.005, EtOH); (Found: C, 50.70; H, 6.12; N, 5.02. $C_{57}H_{82}Br_5N_5O_7$ requires C, 50.76; H, 6.13; N, 5.19%); λ_{max}/nm (20% aqueous 1,4-Dioxane) 389 (ε/dm^3 mol^{-1} cm^{-1} 8 148), 367 (9 291), 349 (4 409), 334 (2 813), 319 (sh) (937); δ_H(DMSO-d_6) 8.63 (1 H, s, Anth*H*), 8.50 (2 H, br s, Anth*H*), 8.02 (2 H, br s, Anth*H*), 7.62 (4 H, br s, Anth*H*), 7.25 (6 H, br s, Ar*H*), 6.85 (6 H, br s, Ar*H*), 5.2-2.2 (49 H, br m, -C*H*, -CH_2-, -O*H*, -N*H* , -O*H* in EtOH & CH_2 in EtOH), 2.05 (9 H, s, -CH_3), 1.06 (3 H, CH_3 in EtOH); δ_C(DMSO-d_6) 156.3 (3 C, Ar, *ipso*), 130.9 (2 C, Anth), 130.8 (6 C, Ar), 129.9 (1 C, Anth), 129.6 (3 C, Ar), 129.4 (2 C, Anth), 129.1 (1 C, Anth), 127.1 (2 C, Anth), 125.6 (2 C, Anth), 124.8 (2 C, Anth), 124.6 (2 C, Anth), 114.4 (6 C, Ar),

70.2 (3 C, O*C*H_2), 56.1 (6 C, exo-CH_2N, exo-CH_2NH, & CH_2 in EtOH), 53.0–46.0 (9 C, cyclen*C*H_2 & Anth*C*H_2), 20.4 (3 C, -*C*H_3), 18.5 (1 C, *C*H_3 in EtOH).

_N_-(2-(-9-anthracenylmethyl)iminoethyl) -1,4,7,10-tetraazacyclododecane, (174).

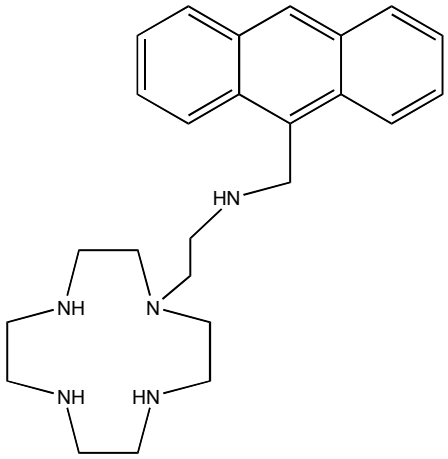


174

The title compound was synthesized using a modification of the method used by Fabbrizzi and co-workers[108] and modified by Campbell[190]. Cyclen (2.85 g, 16.9 mmol) was dissolved in hot dry toluene (60 cm^3) and **149** (1.00 g, 3.2 mmol) was added as a solid. The reaction mixture was stirred under reflux for 3 h. Cyclen hydrobromide precipitated soon after the reaction started. The reaction mixture was allowed to cool, followed by filtration to remove the hydrobromide salt. The clear gold coloured solution was washed with NaOH solution (0.1 M, 5 x 40 cm^3) and distilled water (3 x 20 cm^3). The organic layer was dried over Na_2SO_4, filtered and the solvent removed by reduced pressure. The resultant gold coloured sticky residue, **174**, (1.12 g, 86%) was used without further purification. $\delta_H(CDCl_3)$ 9.53 (1 H, s, N=C*H*), 8.63 (2 H, d, *J* 1.1 Hz, Anth*H*), 8.59 (1 H, s, Anth*H*), 8.02 (2 H, distorted dd, *J* 0.7, 2 Hz, Anth*H*), 7.47 (4 H, m, Anth*H*), 4.09 (2 H, t, *J* 6.8 Hz, -CH_2N=C), 3.05 (2 H, t, *J* 6.8 Hz, exo-*C*H_2N), 2.8-2.1 (19 H, br m, cyclenCH_2 & N*H*);

δ_C($CDCl_3$) 161.0 (1 C, -*C*H=N- APT↓), 131.1 (2 C, Anth, APT↑ *ipso*), 130.0 (2 C, Anth, APT↑ *ipso*), 129.4 (1 C, Anth, APT↓), 128.7 (2 C, Anth, APT↓), 127.6 (1 C, Anth, APT↑ *ipso*), 126.6 (2 C, Anth, APT↓), 125.1 (2 C, Anth, APT↓), 124.9 (2 C, Anth, APT↓), 61.0 (1 C, -C=N-*C*H_2-, APT↑), 55.5 (1 C, CH_2-*C*H_2-N, APT↑), 52.0 (2 C, cyclen*C*H_2, APT↑), 46.8 (2 C, cyclen*C*H_2, APT↑), 45.8 (2 C, cyclen*C*H_2, APT↑), 45.2 (2 C, cyclen*C*H_2, APT↑).

_N_-(2-(-9-anthracenylmethyl)aminoethyl) -1,4,7,10-tetraazacyclododecane, (antac-12), (131).

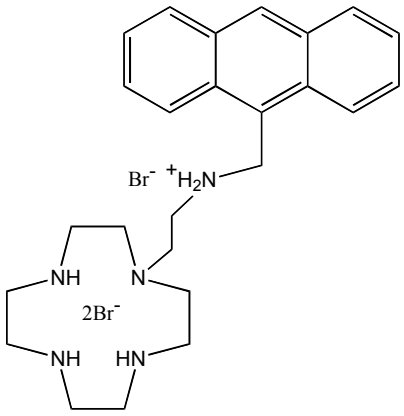


131

Using a procedure devised by Campbell[291] and modified by Plush,[291] crude imine, **174**, (1.20 g) was dissolved in dry EtOH (70 cm^3). Excess $NaBH_4$ (0.150 g, 4.0 mmol) was added in portions and the reaction was stirred overnight. The mixture was diluted with water (50 cm^3) and the organic product was extracted into CH_2Cl_2 (3 x 25 cm^3). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated off. A gold coloured sticky residue resulted (1.21 g). The product was purified by column chromatography on silica gel basified by running a CH_2Cl_2/MeOH/triethylamine (70:24:6) mixture through it. The product was then eluted using $CHCl_3$/MeOH/ aq. NH_3 (28%) (70:24:6), R_f = 0.8; to give **131**, as a

reddish oil (0.62 g, 48%). Purification can also be achieved using a deactivated basic alumina column (2% MeOH/CH_2Cl_2) to yield the product, **131**, as a reddish oil (0.707 g, 55%), λ_{max}/nm (CH_3CN) 386 nm (ε/dm^3 mol^{-1} cm^{-1} 5 771), 366 (6 066), 348 (3 971), 331 (2 128), 316 (1 224); δ_H($CDCl_3$) 8.39-8.35 (3 H, m, Anth*H*), 7.96 (2 H, distorted dd, *J* 1.4, 9.8 Hz, Anth*H*), 7.6-7.4 (4 H, m, Anth*H*), 4.40 (s, 2 H, AnthCH_2), 2.99 (2 H, t, *J* 6.6 Hz, exo-CH_2N), 2.64 (2 H, t, *J* 6.6 Hz, exo-CH_2NH), 2.54-2.16 (20 H, br m, -N*H*-, cyclenCH_2); δ_C($CDCl_3$) 131.9 (1 C, Anth, *ipso*), 131.4 (2 C, Anth, *ipso*), 130.1 (2 C, Anth, *ipso)*), 128.9 (2 C, Anth), 126.9 (1 C, Anth), 125.9 (2 C, Anth), 124.8 (2 C, Anth), 124.3 (2 C, Anth) , 54.8 (1 C, exo-CH_2N), 52.1 (2 C, cyclenCH_2), 48.4 (1 C, exo-CH_2NH), 46.6 (2 C, cyclenCH_2), 45.8 (1 C, AnthCH_2), 45.6 (2 C, cyclenCH_2), 45.0 (2 C, cyclenCH_2).

N-(2-(-9-anthracenylmethyl)aminoethyl) -1,4,7,10-tetraazacyclododecane.3HBr .H_2O, (190).

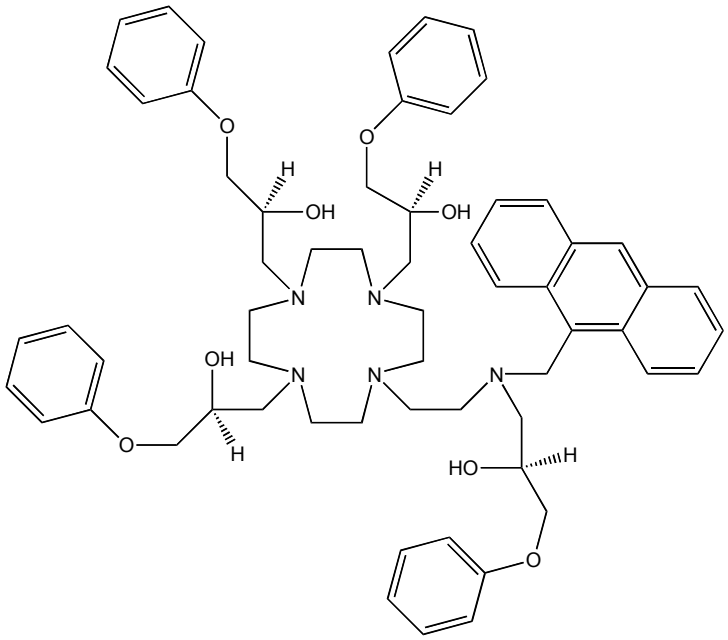


190

Hydrobromic acid (48%, 200 μL, 1.60 mmol) was added dropwise to an ice-cold solution of **131** (0.130 g, 0.3 mmol) in dry ethanol (7 cm^3). Upon addition of the acid, the solution was stirred for a further 1h. During this time a pale brown precipitate formed, which was collected by vacuum filtration. The solid was washed with ice-cold ethanol and dried under vacuum to yield the product, **190** (0.150 g, 57%), (Found: C, 45.20; H, 5.92; N, 10.35. $C_{25}H_{40}Br_3N_5O$ requires: C, 45.06; H,

6.05; N, 10.51%); λ_{max}/nm (CH_3CN/H_2O) 387 nm (ε/dm^3 mol^{-1} cm^{-1} 7493), 367 (8235), 349 (5653), 333 (3152), 317 (1863); ν_{max}/cm^{-1} (KBr) 3420, 3237, 3035, 2800, 2690, 1626, 1560, 1401, 1160, 735; δ_H(DMSO-d_6) 8.44 (1 H, s, Anth*H*), 8.39 (2 H, d, *J* 5 Hz, Anth*H*), 7.95 (2 H, d, *J* 8.2 Hz, Anth*H*), 7.6-7.3 (4 H, m, Anth*H*), 4.74 (2 H, br s, AnthCH_2), 3.00 (2 H, t, *J* 6.4 Hz, exo–CH_2N), 2.60 (2 H, t, *J* 6.4 Hz, exo-CH_2NH), 2.36 (25 H, br m, O*H*, -N*H*- & cyclenCH_2); δ_C($CDCl_3$) 131.5 (1 C, Anth, *ipso*), 131.1 (2 C, Anth, *ipso*), 130.8 (2 C, Anth, *ipso*), 129.5 (2 C, Anth), 128.0 (1 C, Anth), 125.9 (2 C, Anth), 123.9 (2 C, Anth), 121.7 (2 C, Anth), 54.3 (1 C, exo-*C*H_2N), 52.4 (2 C, cyclen*C*H_2), 48.0 (1 C, exo-*C*H_2NH), 46.2 (2 C, cyclen*C*H_2), 45.8 (1 C, Anth*C*H_2), 45.6 (2 C, cyclen*C*H_2), 44.9 (2 C, cyclen*C*H_2).

1-((*N*-(2-(-9-anthracenylmethyl)(*N*-(2*S*)-2-hydroxy-3- phenoxypropyl) amino ethyl))-4,7,10-tris((2*S*)-2-hydroxy-3-phenoxypropyl)-1,4,7,10-tetraazacyclodo decane, ((*S*)-apthppc), (171).

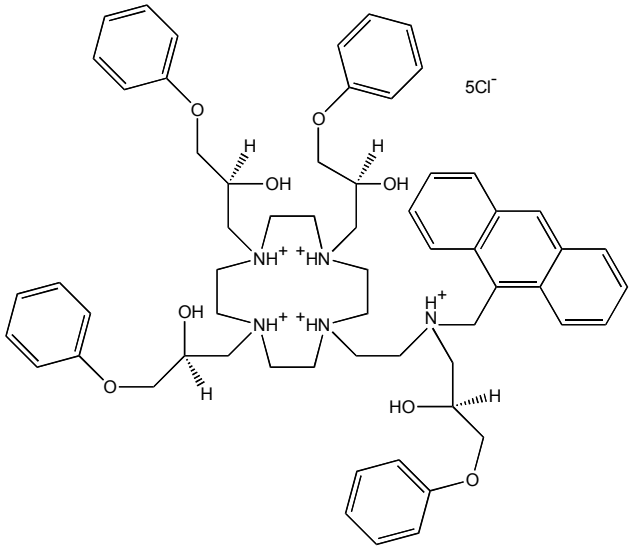


171

131 (0.366 g, 0.9 mmol) was dissolved in dry EtOH (23 cm^3) and stirred whilst warming the reaction to reflux. A solution of **160** (0.550 g, 3.7 mmol) in dry

EtOH (26 cm^3) was added dropwise. The reaction was stirred under reflux for 7 d and monitored by TLC (alumina, MeOH/CH_2Cl_2 4:96). Upon disappearance of the epoxide, the reaction was cooled to RT, and the solvent removed to leave a red/brown oil. This was purified on a basic alumina column (hexane/CH_2Cl_2 1:9) to remove three impurity bands, then flushed with MeOH to recover the product. Removal of solvent from the final fraction, and drying under vacuum yielded a red/brown oil, **171** (0.684 g, 75%), λ_{max}/nm (CH_3CN/H_2O) 388.7 (ε/dm^3 mol^{-1} cm^{-1} 9 529), 368.7 (9 935), 350.3 (6 407), 333.9 (3 381), 320.0 (sh) (1 784); λ_{max}/nm (20% aqueous 1,4-dioxane) 386.4 (ε/dm^3 mol^{-1} cm^{-1} 7891), 366.5 (8562), 348.6 (5580), 332.4 (2947), 319.8 (sh)(1360); δ_H(CD_3CN) 8.55 (2 H, d, *J* 8 Hz, Anth*H*), 8.39 (1 H, s, Anth*H*), 8.00 (2 H, d, *J* 8 Hz, Anth*H*), 7.47 (4 H, m, Anth*H*), 7.35 (8 H, m, Ph*H*), 7.00 (10 H, m, Ph*H*), 6.71 (2 H, d, *J* 8 Hz, Ph*H*); 4.8-1.8 (46 H, br m, -O*H*, -C*H*-, & -CH_2-); δ_C($CDCl_3$) 157.8 (4 C, Ph, *ipso*), 130.9 (2 C, Anth, *ipso*), 130.8 (2 C, Anth, *ipso*), 129.3 (1 C, Anth, ipso), 129.0 (8 C, Ph), 128.8 (2 C, Anth), 127.4 (1 C, Anth), 125.6 (2 C, Anth), 124.5 (2 C, Anth), 124.1 (2 C, Anth), 120.4 (4 C, Ph), 114.2 (8 C, Ph), 71.1 (1 C, O*C*H_2), 69.8 (1 C, O*C*H_2), 69.4 (1 C, O*C*H_2), 68.7 (1 C, O*C*H_2), 68.4 (1 C, methine), 67.2 (1 C, methine), 66.6 (1 C, methine), 65.8 (1 C, methine), 65.2 (1 C, exo-*C*H_2N), 60.1 (1 C, exo-*C*H_2N), 58.2 (1 C, exo-*C*H_2N), 57.5 (1 C, exo-*C*H_2N), 55.0 (1 C, exo-*C*H_2N), 54.2 (1 C, exo-*C*H_2N), 52.8 (2 C, cyclen*C*H_2), 51.8 (2 C, cyclen*C*H_2), 51.4 (2 C, cyclen*C*H_2), 50.1 (2 C, cyclen*C*H_2), 46.0 (1 C, Anth-*C*H_2N-).

1-((*N*-(2-(-9-anthracenylmethyl)(*N*-(2*S*)-(-)-2-hydroxy-3- phenoxypropyl)amino ethyl))-4,7,10-tris((2*S*)-2-(-)-hydroxy-3-phenoxypropyl)-1,4,7,10-tetraazacyclo dodecane.5HCl, ((*S*)-apthppc.5HCl), (192).

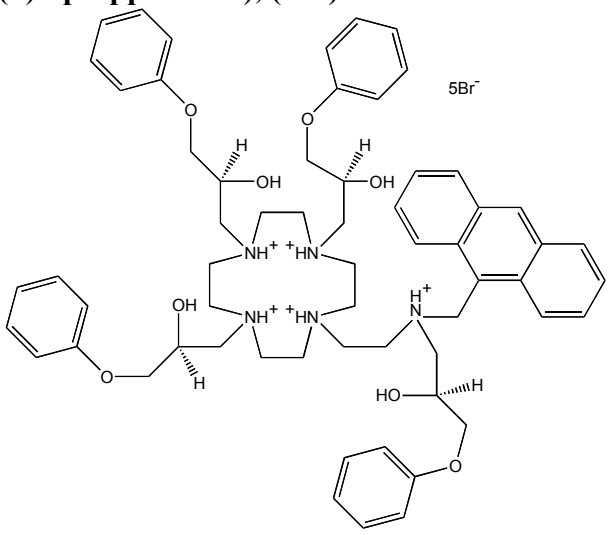


192

171 (0.960 g, 1.1 mmol) was dissolved in EtOH (14 cm^3) and cooled in ice and treated dropwise with 36% aqueous HCl (0.76 cm^3, 9.9 mmol). The mixture was allowed to stir overnight, then the solvent was evaporated. The residue was triturated with ether. The white solid was collected by filtration, and dried under vacuum to yield the product, **192**, as an off-white powder (0.866 g, 55%), mp 121-123°; (Found: C, 61.60; H, 7.10; N, 5.60. $C_{61}H_{80}Cl_5N_5O_8$ requires C, 61.60; H, 6.80; N, 5.90%); λ_{max}/nm (20% aqueous 1,4-dioxane) 389 (ε/dm^3 mol^{-1} cm^{-1} 8 148), 369 (ε/dm^3 mol^{-1} cm^{-1} 8 982), 350 (ε/dm^3 mol^{-1} cm^{-1} 6 144), 334 (ε/dm^3 mol^{-1} cm^{-1} 3 201), 318 (sh) (ε/dm^3 mol^{-1} cm^{-1} 1 463); $[\alpha]_{589}^{298}$ = -40.9 (*c* 0.005, EtOH); δ_H(DMSO-d_6) 8.83 (1 H, s, Anth*H*), 8.73 (2 H, br m, Anth*H*), 8.18 (2 H, d, *J* 8 Hz, Anth*H*), 7.5-7.8 (4 H, m, Anth*H*), 7.25 (8 H, m, Ph*H*), 6.90 (8 H, m, Ph*H*), 6.70 (4 H, m, Ph*H*), 4.50 (4 H, br s, -O*H*), 4.40-1.80 (47 H, br m, -C*H*-, -N*H* & -CH_2-); δ_C(DMSO-d_6) 158.5 (1 C, Ph *ipso*, APT↓), 158.3 (2 C, Ph *ipso*, APT↓), 158.2 (1 C, Ph *ipso*, APT↓), 131.6 (2 C, Anth *ipso*, APT↓), 131.3 (1 C, Anth *ipso*, APT↓),

130.84 (2 C, Anth *ipso*, APT↓), 129.9 (2 C, Anth, APT↑), 129.4 (6 C, Ph, APT↑), 129.2 (2 C, Ph, APT↑), 127.6 (2 C, Anth, APT↑), 125.5 (2 C, Anth, APT↑), 124.8 (2 C, Anth, APT↑), 124.1 (1 C, Anth, APT↑), 120.9 (2 C, Ph, APT↑), 120.8 (1 C, Ph, APT↑), 120.7 (1 C, Ph, APT↑), 114.3 (4 C, Ph, APT↑), 114.2 (4 C, Ph, APT↑), 70.4 (1 C, O*C*H_2, APT↓), 69.9 (2 C, O*C*H_2, APT↓), 69.7 (1 C, O*C*H_2, APT↓), 65.1 (1 C, methine, APT↑), 64.0 (2 C, methine, APT↑), 63.5 (1 C, methine, APT↑), 61.4 (1 C, exo-*C*H_2N, APT↓), 58.4 (1 C, exo-*C*H_2N, APT↓), 58.0 (1 C, exo-*C*H_2N, APT↓), 57.8 (1 C, exo-*C*H_2N, APT↓), 56.5 (1 C, exo-*C*H_2N, APT↓), 51.0 (1 C, exo-*C*H_2N, APT↓), 50.5 (2 C, cyclen*C*H_2, APT↓), 50.1 (2 C, cyclen*C*H_2, APT↓), 49.5 (2 C, cyclen*C*H_2, APT↓), 48.0 (2 C, cyclen*C*H_2, APT↓), 45.9 (1 C, Anth*C*H_2, APT↓).

1-((*N*-(2-(-9-anthracenylmethyl)(*N*-(2*S*)-(-)-2-hydroxy-3-phenoxypropyl)amino ethyl))-4,7,10-tris((2*S*)-(-)-2-hydroxy-3-phenoxypropyl)-1,4,7,10-tetraazacyclo dodecane.5HBr, ((*S*)-apthppc.5HBr), (193).

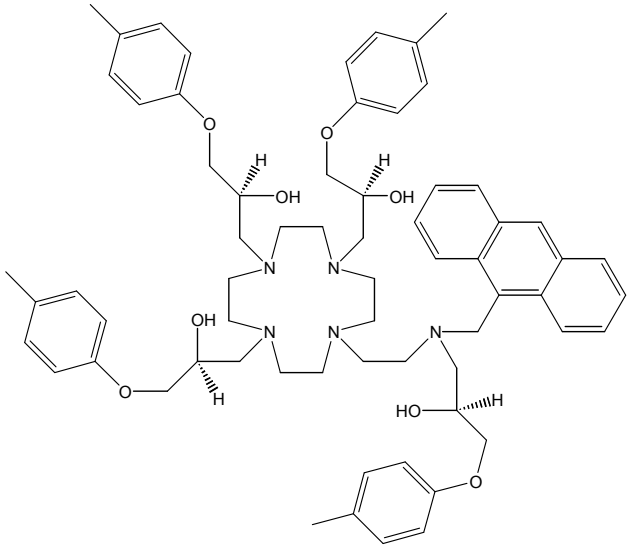


193

171 (0.955 g, 0.1 mmol) was dissolved in acetic acid (3 cm^3) and cooled in ice and treated dropwise with a 1:1 mixture of HBr/acetic acid (0.166 cm^3). The mixture was allowed to stir for 5 h, then the solvent was evaporated. The residue

was triturated with ether. The white solid was collected by filtration, and dried under vacuum to yield the product as an off-white powder, **193** (0.052 g, 38%), mp 121-123°; $[\alpha]_D^{298}$ = -40.89 (c 0.007, EtOH); (Found: C, 51.90; H, 6.00; N, 5.00. $C_{61}H_{80}Br_5N_5O_8$ requires C, 51.93; H, 5.72; N, 4.96%); δ_H(DMSO-d_6) 8.85 (1 H, br s, Anth*H*), 8.65 (2 H, br m, Anth*H*), 8.18 (2 H, br m, Anth*H*), 7.60 (4 H, br m, Anth*H*), 7.26 (8 H, br s, Ph*H*), 6.95 (10 H, br s, Ph*H*), 6.58 (2 H, br s, Ph*H*), 5.8-2.6 (51 H, br m, -C*H*-, -N*H*, -O*H* & -CH_2-); δ_C(DMSO-d_6) 158.3 (1 C, Ph, *ipso*), 158.2 (3 C, Ph, *ipso*), 131.9 (1 C, Anth, *ipso*), 130.9 (2 C, Anth, *ipso*), 130.8 (2 C, Anth, *ipso*), 129.6 (8 C, Ph), 127.8 (2 C, Anth), 126.1 (1 C, Anth), 125.8 (2 C, Anth), 124.8 (2 C, Anth), 124.0 (2 C, Anth), 121.0 (4 C, Ph), 114.5 (8 C, Ph), 70.4 (1 C, O*C*H_2), 69.8 (3 C, O*C*H_2), 65.0 (2 C, methine), 63.8 (1 C, methine), 62.9 (1 C, methine), 56.0 (3 C, exo-*C*H_2N), 55.3 (3 C, exo-*C*H_2N), 51.7 (2 C, cyclen*C*H_2), 50.0 (4 C, cyclen*C*H_2), 47.8 (2 C, cyclen*C*H_2), 46.0 (1 C, Anth*C*H_2).

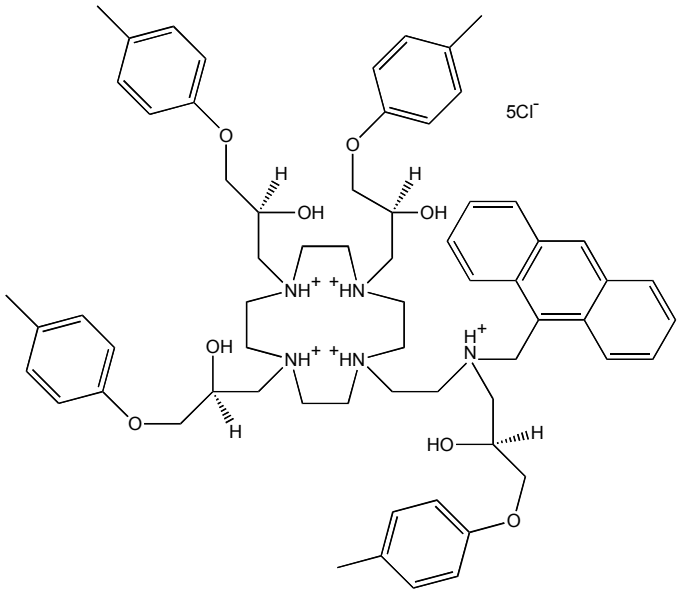
1-((*N*-(2-(-9-anthracenylmethyl)(*N*-(2*S*)-2-hydroxy-3-[(4'-methyl)phenoxy] propyl)aminoethyl))-4,7,10-tris((2*S*)-2-hydroxy-3-[(4'-methyl)phenoxy]propyl)-1,4,7,10-tetraazacyclododecane, ((*S*)-amthmppc), (172).



172

131 (0.320 g, 0.8 mmol) was dissolved in dry EtOH (16 cm^3) and stirred whilst warming the reaction to reflux. A solution of **161** (0.532 g, 3.2 mmol) in dry EtOH (16 cm^3) was added dropwise. The reaction was stirred under reflux for 10 d and monitored by TLC (alumina, 4% MeOH/CH_2Cl_2). Upon disappearance of the starting epoxide, the reaction was cooled to RT, and the solvent removed to leave an orange oil (0.910 g). This was purified on a basic alumina column (10% hexane/CH_2Cl_2) giving a red/brown oil, **172** (0.684 g, 82%); λ_{max}/nm (20% aqueous 1,4-Dioxane) 388.7 nm (ε/dm^3 mol^{-1} cm^{-1} 9 522), 368.7 (9 941), 350.3 (6 532), 334.0 (3 607), 320.2 (2 054); δ_H($CDCl_3$) 8.49 (2 H, d, *J* 8.6 Hz, Anth*H*); 8.38 (1 H, s, Anth*H*); 7.97 (2 H, distorted d, *J* 7.6 Hz, Anth*H*); 7.46 (4 H, m, Anth*H*); 7.03 (8 H, br s, Ar*H*); 6.78 (8 H, m, Ar*H*); 4.8-1.2 (46 H, br m, -O*H*, -C*H*- & -CH_2-); 2.26 (12 H, s, -CH_3); δ_C($CDCl_3$) 156.4 (4 C, Ar, *ipso*), 131.8 (2 C, Anth, *ipso*), 131.6 (1 C, Anth, *ipso*), 130.0 (8 C, Ar), 129.9 (4 C, Ar), 129.0 (2 C, Anth, *ipso*), 128.0 (2 C, Anth), 127.9 (2 C, Anth), 127.0 (2 C, Anth), 126.0 (1 C, Anth), 124.8 (2 C, Anth), 114.4 (8 C, Ar), 114.1 (2 C, Ar), 70.3 (4 C, O*C*H_2), 67.9 (1 C, methine), 66.9 (1 C, methine), 65.5 (1 C, methine), 65.3 (1 C, methine), 60.4 (1 C, exo-*C*H_2N), 58.3 (1 C, exo-*C*H_2N), 58.0 (1 C, exo-*C*H_2N), 57.8 (1 C, exo-*C*H_2N), 56.3 (1 C, exo-*C*H_2N), 53.8 (1 C, exo-*C*H_2N), 53.2 (1 C, cyclen*C*H_2), 53.0 (1 C, cyclen*C*H_2), 52.3 (1 C, cyclen*C*H_2), 52.1 (1 C, cyclen*C*H_2), 51.8 (1 C, cyclen*C*H_2), 50.3 (1 C, cyclen*C*H_2), 50.0 (1 C, cyclen*C*H_2), 49.8 (1 C, cyclen*C*H_2), 47.8 (1 C, Anth*C*H_2), 20.1 (4 C, -*C*H_3).

1-((*N*-(2-(-9-anthracenylmethyl)(*N*-(2*S*)-(-)-2-hydroxy-3-[4'-methyl)phenoxy] propyl)aminoethyl))-4,7,10-tris((2*S*)-(-)-2-hydroxy-3-[(4'-methyl)phenoxy] propyl)-1,4,7,10-tetraazacyclododecane.5HCl.3H_2O, ((*S*)-amthmppc.5HCl. 3H_2O), (194).

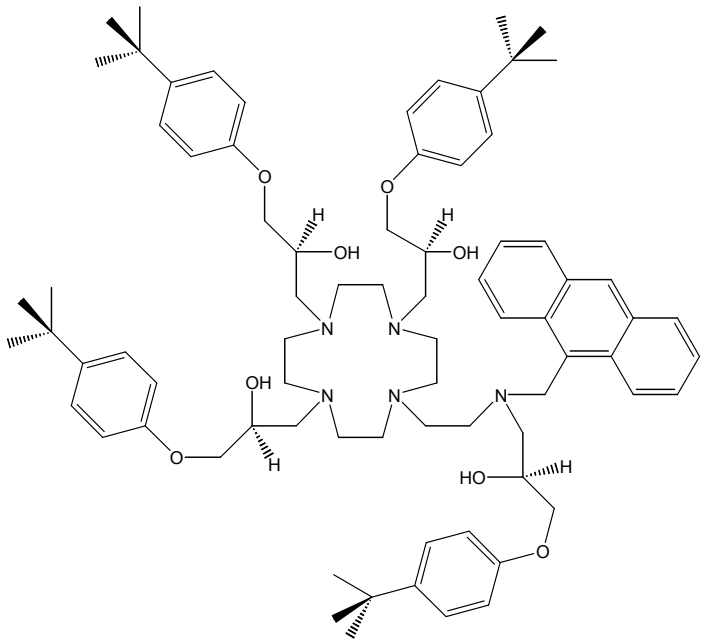


194

172 (0.910 mg, 0.9 mmol) was dissolved in EtOH (11 cm^3) and cooled in ice. The stirring ice-cold solution was treated dropwise with 36% aqueous HCl (0.6 cm^3, 7.6 mmol) and allowed to continue stirring overnight. The solvent was then evaporated and the residue triturated with ether. The brown solid was collected by filtration and dried under vacuum (0.800 g, 94%), $[\alpha]_{589}^{298}$ = -42.15 (c 0.007, EtOH); (Found: C, 60.06; H, 7.13; N, 5.60. $C_{65}H_{94}Cl_5N_5O_{11}$ requires C, 60.11; H, 7.29; N, 5.39%); λ_{max}/nm (1,4-dioxane/H_2O) 389 (ε/dm^3 mol^{-1} cm^{-1} 6 720), 369 (7 415), 350 (5 160), 335 (2 846), 318 (sh) (1 463); δ_H(DMSO-d_6) 8.83 (1 H, s, Anth*H*), 8.70 (2 H, br s, Anth*H*), 8.18 (2 H, d, *J* 7 Hz, Anth*H*), 7.59 (4 H, m, Anth*H*), 7.06 (6 H, br s, Ar*H*), 6.85 (7 H, d, *J* 8.2 Hz, Ar*H*), 6.53 (3 H, br s, Ar*H*), 5.66 (2 H, br s, -O*H*), 4.8-2.6 (55 H, br m, -N*H*, -O*H*, -C*H*- & -CH_2-), 2.21 (12 H, s, -CH_3); δ_C(DMSO-d_6) 156.2 (4 C, Ar, *ipso*), 131.8 (1 C, Anth, *ipso*), 130.9 (2 C, Anth, *ipso*), 129.8 (8 C, Ar), 129.6 (4 C, Ar), 129.5 (2 C, Anth, *ipso*), 129.3 (2 C, Anth), 128.7 (1 C, Anth),

127.6 (2 C, Anth), 125.5 (2 C, Anth), 124.8 (2 C, Anth), 114.4 (6 C, Ar), 114.2 (2 C, Ar), 70.5 (1 C, O*C*H_2), 69.8 (3 C, O*C*H_2), 64.9 (2 C, methine), 64.0 (2 C, methine), 58.0 (1 C, exo-*C*H_2N), 56.0 (5 C, exo-*C*H_2N), 50.4 (2 C, cyclen*C*H_2), 50.0 (2 C, cyclen*C*H_2), 48.5 (2 C, cyclen*C*H_2), 48.0 (2 C, cyclen*C*H_2), 46.0 (1 C, Anth*C*H_2), 20.1 (4 C, -*C*H_3).

1-((*N*-(2-(-9-anthracenylmethyl)(*N*-(2*S*)-(-)-2-hydroxy-3-[(4'-*tert*-butyl)phenoxy] propyl)aminoethyl))-4,7,10-tris((2*S*)-(-)-2-hydroxy-3-[4'-*(tert*-butyl)phenoxy propyl)-1,4,7,10-tetraazacyclododecane, ((*S*)-abthbppc), 173.

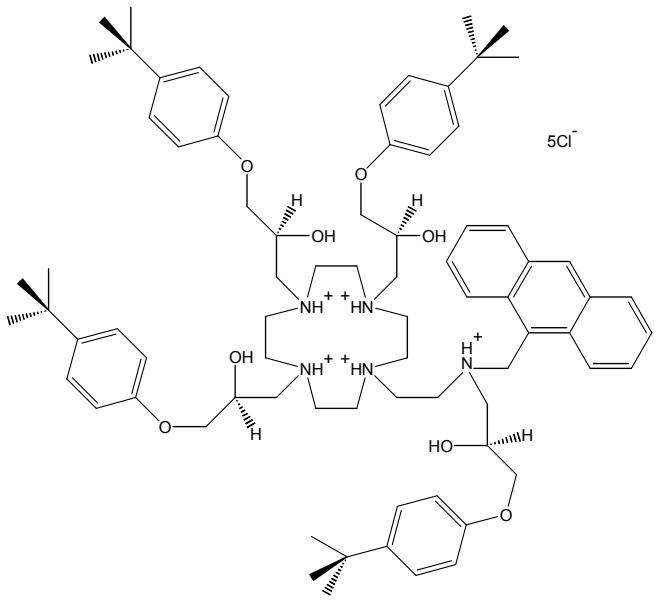


173

131 (0.268 mg, 0.7 mmol) was dissolved in dry EtOH (20 cm^3) and stirred. (2*S*)-(+)-3-[4'-(*tert*-butyl)phenoxy]-1,2-epoxy propane, **137**, (0.541 g, 2.6 mmol) was added in EtOH (20 cm^3). The reaction mixture was refluxed for 10 d, whilst monitoring by TLC (CH_2Cl_2/hexane, 9:1). Upon loss of starting material the reaction was cooled to RT, filtered and the filtrate was evaporated to leave a reddish oil, **173** (0.700 g, 86%), $[\alpha]_{589}^{298}$ = -30.5 (c 0.012, MeCN); λ_{max}/nm (20% aqueous 1,4-dioxane) 388.6 nm (ε/dm^3 mol^{-1} cm^{-1} 7 753), 368.5 (8 159), 350.2 (5 350), 334.1 (2

786), 319.0 (sh) (1444); $\delta_H(CD_3CN)$ 8.51 (2 H, d, *J* 5.8 Hz, Anth*H*), 8.43 (1 H, d, *J* 5.8 Hz, Anth*H*), 7.99 (2 H, d, *J* 6.4 Hz, Anth*H*), 7.45 (4H, br s, Anth*H*), 7.4-7.1 (8 H, m, Ar*H*), 7.0-6.4 (8 H, m. Ar*H*), 4.62 (4 H, br s, -O*H*), 4.50-1.80 (42 H, br m, -C*H*- & -CH_2-) 1.27 (36 H, br s, -CH_3); $\delta_C(CD_3CN)$ 157.7 (3 C, Ar, *ipso*), 157.5 (1 C, Ar, *ipso*), 144.3 (4 C, Ar, ipso), 135.3 (2 C, Anth, *ipso*), 132.4 (2 C, Anth, *ipso*), 131.4 (1 C, Anth, *ipso*), 130.0 (2 C, Anth), 128.6 (2 C, Anth), 127.8 (1 C, Anth), 127.2 (6 C, Ar), 127.0 (2 C, Ar), 126.1 (2 C, Anth), 124.5 (2 C, Anth), 118.3 (4 C, Ar), 115.0 (4 C, Ar), 72.5 (1 C, O*C*H_2), 71.3 (1 C, O*C*H_2), 70.5 (1 C, O*C*H_2), 70.2 (1 C, O*C*H_2), 69.8 (1 C, methine), 68.6 (1 C, methine), 67.3 (1 C, methine), 67.2 (1 C, methine), 66.6 (1 C, exo-N*C*H_2), 64.1 (1 C, exo-*C*H_2N), 61.5 (1 C, exo-*C*H_2N), 58.8 (1 C, exo-*C*H_2N), 57.7 (1 C, exo-*C*H_2N), 54.4 (1 C, exo-*C*H_2N), 52.9 (2 C, cyclen*C*H_2), 52.6 (2 C, cyclen*C*H_2), 52.3 (2 C, cyclen*C*H_2), 51.7 (2 C, cyclen*C*H_2), 47.4 (1 C, Anth*C*H_2), 34.7 (4 C, -*C*(CH_3)), 31.8 (12 C, -*C*H_3).

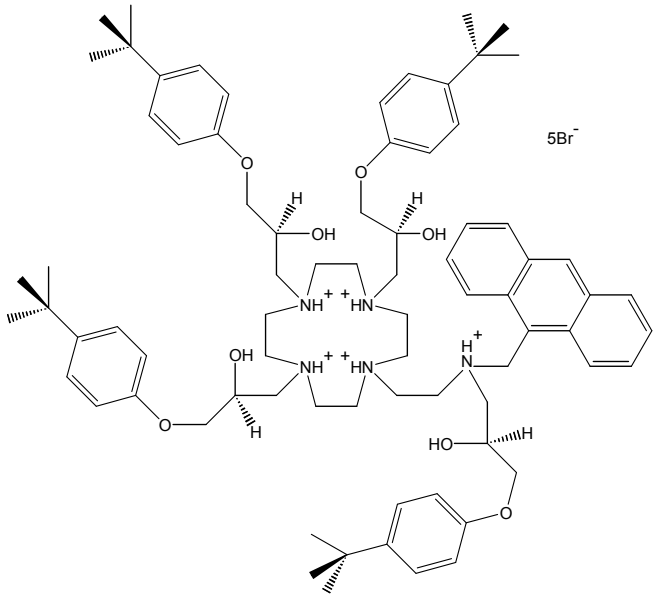
1-((*N*-(2-(-9-anthracenylmethyl)(*N*-(2*S*)-(-)-2-hydroxy-3-[(4'-*tert*-butyl)phenoxy] propyl)aminoethyl))-4,7,10-tris((2*S*)-(-)-2-hydroxy-3-[4'-*(tert*-butyl)phenoxy propyl)-1,4,7,10-tetraazacyclododecane.5HCl, ((*S*)-abthbppc.5HCl), (195).



195

A stirred ice-cold solution of **173** (0.601 g, 0.5 mmol) in EtOH (10 cm^3) as treated with 36% HCl (1 cm^3) and allowed to continue stirring for 1 h. The solvent was evaporated and the residue was triturated with ether. The light brown solid was collected by filtration and dried under vacuum. Yield: (0.466 g, 67%), $[\alpha]_{589}^{298}$ -29.3 (c 0.008, EtOH); λ_{max}/nm (20% aqueous 1,4-dioxane) 388 (ε/dm^3 mol^{-1} cm^{-1} 4 861), 369 (5 562), 350 (3 949), 334 (2 333), 319 (sh) (1 398); δ_H(DMSO-d_6) 8.83 (1 H, br s, Anth*H*), 8.71 (2 H, br s, Anth*H*), 8.19 (2 H, br s, Anth*H*), 7.62 (4 H, br s, Anth*H*), 7.26 (8 H, br s, Ar*H*), 6.90 (8 H, br s, Ar*H*), 6.0-2.4 (51 H, br m, -O*H* , -N*H*, -C*H*- & -CH_2-), 1.22 (36 H, br s, -C(CH_3)$_3$); δ_C(DMSO-d_6) 156.0 (4 C, Ar, *ipso*), 142.8 (4 C, Ar, *ipso*), 131.5 (1 C, Anth), 130.7 (2 C, Anth), 129.1 (2 C, Anth), 127.5 (2 C, Anth), 126.9 (2 C, Anth), 125.9 (8 C, Ar), 125.4 (2 C, Anth), 124.6 (2 C, Anth), 124.5 (1 C, Anth), 113.9 (8 C, Ar). 69.6 (4 C, O*C*H_2), 65.5 (1 C, methine), 64.8 (2 C, methine), 63.9 (1 C, methine), 59.0 (1 C, exo-C*H*$_2$N), 58.0 (2 C, exo-C*H*$_2$N), 55.9 (3 C, exo-*C*H_2N), 49.7 (6 C, cyclen*C*H_2), 48.0 (2 C, cyclenCH_2), 46.0 (1 C, Anth*C*H_2), 33.6 (4 C, -*C*(CH_3)$_3$), 31.2 (12 C, -C(*C*H_3)$_3$).

1-((*N*-(2-(-9-anthracenylmethyl)(*N*-(2*S*)-2-hydroxy-3-[(4'-*tert*-butyl)phenoxy] propyl)aminoethyl))-4,7,10-tris((2*S*)-2-hydroxy-3-[4'-(*tert*-butyl)phenoxy propyl)-1,4,7,10-tetraazacyclododecane.5HBr.H_2O, ((*S*)-abthbppc.5HBr.H_2O), (196).



196

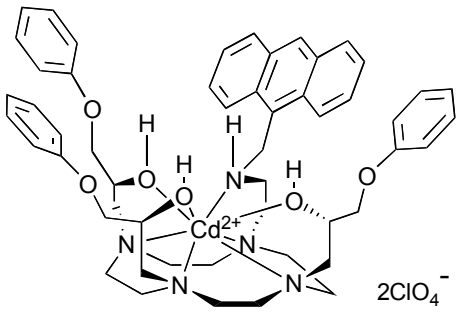
A stirred ice-cold solution of **173** (0.100 g, 0.1 mmol) in EtOH (5 cm^3) was treated with 48% HBr (100 μL) and allowed to continue stirring for 1h. The solvent was evaporated and the residue was triturated with ether. The light brown solid was collected by filtration and dried under vacuum. Yield: (0.094 g, 71%), (Found C, 55.80; H, 7.20; N, 4.15. $C_{77}H_{114}Br_5N_5O_9$ requires C, 55.94; H, 6.95; N, 4.24%); λ_{max}/nm (20% aqueous 1,4-dioxane) 388 (ε/dm^3 mol^{-1} cm^{-1} 4 861), 369 (5 562), 350 (3 949), 334 (2 333), 319 (sh) (1 398); δ_H(DMSO-d_6) 8.87 (1 H, s, Anth*H*), 8.61 (2 H, br s, Anth*H*), 8.21 (2 H, d, *J* 7.2 Hz, Anth*H*), 7.62 (4 H, br m, Anth*H*), 7.28 (8 H, br m, Ar*H*), 6.86 (8 H, br m, Ar*H*), 5.63 (4 H, br s, -O*H*), 4.80-2.60 (49 H, br m, -C*H*-, -N*H* & -CH_2-), 1.243 (36 H, br s, CH_3); δ_C(DMSO-d_6) 156.0 (4 C, Ar, *ipso*), 143.2 (4 C, Ar), 131.6 (2 C, Anth, *ipso*), 131.3 (2 C, Anth, *ipso*), 130.9 (1 C, Anth, *ipso*), 129.9 (2 C, Anth), 128.8 (2 C, Anth), 127.7 (2 C, Anth), 127.2 (1 C, Anth), 126.1 (6 C, Ar), 125.6 (2 C, Ar), 124.4 (2 C, Anth), 114.0 (8 C, Ar), 70.0 (1 C,

O*C*H$_2$), 69.9 (2 C, O*C*H$_2$), 69.8 (1 C, O*C*H$_2$), 68.5 (1 C, methine), 67.0 (1 C, methine), 66.0 (1 C, methine), 64.8 (1 C, methine), 60.0 (1 C, exo-*C*H$_2$N), 58.0 (1 C, exo-*C*H$_2$N), 56.0 (2 C, exo-*C*H$_2$N), 55.6 (2 C, exo-*C*H$_2$N), 50.1 (4 C, cyclen*C*H$_2$), 49.8 (4 C, cyclen*C*H$_2$), 45.5 (1 C, Anth*C*H$_2$), 33.8 (4 C, -C(*C*H$_3$)$_3$), 31.3 (12 C, -C(*C*H$_3$)$_3$).

6.7.4. Synthesis of receptor complexes.

Safety Note: Perchlorate salts are potentially explosive. Although no problems were encountered, extreme care should be taken when handling these substances.

[Cd((*S*)-athppc)](ClO$_4$)$_2$.2H$_2$O, (4).

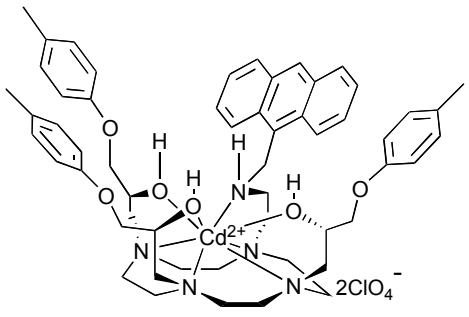


4

A solution of cadmium(II) perchlorate hexahydrate (0.117 g, 0.3 mmol) in EtOH (2.3 cm^3) was added dropwise over 5 min to a refluxing solution of **146** (0.214 g, 0.3 mmol) in EtOH (7 cm^3). A sticky white precipitate formed instantly. The suspension was left refluxing for 1 h, then cooled to RT. The solvent was concentrated by rotatory evaporation and then trituration of the residue with ether produced a light cream powder. This was collected by filtration, washed with ice-cold water (1 cm^3), and dried under vacuum to give the product (0.203 g, 70%),

$[\alpha]_{589}^{298}$ = -60.1 (c 0.003, EtOH); (Found C, 51.85; H, 5.98; N, 5.60. $C_{52}H_{69}CdCl_2N_5O_{16}$ requires C, 51.90; H, 5.78; N, 5.89%); Λ_M 175 Ω^{-1} cm^2 mol^{-1} (1 x 10^{-3} mol dm^{-3}, DMF) (2:1);; λ_{max}/nm (CH_3CN/H_2O 4:1) 388.6 (ε/dm^3 mol^{-1} cm^{-1} 6 300), 368.5 (6 540), 350.4 (4 056), 334.6 (1 739), 319.6 (sh) (643); λ_{max}/nm (20% aqueous 1,4-dioxane) 387.7 (ε/dm^3 mol^{-1} cm^{-1} 6 733), 367.7 (7 202), 349.8 (4 700), 333.3 (2 619), 318.3 (sh)(1 190); δ_H(DMSO-d_6) 8.8-8.2 (3 H, br m, Anth*H*), 8.14 (2 H, br d, Anth*H*), 7.58 (4 H, br m, Anth*H*), 7.30 (6 H, br s, Ph*H*), 6.95 (9 H, br s, Ph*H*), 5.05 (3 H, br m, -O*H*), 4.60-2.00 (38 H, br m, -N*H*-, -C*H*- & -CH_2-); δ_C(CD_3CN) 159.4 (3 C, Ph, *ipso*), 132.4 (1 C, Anth, *ipso*), 130.6 (6 C, Ph), 130.3 (2 C, Anth, *ipso*), 129.6 (2 C, Anth, *ipso*), 127.7 (2 C, Anth), 126.7 (1 C, Anth), 126.3 (2 C, Anth), 124.9 (2 C, Anth), 124.4 (2 C, Anth), 122.4 (1 C, Ph), 122.3 (2 C, Ph), 115.8 (2 C, Ph), 115.6 (4 C, Ph), 70.6 (1 C, O*C*H_2), 70.2 (1 C, O*C*H_2), 69.6 (1 C, O*C*H_2), 66.1 (1 C, methine), 65.6 (1 C, methine), 64.8 (1 C, methine), 60.0 (1 C, exo-CH_2N), 57.0 (1 C, exo-CH_2NH), 55.3 (2 C, exo-CH_2N), 54.7 (1 C, exo-CH_2N), 53.3 (1 C, cyclen*C*H_2), 52.7 (1 C, cyclen*C*H_2), 51.2 (1 C, cyclen*C*H_2), 51.0 (1 C, cyclen*C*H_2), 50.4 (1 C, cyclen*C*H_2), 50.2 (1 C, cyclen*C*H_2), 49.8 (1 C, cyclen*C*H_2), 49.1 (1 C, cyclen*C*H_2), 45.8 (1 C, AnthCH_2).

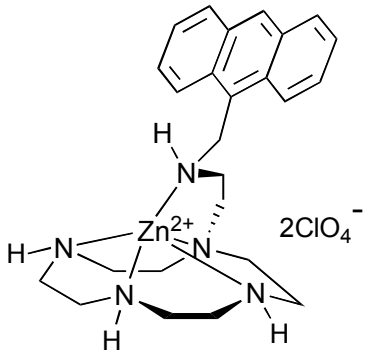
[Cd((*S*)-athmppc)]$(ClO_4)_2.4H_2O$, (5).



5

A solution of cadmium(II) perchlorate hexahydrate (0.183 g, 0.4 mmol) in EtOH (3.5 cm^3) was added dropwise over 5 minutes to a refluxing solution of **170** (0.302 g, 0.4 mmol) in EtOH (10 cm^3). A sticky white precipitate formed instantly. The suspension was left refluxing for 1 h, then cooled to RT. The solvent was evaporated and then trituration of the residue with ether produced a light cream powder, which was collected by filtration, washed with ice-cold water (1 cm^3), and dried under vacuum, to yield **5** (0.261 g, 50%); (Found: C, 51.90; H, 6.50; N, 5.60. $C_{55}H_{79}CdCl_2N_5O_{18}$ requires C, 51.60; H, 6.20; N, 5.50%); λ_{max}/nm (1,4-dioxane/H_2O 4:1) 386.4 (ε/dm^3 mol^{-1} cm^{-1} 6 464), 366.4 (6 960), 348.6 (4 564), 332.6 (2 274), 319.5 (sh) (1 008); δ_H(DMSO-d_6) 8.78-8.30 (3 H, br m, Anth*H*), 8.10 (2 H, m, Anth*H*), 7.53 (4 H, m, Anth*H*), 7.26 (4 H, m, Ar*H*), 6.90 (8 H, m, Ar*H*), 5.00 (3 H, br m, -O*H*), 4.7-2.1 (38 H, br m, -N*H*-, -C*H*- & -CH_2-), 2.00 (9 H, -CH_3); δ_C(DMSO-d_6) 156.4 (3 C, Ar, *ipso*), 131.4 (2 C, Anth, *ipso*), 130.7 (2 C, Anth, *ipso*), 130.0 (6 C, Ar), 129.5 (3 C, Ar, *ipso*), 129.2 (1 C, Anth, *ipso*), 127.6 (1 C, Anth), 127.2 (2 C, Anth), 125.9 (2 C, Anth), 125.2 (2 C, Anth), 121.8 (2 C, Anth), 115.3 (6 C, Ar), 71.3 (3 C, O*C*H_2), 68.0 (1 C, methine), 67.0 (1 C, methine), 66.0 (1 C, methine), 61.8 (1 C, exo-CH_2N), 59.8 (1 C, exo-CH_2NH), 58.3 (1 C, exo-CH_2-N), 57.0 (1 C, exo-CH_2N), 56.0 (1 C, exo-CH_2N), 53.9 (2 C, cyclen*C*H_2), 54.0 (2 C, cyclen*C*H_2), 52.8 (2 C, cyclen*C*H_2), 51.3 (2 C, cyclen*C*H_2), 45.9 (1 C, Anth*C*H_2), 20.2 (3 C, -*C*H_3).

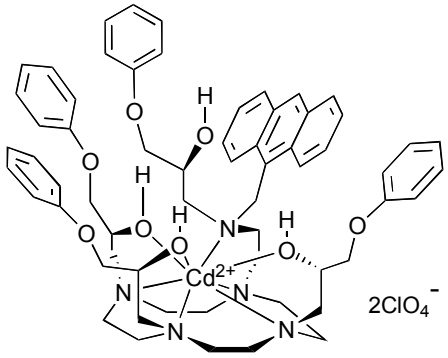
[Zn(antac-12)]$(ClO_4)_2.H_2O$, (176).



176

Zinc (II) perchlorate hexahydrate (0.240 g, 0.6 mmol) in dry ethanol (10 cm^3) was added dropwise over 5 min to a refluxing solution of **131** (0.230 g, 0.6 mmol) in dry EtOH (30 cm^3). The solution went cloudy on addition of the salt and a brown oily residue formed. The solution was refluxed for a further 1 h, then allowed to cool to RT. The trituration of the oily residue in cold ethanol induced a fine pale brown solid. Filtration under N_2 and washing with ice-cold EtOH (4 x 5cm^3) yielded **176** (0.200 g, 53%), (Found: C, 43.48; H, 9.93; N, 5.05. $C_{25}H_{37}Cl_2N_5O_9Zn$ requires: C, 43.65; H, 10.18; N, 5.42%); λ_{max}/nm (CH_3CN/H_2O 4:1) 388nm (ε/dm^3 mol^{-1} cm^{-1} 5 969), 368 (6 562), 350 (4 794), 334 (3 049), 319 (2 134); ν_{max}/cm^{-1} 3483, 3291, 3058, 2929, 2881, 1653, 1449, 742, 625 (KBr); δ_H(DMSO-d_6) 8.74 (1 H, s, Anth*H*), 8.57 (2 H, d, *J* 8.0 Hz, Anth*H*), 8.19 (2 H, d, *J* 8.0 Hz, Anth*H*), 7.67 (4 H, m, Anth*H*), 5.12 (2 H, s, H_2O), 4.48 (2 H, s, AnthCH_2), 4.25 (1 H, br s, N*H*), 3.40 (7 H, br s, exo-CH_2N & N*H*), 3.1-2.2 (16 H, br m, cyclenCH_2); δ_C(DMSO-d_6) 131.0 (2 C, Anth, *ipso*), 130.3 (2 C, Anth, *ipso*), 129.3 (2 C, Anth), 128.8 (1 C, Anth, *ipso*), 128.0 (1 C, Anth, *ipso*), 127.0 (2 C, Anth), 125.4 (2 C, Anth), 124.3 (2 C, Anth), 50.6 (1 C, exo-CH_2N), 49.6 (1 C, exo-CH_2NH), 45.9 (1 C, AnthCH_2), 44.7 (2 C, cyclenCH_2), 44.0 (2 C, cyclenCH_2), 43.5 (2 C, cyclenCH_2), 42.7 (2 C, cyclenCH_2).

[Cd((*S*)-apthppc)](ClO$_4$)$_2$.5H$_2$O, (6).

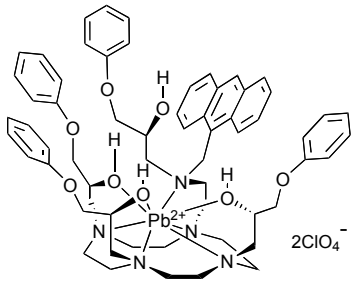


6

A solution of cadmium(II) perchlorate hexahydrate (0.106 g, 0.3 mmol) in dry EtOH (5 cm^3) was added dropwise over 5 min to a refluxing solution of **171** (0.232 g, 0.2 mmol) in dry EtOH (5 cm^3). A sticky white precipitate formed instantly. The suspension was left refluxing for 1 h, then cooled to RT. The solvent was concentrated by rotatory evaporation and then the residue was triturated with ether to produce a light cream powder. This was collected by filtration, washed with ice-cold water (1 cm^3) and dried under vacuum to give the product, **6**, (0.252 g, 83%), (Found: C, 51.85; H, 5.98; N, 4.97. $C_{61}H_{85}CdCl_2N_5O_{21}$ requires C, 52.05; H, 6.09; N, 4.98%); λ_{max}/nm (20% aqueous 1,4-dioxane) 388.7 (ε/dm^3 mol^{-1} cm^{-1} 9 481), 368.7 (9 935), 350.3 (6 423), 334.4 (3 364), 320.2 (sh) (1 763); δ_H(DMSO-d$_6$) 8.61 (3 H, br s, Anth*H*), 8.09 (2 H, br s, Anth*H*), 7.52 (4 H, br s, Anth*H*), 7.28 (8 H, br m, Ph*H*), 7.0-6.4 (12 H, br m, Ph*H*), 5.1-1.8 (46 H, br m, -O*H*, -C*H*- & -C*H*$_2$-); δ_C(DMSO-d$_6$) 158.5 (1 C, Ph, *ipso*), 158.2 (3 C, Ph, *ipso*), 131.0 (2 C, Anth), 130.9 (1 C, Anth), 130.3 (8 C, Ph), 129.6 (2 C, Anth), 127.6 (2 C, Anth), 126.8 (1 C, Anth), 126.1 (2 C, Anth), 125.1 (2 C, Anth), 124 (2 C, Anth), 121.3 (3 C, Ph), 121.0 (1 C, Ph), 115.6 (8 C, Ph), 71.0 (1 C, O*C*H$_2$), 70.6 (1 C, O*C*H$_2$), 70.3 (2 C, O*C*H$_2$), 67.7 (1 C, methine), 67.0 (1 C, methine), 66.2 (1 C, methine), 64.4 (1 C, methine), 61.5 (1 C, exo-*C*H$_2$N), 60.0 (1 C, exo-*C*H$_2$N), 57.5 (1 C, exo-*C*H$_2$N), 56.1 (1 C, exo-*C*H$_2$N),

54.2 (1 C, exo-*C*H$_2$N), 52.0 (1 C, exo-*C*H$_2$N), 51.3 (2 C, cyclen*C*H$_2$), 50.2 (2 C, cyclen*C*H$_2$), 49.0 (2 C, cyclen*C*H$_2$), 48.2 (2 C, cyclen*C*H$_2$), 44.8 (1 C, Anth-*C*H$_2$-N).

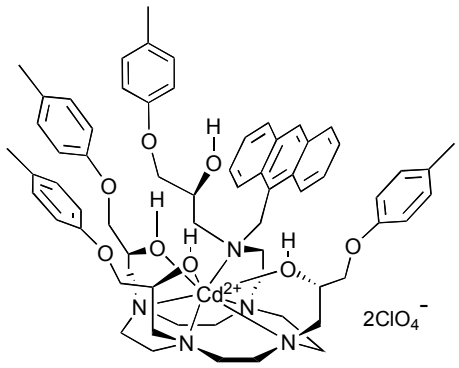
[Pb((*S*)-apthppc)](ClO$_4$)$_2$.2H$_2$O, (177).



177

A solution of lead(II) perchlorate hexahydrate (0.088 g, 0.1 mmol) in EtOH (5 cm^3) was added dropwise over 5 min to a refluxing solution of **171** (0.129 g, 0.1 mmol) in EtOH (5 cm^3). A sticky white precipitate formed instantly. The suspension was left refluxing for 1h, then cooled to RT. The solvent was evaporated and the residue triturated with ether to produce a light cream powder. This was collected by filtration, washed with water (1 cm^3) and dried under vacuum to give **177** (0.169 g, 63%), (Found: C, 48.31; H, 5.50; N, 5.54. $C_{52}H_{69}Cl_2N_5O_{16}Pb$ requires C, 48.11; H, 5.36; N, 5.39%); δ_H(CD_3OD) 8.63 (3 H, m, Anth*H*), 8.12 (2 H, m, Anth*H*), 7.54 (4 H, m, Anth*H*), 7.32 (8 H, br m, Ph*H*), 7.00-6.60 (12 H, br m, Ph*H*), 5.0-1.7 (46 H, br m, -O*H*, -C*H*- & -C*H*$_2$-); δ_C(CD_3CN) 160.3 (4 C, Ph, *ipso*), 132.8 (2 C, Anth, *ipso*), 132.2 (2 C, Anth, *ipso*), 130.6 (8 C, Ph), 129.0 (1 C, Anth, *ipso*), 128.5 (1 C, Anth), 127.7 (2 C, Anth), 126.8 (2 C, Anth), 126.1 (2 C, Anth), 124.9 (2 C, Anth), 122.4 (4 C, Ph), 115.8 (8 C, Ph), 71.5 (2 C, O*C*H$_2$), 70.7 (2 C, O*C*H$_2$), 68.5 (1 C, methine), 66.5 (2 C, methine), 65.9 (1 C, methine), 62.0-50.0 (m, 14 C, *C*H$_2$), 45.8 (2 C, Anth*C*H$_2$).

[Cd((*S*)-amthmppc)]$(ClO_4)_2.2Et_2O.2H_2O$, (7).

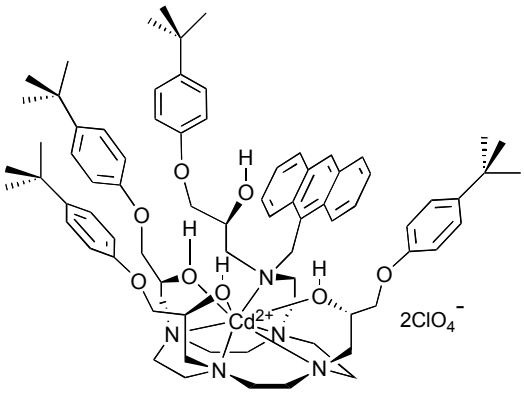


7

A solution of cadmium(II) perchlorate hexahydrate (1.15 g, 3.0 mmol) in EtOH (20 cm^3) was added dropwise over 5 min to a refluxing solution of **172** (1.91 g, 2.5 mmol) in EtOH (63 cm^3). A sticky white precipitate formed instantly. The suspension was left refluxing for 1 h, then cooled to RT. The solvent was evaporated and trituration of the residue with ether produced a light cream powder. This was collected by filtration, washed with water (1 cm^3) and dried under vacuum to give **7** (1.83 g, 74%), (Found: C, 56.09; H, 7.09; N, 4.20. $C_{73}H_{107}CdCl_2N_5O_{20}$ requires C, 56.28; H, 6.92; N, 4.50%); λ_{max}/nm (20% aqueous 1,4-dioxane) 388.7 (ε dm^3 mol^{-1} cm^{-1} 9 596), 368.7 (10 120), 350.3 (6 678), 334.1 (3 644), 320.4 (sh) (2 038); δ_H(DMSO-d_6) 8.90 (3 H, br s, Anth*H*), 8.39 (2 H, br s, Anth*H*), 7.81 (4 H, br s, Anth*H*), 7.35 (8 H, br m, Ar*H*), 7.4-6.6 (8 H, br m, Ar*H*), 5.6-2.0 (50 H, br m, -O*H*, -C*H*-, -CH_2- & CH_2 of ether), 2.30 (12 H, br s, -CH_3), 1.10 (6 H, m, CH_3 of ether); δ_C(DMSO-d_6) 156.5 (2 C, Ar, *ipso*), 156.2 (2 C, Ar, *ipso*), 131.1 (2 C, Anth, *ipso*), 131.0 (2 C, Anth, *ipso*), 130.0 (8 C, Ar), 129.1 (4 C, Ar), 128.6 (1 C, Anth, *ipso*), 127.6 (2 C, Anth), 127.1 (1 C, Anth), 126.2 (2 C, Anth), 125.2 (2 C, Anth), 114.5 (8 C, Ar), 72.0 (2 C, O*C*H_2), 70.0 (1 C, O*C*H_2), 69.1 (1 C, O*C*H_2), 67.9 (2 C, methine), 66.0 (2 C, methine), 65.0 (1 C, exo-*C*H_2N), 64.8 (1 C, exo-*C*H_2N), 64.2 (1 C, exo-*C*H_2N), 62.5 (1 C, exo-*C*H_2N), 57.5 (4 C, CH_2 of ether), 57.0 (1 C, exo-*C*H_2N), 53.0

(1 C, exo-*C*H_2N), 51.4 (2 C, cyclen*C*H_2), 50.5 (2 C, cyclen*C*H_2), 49.4 (2 C, cyclen*C*H_2), 48.0 (2 C, cyclen*C*H_2), 45.1 (1 C, Anth*C*H_2), 20.2 (4 C, -C*H*$_3$), 15.3 (4 C, C*H*$_3$ of ether).

[Cd((*S*)-abthbppc)]$(ClO_4)_2$.CH_3CN, (8).



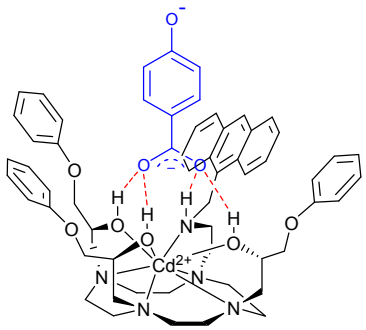
8

A solution of cadmium(II) perchlorate hexahydrate (0.183 g, 0.4 mmol) in dry EtOH (3.5 cm^3) was added dropwise over 5 min to a refluxing solution of **173** (0.350 g, 0.4 mmol) in dry EtOH (11 cm^3). A sticky white precipitate formed instantly. The suspension was left refluxing for 1 h, then cooled to RT. The solvent was evaporated and then trituration of the residue with ether produced a light cream powder. This was collected by filtration, washed with ice-cold MeCN, followed by drying under vacuum, to give **8** (0.272 g, 45%); (Found C, 60.06; H, 7.13; N, 5.60. $C_{79}H_{110}CdCl_2N_6O_{16}$ requires: C, 59.94; H, 7.00; N, 5.31%.); λ_{max}/nm (20% aqueous 1,4-dioxane) 388.2 (ε/dm^3 mol^{-1} cm^{-1} 4 865), 367.8 (5 565), 349.9 (3 950), 333.2 (2 335), 317.9 (sh)(1 400); δ_H(CD_3CN); 8.96 (3 H, br s, Anth*H*), 8.52 (2 H, br s, Anth*H*), 7.97 (4 H, br s, Anth*H*), 7.29 (8 H, br s, Ar*H*), 6.8-6.4 (8 H, br s, Ar*H*), 4.9-2.0 (46 H, br m, -O*H*, -C*H*- & -CH_2-), 2.30 (36 H, br s, -CH_3), 1.96 (3 H, s, CH_3 of CH_3CN); δ_C(CD_3CN); 157.7 (3 C, Ar, *ipso*), 157.5 (1 C, Ar, *ipso*), 144.0 (4 C, Ar,

ipso), 135.6 (2 C, Anth, *ipso*), 135.3 (1 C, Anth, *ipso*), 132.4 (2 C, Anth, *ipso*), 131.7 (1 C, Anth), 130.0 (2 C, Anth), 128.0 (2 C, Anth), 127.8 (2 C, Anth),127.2 (8 C, Ph), 60 (2 C, Anth), 118.3 (1 C, CN of CH_3CN), 116.1 (2 C, Ar), 115.0 (6 C, Ar), 72.5 (1 C, O*C*H_2), 71.3 (3 C, O*C*H_2), 69.8 (1 C, methine), 67.8 (1 C, methine), 67.3 (1 C, methine), 66.0 (1 C, methine), 58.7 (2 C, exo-*C*H_2N), 58.2 (2 C, exo-*C*H_2N), 57.7 (2 C, exo-*C*H_2N), 54.4 (1 C, cyclen*C*H_2), 52.9 (1 C, cyclen*C*H_2), 52.3 (1 C, cyclen*C*H_2), 52.0 (1 C, cyclen*C*H_2), 51.6 (1 C, cyclen*C*H_2), 50.5 (1 C, cyclen*C*H_2), 49.4 (1 C, cyclen*C*H_2), 47.4 (1 C, cyclen*C*H_2), 45.2 (1 C, Anth*C*H_2), 34.7 (4 C, -*C*$(CH_3)_3$), 30.2 (12 C, -C*H*$_3$), 1.8 (C*H*$_3$ of CH_3CN).

6.7.5. Isolation of inclusion complexes.

[Cd((*S*)-athppc)(4-carboxylatephenolate)].EtOH.2H_2O, (197).

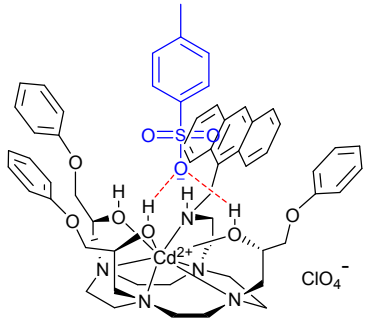


197

p-Hydroxybenzoic acid disodium salt, **17**, (11.5 mg, 0.06 mmol) was added to a boiling solution of **4** (50.0 mg, 0.06 mmol) in CH_3CN (5 cm^3). The suspension was heated under reflux for 2 h, then allowed to cool to RT. The solvent was evaporated, then the residue was triturated with ether (5 cm^3). The solid was filtered off, then boiled in EtOH (5 cm^3) to removed the occluded sodium perchlorate. The

product, **197**, remained as a powder (53.0 mg, 70%), (Found: C, 61.60; H, 6.73; N, 5.88. $C_{61}H_{79}CdN_5O_{12}$ requires C, 61.74; H, 6.71; N, 5.90%); Λ_M 89 Ω^{-1} cm^2 mol^{-1} (1 x 10^{-3} mol dm^{-3}, DMF)(1:1)[244]; λ_{max}/nm (20% aqueous 1,4-dioxane) 388.2 nm (ε/dm^3 mol^{-1} cm^{-1} 4 160), 368.0 (4 470), 350.0 (2 850), 333.3 (1 260), 318.2 (470); δ_H(CD_3CN) 8.79-8.40 (3 H, br m, Anth*H*), 8.14 (2 H, br d, Anth*H*), 7.80 (2 H, br s, guest*H*), 7.58 (4 H, br m, Anth*H*), 7.30 (6 H, br s, Ph*H*), 6.95 (9 H, br s, Ph*H*), 6.73 (2 H, br s, guest*H*), 5.05 (3 H, br m, -O*H*), 4.63 (1 H, br s, EtO*H*), 4.6-2.0 (40 H, br m, -N*H*-, -C*H*-, -CH_2- & CH_3CH_2OH), 1.06 (3 H, br s, CH_3CH_2OH); δ_C(CD_3CN) 171.1 (1 C, guestCO_2^-), 159.4 (3 C, Ph, *ipso*), 159.3 (1 C, guest*C*-O^-, *ipso*), 132.4 (2 C, Anth, *ipso*), 130.7 (2 C, guest*C*), 130.6 (6 C, Ph), 130.3 (2 C, Anth, *ipso*), 130.0 (1 C, Anth, *ipso*), 129.6 (2 C, Anth), 129.4 (1 C, guest*C*, *ipso*),128.2 (2 C, Anth), 126.7 (1 C, Anth), 126.4 (2 C, Anth), 124.9 (2 C, Anth), 122.3 (3 C, Ph), 115.7 (3 C, Ph), 115.6 (3 C, Ph), 113.9 (2 C, guest*C*), 70.6 (2 C, OCH_2), 70.2 (1 C, OCH_2), 67.5 (2 C, methine), 66.6 (1 C, methine), 60.5 (1 C, exo-CH_2N), 57.0 (1 C, exo-CH_2NH), 56.1 (1 C, CH_3CH_2OH), 55.3 (1 C, exo-CH_2N), 54.0 (1 C, exo-CH_2N), 53.3 (1 C, exo-CH_2N), 52.0 (2 C, cyclenCH_2), 51.0 (2 C, cyclenCH_2), 50.2 (2 C, cyclenCH_2), 49.1 (2 C, cyclenCH_2), 45.8 (1 C, AnthCH_2), 18.5 (1 C, CH_3CH_2OH).

[Cd((*S*)-athppc)(4-toluenesulfonate)](ClO_4).EtOH, (198).



198

p-Toluene sulfonic acid sodium salt, **30**, (15.8 mg, 0.06 mmol) was added to a boiling solution of **4** (50.0 mg, 0.06 mmol) in CH_3CN (5 cm^3). The suspension was heated under reflux for 2 h, then allowed to cool to RT. The solvent was evaporated, then the residue was triturated with ether (5 cm^3). The solid was filtered off, then boiled in EtOH (5 cm^3) to removed the occluded sodium perchlorate. The product, **198**, was isolated as a powder (60.0 mg, 79%), (Found: C, 57.13; H, 6.31; N, 5.69. $C_{61}H_{78}CdClN_5O_{14}S$ requires C, 57.01; H, 6.12; N, 5.45%); Λ_M 62 Ω^{-1} cm^2 mol^{-1} (1 x 10^{-3} mol dm^{-3}, DMF) (1:1)[244]; λ_{max}/nm (20% aqueous 1,4-dioxane) 388.6 nm (ε/dm^3 mol^{-1} cm^{-1} 5 720), 368.7 (6 120), 350.7 (4 050), 334.6 (2 260), 320.0 (sh)(1 120); δ_H(CD_3CN) 8.8-8.4 (3 H, br m, Anth*H*), 8.14 (2 H, br d, Anth*H*), 7.78 (2 H, br s, guest*H*), 7.58 (4 H, br m, Anth*H*), 7.34 (2 H, br s, guest*H*), 7.30 (6 H, br s, Ph*H*), 6.95 (9 H, br s, Ph*H*), 5.05 (3 H, br m, -O*H*), 4.65 (1 H, br s, EtO*H*), 4.60-2.00 (43 H, br m, -N*H*-, -C*H*-, -CH_2-, guestCH_3 & CH_3CH_2OH), 1.06 (3 H, br s, CH_3CH_2OH); δ_C(CD_3CN) 159.4 (3 C, Ph, *ipso*), 144.9 (1 C, guest*C*, *ipso*), 133.1 (1 C, guest*C*, *ipso*), 132.4 (2 C, Anth, *ipso*), 130.7 (1 C, Anth, *ipso*), 130.6 (6 C, Ph), 129.9 (2 C, guest*C*), 129.6 (2 C, Anth, *ipso*), 128.2 (2 C, Anth), 127.9 (2 C, guest*C*), 126.7 (1 C, Anth), 126.4 (2 C, Anth), 124.9 (2 C, Anth), 124.3 (2 C, Anth), 122.3 (3 C, Ph), 115.7 (6 C, Ph), 70.6 (2 C, OCH_2), 70.2 (1 C, OCH_2), 66.6 (2 C, methine), 66.0 (1 C, methine), 65.0 (1 C, exo-CH_2N), 60.5 (1 C, exo-CH_2N), 57.1 (1 C, exo-CH_2N), 56.1 (1 C, CH_3CH_2OH), 54.0 (1 C, exo-CH_2NH), 53.3 (1 C, exo-CH_2N), 52.0 (2 C, cyclenCH_2), 51.1 (2 C, cyclenCH_2), 50.6 (2 C, cyclenCH_2), 49.0 (2 C, cyclenCH_2), 45.8 (1 C, AnthCH_2), 21.6 (1 C, guestCH_3), 18.5 (1 C, CH_3CH_2OH).

Appendix A Binding Constant determination procedures

A.1. Outline of theory used in determination of binding constants using ^{1}H NMR titration experiments.[243]

To obtain the binding constants, *K*, for the host-guest combinations that have been reported the chemical shift data obtained in the ^{1}H NMR titration experiments outlined in **Chapter 3** were subjected to a non-linear least squares curve fitting analysis. This was achieved using a procedure written by Dr. A. K. W. Stephens of the Flinders University of South Australia, utilizing the Igor data analysis software.[282]

The binding constant *K*, which is sought, pertains to the following equilibrium:

$$\mathbf{H + G} \overset{K}{\rightleftharpoons} \mathbf{HG} \qquad \textbf{(1.1)}$$

where $K = \mathbf{HG} / \mathbf{H} \times \mathbf{G}$

H is the free binary receptor complex (host) concentration, and **G** is the free guest concentration. **HG** is the concentration of the ternary (host-guest) complex.

The total amount of host present ($\mathbf{H_T}$) is given by the formula:

$$\mathbf{H_T = HG + H} \qquad \textbf{(1.2)},$$

Likewise, $\mathbf{G_T}$ is the total concentration of guest present in solution, and corresponds to:

$$\mathbf{G_T = HG + G} \qquad \textbf{(1.3)},$$

Therefore, equation (1.1) can be rewritten using equations 1.2 and 1.3 as:

$$K = \frac{\mathbf{G_T - G}}{\mathbf{(H_T - G_T + G) \times G}} \qquad \mathbf{(1.4)}$$

Rearranging equation 1.4 gives equation 1.5:

$$K\mathbf{G}^2 + \mathbf{G}(K\mathbf{H_T} - K\mathbf{G_T} + 1) - \mathbf{G_T} = 0 \qquad \mathbf{(1.5)},$$

which can be solved to give the concentration of G by using equation 1.6:

$$\mathbf{G} = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \qquad \mathbf{(1.6)},$$

where $a = K$
$b = KH_T - KG_T + 1$
$c = -G_T$

Equation 1.5 can be related to the observed ^{1}H NMR guest chemical shifts through the use of equation 1.7:

$$\delta_{calc} = \delta_G\chi_G + \delta_{HG}\chi_{HG} \qquad \mathbf{(1.7)},$$

where: $\chi_G = G/G_T$, mole fraction of unbound guest
χ_{HG} = mole fraction of bound guest = $1 - \chi_G$
δ_G = chemical shift of unbound guest
δ_{HG} = chemical shift of bound guest

An estimate of G at each H_T value is obtained by the computer subjecting a trial value of *K* and known values of H_T and G_T to equation 1.6. Equation 1.7 then allows the determination of preliminary values for δ_{calc}, at each H_T, for a trial value of δ_{HG}. The computer program then iteratively varies *K* and δ_{HG}, until the best match of δ_{calc} at each H_T with δ_{obs} at that H_T is obtained.

Several sample titration curves are shown in Figure A.1. These simulations show the variation in guest chemical shift (δ_{obs}) for illustrative values of the binding constant (log*K*), and indicate the difference in the shape of these curves as the binding constant varies. A chemical shift difference of 1.0 ppm between bound and complexed guest is assumed, and the guest concentration is set at 1×10^{-3} mol dm^{-3}, which was the concentration used in the experimental work described in this thesis.

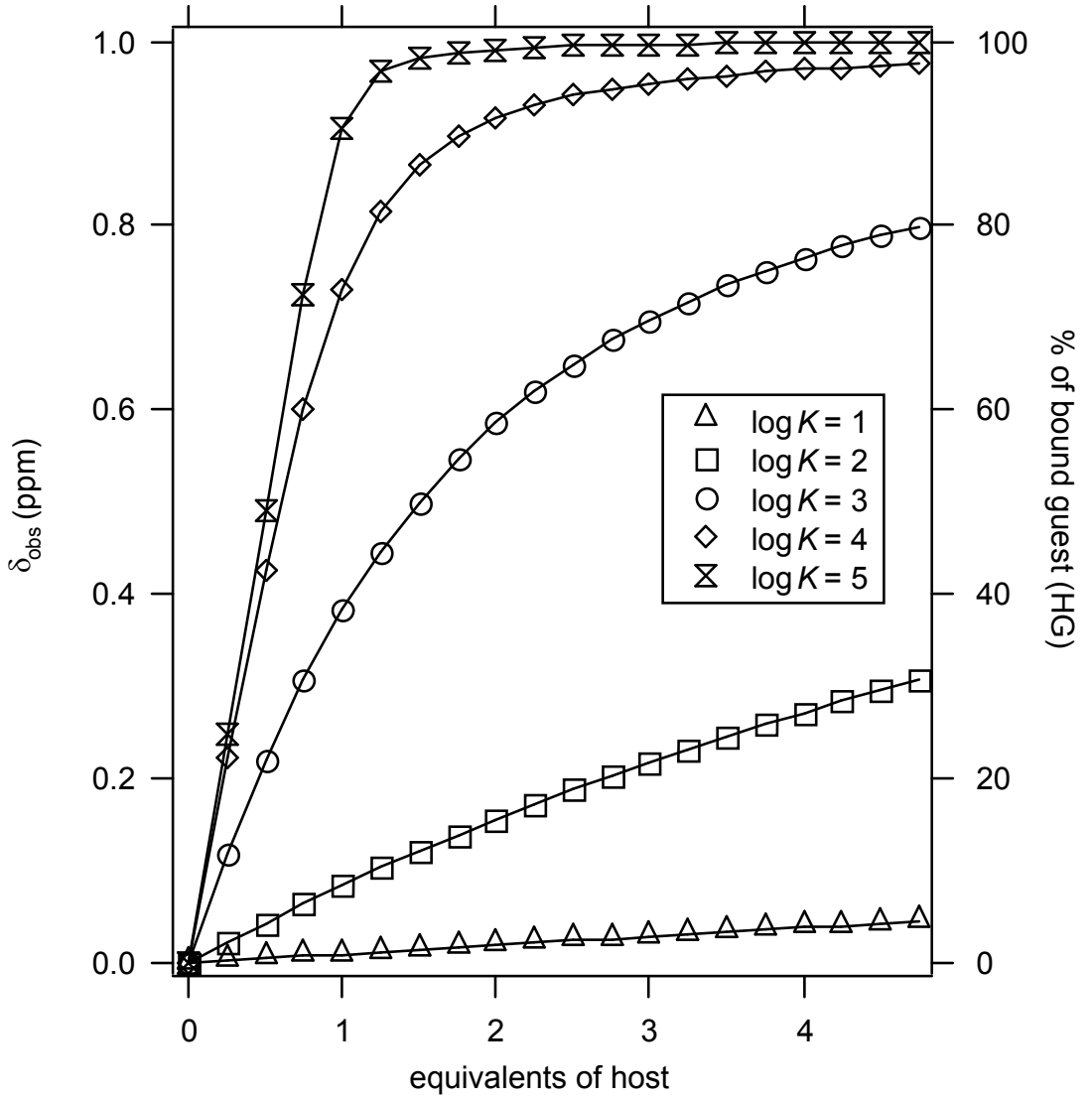


Figure A.1: Titration curve simulations for different log*K* values at an assumed guest concentration of 1 x 10^{-3} mol dm^{-3} and a chemical shift difference of 1.0 ppm between free and bound guest. The typical titration points correspond to the guest chemical shift (left Y-axis) at each host concentration. The curves represent the changing percentage of bound guest (HG) (right Y-axis) as a function of increasing host concentration.

A.2. Outline of theory used in determination of binding constants using fluorescence titration experiments.

To obtain the binding constants, *K*, for the host-guest combinations that have been reported the molar fluorescence data obtained in the fluorescence titration experiments outlined in **Chapter 5** were subjected to a non-linear least squares curve

fitting analysis. This was achieved using a modification of the procedure written by Dr. A. K. W. Stephens of the Flinders University of South Australia, utilizing the Igor data analysis software.[282]

The binding constant *K*, which is sought pertains to the following equilibrium:

$$\mathbf{H} + \mathbf{G} \underset{}{\overset{K}{\rightleftharpoons}} \mathbf{HG} \qquad \textbf{(2.1)}$$

where $K = \mathbf{HG} / \mathbf{H} \times \mathbf{G}$

H is the free binary receptor complex (host) concentration, and **G** is the free guest concentration. **HG** is the concentration of the ternary (host-guest) complex.

The total amount of host present ($\mathbf{H_T}$) is given by the formula:

$$\mathbf{H_T} = \mathbf{HG} + \mathbf{H} \qquad \textbf{(2.2)}$$

Likewise, $\mathbf{G_T}$ is the total concentration of guest present in solution, and corresponds to:

$$\mathbf{G_T} = \mathbf{HG} + \mathbf{G} \qquad \textbf{(2.3)}$$

Therefore, equation (2.1) can be rewritten using equations 2.2 and 2.3 as:

$$K = \frac{\mathbf{H_T} - \mathbf{H}}{(\mathbf{G_T} - \mathbf{H_T} + \mathbf{H}) \times \mathbf{H}} \qquad \textbf{(2.4)}$$

Rearranging equation 2.4 gives equation 2.5:

$$K\mathbf{H}^2 + \mathbf{H}(K\mathbf{G_T} - K\mathbf{H_T} + 1) - \mathbf{H_T} = 0 \qquad \textbf{(2.5)}$$

which can be solved to give the concentration of G by using equation 2.6:

$$\mathbf{H} = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \qquad \textbf{(2.6)},$$

where $a = K$
$b = KG_T - KH_T + 1$
$c = -H_T$

Equation 2.5 can be related to the observed fluorescence changes in the following way:

In the titration experiment the observed fluorescence intensity, F_{obs}, is dependent on the molar fluorescence intrinsic to the fluorophores used, and the concentration of the fluorophores present, as described by equation 2.7.

$$F_{obs} = \varepsilon_H H + \varepsilon_G G + \varepsilon_{HG} HG \qquad \textbf{(2.7)}$$

where: ε_H = molar fluorescence of unbound host
ε_G = molar fluorescence of unbound guest
ε_{HG} = molar fluorescence of bound host

For the cases where the guest is non-fluorescent, or that $\varepsilon_G = 0$, then:

$$F_{obs} = \varepsilon_H[H] + \varepsilon_{HG}[HG] \qquad \textbf{(2.8)}$$

consider now that: $F_{obs} = \varepsilon_{obs}[H_T]$

then $\varepsilon_{obs}[H_T] = \varepsilon_H[H] + \varepsilon_{HG}[HG]$ **(2.9)**

thus $\varepsilon_{obs} = \varepsilon_H([H]/[H_T]) + \varepsilon_{HG}([HG]/[H_T])$ **(2.10)**

which becomes: $\varepsilon_{obs} = \varepsilon_H\chi_H + \varepsilon_{HG}\chi_{HG}$ **(2.11)**

which shows that ε_{obs} = the weighted mean molar fluorescence of H and HG (ε_H and ε_{HG} respectively) where the weightings are their respective mole fractions, H/H_T and HG/H_T, respectively.

Since these mole fractions change during the titrations, then so does ε_{obs}, providing that $\varepsilon_H \neq \varepsilon_{HG}$ at λ_{obs} (the observed emission wavelength common to H and HG).

An estimate of H at each G_T value is obtained by the computer subjecting a trial value of *K* and known values of G_T and H_T to equation 2.6. Equation 2.11 then allows the determination of preliminary values for ε_{obs}(calculated), at each G_T, for a trial value of ε_{HG}. The computer program then iteratively varies *K* and ε_{HG}, until the best match of ε_{obs}(calculated) at each G_T with ε_{obs} at that G_T is obtained.

Several sample titration curves are shown in Figure A.2. These simulations show the variation in host molar fluorescence (ε_{obs}) for illustrative values of the

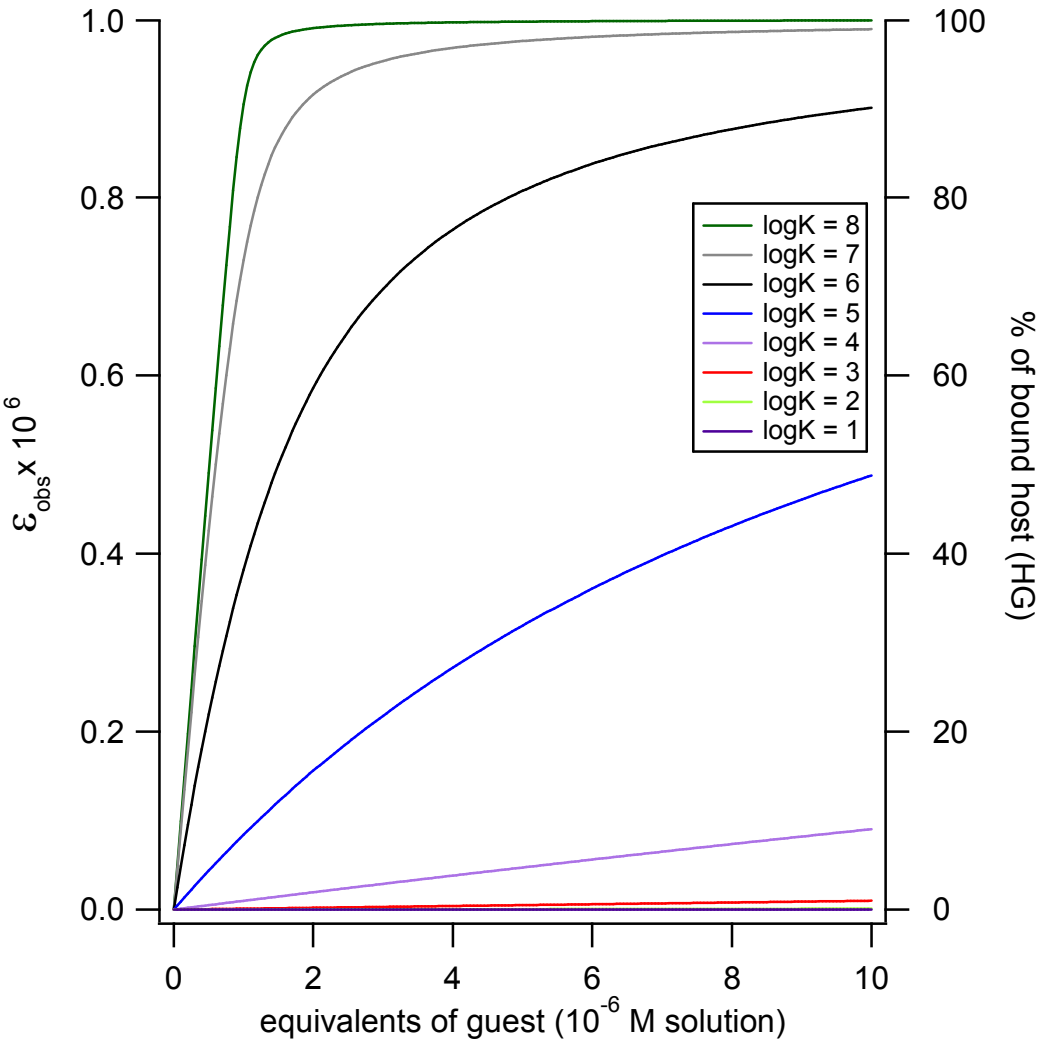


Figure A.2: Titration curve simulations for different log*K* values at an assumed guest concentration of $1x10^{-6}$ M, and a molar fluorescence change of $1x10^{6}$ between free and bound host. The curves represent the changing percentage of bound host (HG) (right Y-axis) as a function of increasing guest concentration.

binding constant (log*K*), and indicate the difference in the shape of these curves as the binding constant varies. A molar fluorescence change of $1x10^{6}$ between H and HG is assumed, and the host concentration is set at $1x10^{-6}$ M, which was a concentration used in the experimental work described in this thesis.

A.3. Outline of theory used in determination of binding constants using absorbance titration experiments.

The process described in A.2 for determining binding constants from fluorescence titrations can also be used for determining binding constants from UV-visible absorption titrations. The only changes are that ε is no longer referring to molar fluorescence but molar absorption, and that the term fluorescence (F) is replaced by absorbance (A), such that:

$$A_{obs} = \varepsilon_H[H] + \varepsilon_{HG}[HG] \qquad \textbf{(3.1)}$$

and

$$\varepsilon_{obs} = \varepsilon_H\chi_H + \varepsilon_{HG}\chi_{HG} \qquad \textbf{(3.2)}$$

where ε = molar extinction coefficient (molar absorptivity).

Equation 3.2 is the same as that in A.2, allowing the same non-linear least squares regression analysis procedure to be used.

Several sample titration curves are shown in Figure A.3. These simulations show the variation in host molar absorptivity (ε_{obs}) for illustrative values of the binding constant (log*K*), and indicate the difference in the shape of these curves as the binding constant varies. A molar absorptivity change of $1x10^{3}$ between H and HG is assumed, and the host concentration is set at $1x10^{-4}$ M, which was the concentration used in the experimental work described in this thesis.

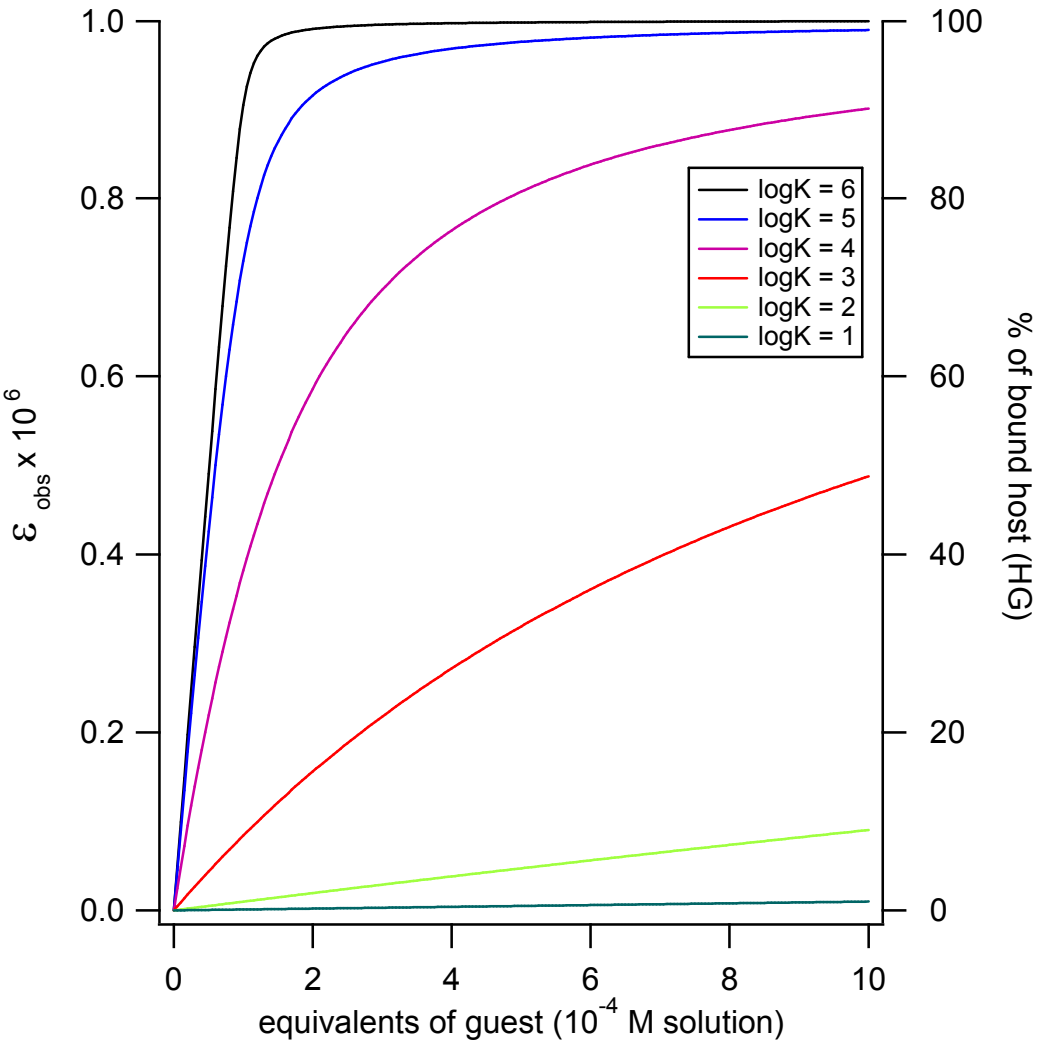


Figure A.3: Titration curve simulations for different log*K* values at an assumed guest concentration of $1x10^{-4}$ M, and a molar absorptivity change of $1x10^{3}$ between free and bound host. The curves represent the changing percentage of bound host (HG) (right Y-axis) as a function of increasing guest concentration.

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