The Design of Artificial Receptors for Complexation and Controlled Aggregation

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The design of artificial receptors for complexation and controlled aggregation

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Simple synthetic receptors have been developed that function via directed hydrogen bonding interactions in highly competitive solvents. Strong binding of this type in polar solvents may be due to a number of factors including favourable secondary hydrogen bonding interactions between the carboxylate and urea, the use of charged H-bond acceptors, an inefficient solvation of the closely spaced H-bond donor sites in the urea, and an entropically favourable release of solvent and/or counterion molecules on complex formation. We also demonstrate that these types of interactions can be used to induce, both in solution and the solid state, discrete $2+2$ aggregates stabilized by a network of hydrogen bonds.

1. Introduction

In recent years there has been intense activity in the design of synthetic molecules capable of enzyme-like recognition and binding of small substrates (Diederich 1991; Hamilton 1991; Rebek 1991). Two fundamental approaches have been taken. The first has generally involved non-directional binding forces (such as solvophobic, π-stacking and dispersion interactions) in water-soluble cyclophane frameworks (Diederich 1991; Odashima *et al.* 1985). This approach has led to extremely important and quantitative insights into the hydrophobic effect and the enthalpic and entropic contributions of solvent reorganization to binding (Smithrud *et al.* 1991). However, the weakly orientated nature of the binding interactions has resulted in only moderate substrate selectivity beyond the shape recognition permitted by the cavity. In nature such selectivity is a prerequisite for the chiral recognition and catalytic activity of enzymes and is achieved by hydrogen bonding and electrostatic interactions. The second major approach to artificial receptors makes use of these more directional interactions by incorporating several hydrogen bonding groups into a cleft or cavity of defined geometry (Hamilton 1991). The resulting hosts form strong and selective complexes to those substrates with complementary shape and hydrogen bonding characteristics. In these cases, however, the binding free energy is solvent dependent, diminishing to zero as the polarity of the medium increases, due to the strong solvation of the hydrogen bonding sites. A central goal in contemporary molecular recognition research must be to develop receptors that effectively use directed hydrogen bonding interactions in competitive solvents. Success will likely require a combining of strong (possibly charged) hydrogen bonding groups with hydrophobic sites capable not only of effective apolar association with the substrate but also of protecting the polar sites from full solvation.

Two essential strategies have been taken to the design of hydrogen bonding

receptors. The first has involved incorporating the simple functional groups found in enzyme active sites such as carboxylic acids, carboxamides, etc., into molecular frameworks. To direct several of these functional groups onto a binding site it is necessary to choose a framework containing a 'U-turn', as illustrated in **1**. The Kemp's triacid derivatives of Rebek (1991) (**2**), the Trőger's base receptors of Wilcox (1989) (**3**) and the molecular tweezers of Zimmerman (1989) (**4**) are all examples of this approach. A second strategy is to use heterocyclic analogs of these simple functional groups which have the same hydrogen bonding characteristics but are easily functionalized and incorporated into macrocyclic or cleft frameworks, as in **5**. The recently reported receptors from our group (e.g. **6**) (Chang *et al.* 1991) and those of Kelly (**7**) (1987), Thummel (Hedge 1990), Bell (1988) and Anslyn (Huang *et al.* 1992) all use this strategy.
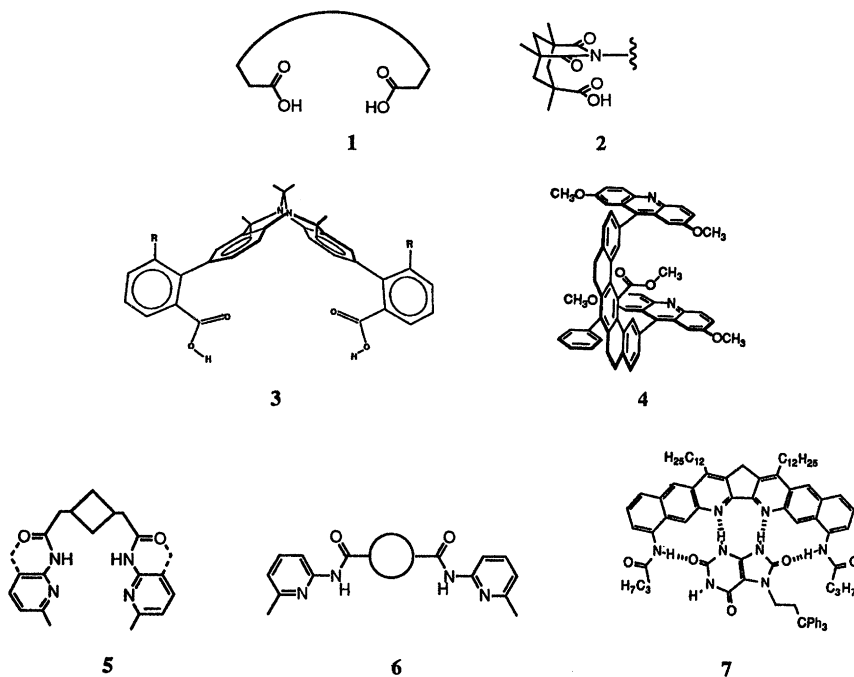

What can be learned from or achieved with artificial receptor molecules and why is their study important? This is a critical question at the heart of all contemporary molecular recognition research and the answer is manifold. While the study of the natural system may answer how an enzyme functions, the study of small synthetic analogues can help us understand why it works. Synthetic receptors provide an opportunity to study the intrinsic chemistry of molecular recognition and transition state stabilization away from the complex environment of the biopolymer. Small molecules provide considerably greater detail and precision in the study of their structure and of the thermodynamics and kinetics of their binding interactions. Modifications can be easily made to the position, orientation and nature of the binding groups as well as the solvent environment leading to new insights into the underlying chemistry of the biological process. Understanding the why of an enzyme function gives us not only increased mechanistic understanding but also the ability to reproduce the reactivity in synthetic systems. Successful development of such artificial receptors that function in polar solvents will find important applications in

the design of molecule selective sensors and in the use of hosts to interfere with physiological processes.

2. Recognition of barbiturate substrates

Linking two 2,6-diaminopyridine units through an isophthalate spacer (as in **8**) creates a cavity that is complementary to both the shape and hydrogen bonding features of barbiturates. An X-ray structure of one receptor (**9**) shows a preorganized cavity with all six hydrogen bonding sites directed into the centre of the ring. Complexation can be easily followed using ^{1}H NMR. Addition of one equivalent of diethylbarbituric acid to a $CDCl_3$ solution of **8** caused large downfield shifts in the amide proton resonances characteristic of intermolecular hydrogen bonding. A significant shift was also seen in the 2H-proton of the isophthaloyl spacer indicating its position close to the bound substrate and confirming the structure of the complex shown in **10**. Monitoring the changes in the ^{1}H NMR as a function of substrate concentration leads to a binding curve that can be analysed by a Scatchard plot or by nonlinear regression analysis to give the association constant. The large values of K_a measured for **10** (*ca.* 10^5–10^6 M^{-1}) are indicative of strong complexation via six hydrogen bonds (Chang *et al.* 1991). An X-ray structure (**11**) showed the position of the barbiturate in the centre of the cavity as well as details of the distances (2.9, 3.0 and 3.2 Å) and orientations for the three types of the hydrogen bonds in the complex. By removing different functional groups in the receptor and substrate we have carried out a systematic investigation of the strength of different hydrogen bonds in the complex and have found an average value for ΔG° of 1.2–1.5 kcal mol^{-1}.

8

9

10

11
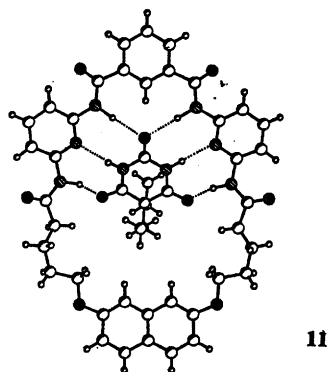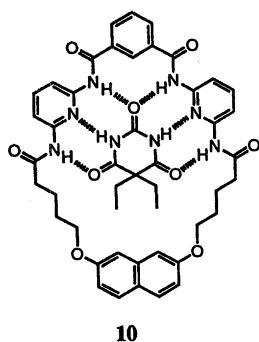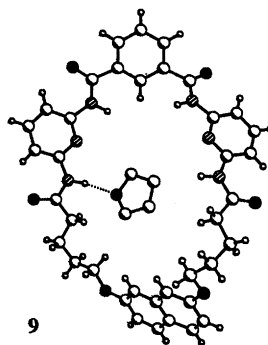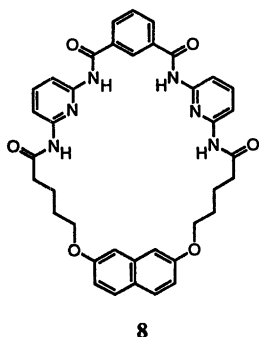
3. Dicarboxylic acid recognition

An extremely simple receptor for dicarboxylic acid substrates can be prepared from the reaction of 2-amino-6-methylpyridine with terephthaloyl dichloride. The resulting diamide **12** contains two acylaminopyridine groups linked by an easily variable, rigid spacer. An X-ray structure of the uncomplexed host **13** shows an unproductive conformation with the two binding groups in a trans orientation due to intermolecular interactions in the crystal. However, there is a low barrier to rotation about the phenyl-CO bond and the host can readily undergo a conformational change to position the binding sites on the same side of the receptor. Again, ^{1}H NMR is invaluable in the study of these simple diacid hosts. Addition of a complementary diacid to a CDCl$_3$ solution of **12** leads to large downfield shifts of the amide-NH resonances consistent with the formation of a tetrahydrogen bonded complex of the type shown in **14**. Selectivity is dependent on the spacer length and its fit to the length of the diacid; strongest complexes being formed between **12** and adipic or glutaric acid ($K_a \approx 10^4$–10^5 M^{-1}). An X-ray structure of the complex to adipic acid is shown in **15** and supports the formation of four hydrogen bonds between receptor and substrate. That this conformation is also taken up in solution was confirmed by the observation of an intermolecular NOE between the central CH$_2$ groups on the adipic acid guest and the aromatic hydrogens on the terephthalic acid spacer in **12** (Garcia-Tellado 1990).

12   **13**

14   **15**
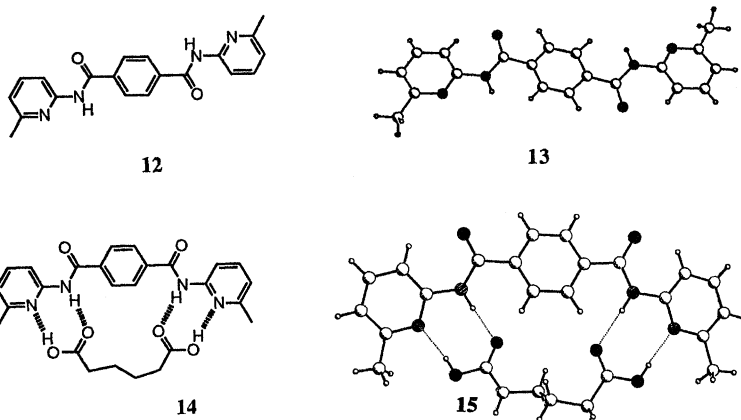
These hosts are only effective in non-polar organic solvents and they are characterized by large unfavourable entropies of binding. In 5% THF/CDCl$_3$ the complex between receptor **12** and glutaric acid shows a significant reduction in stability (at 295 K, $K_a = 6.4 \pm 1.4 \times 10^2$ M^{-1}, $\Delta G_{295} = -3.8$ kcal mol^{-1}) compared with the corresponding complex in CDCl$_3$ ($K_a \geqslant 6.0 \times 10^4$ M^{-1}). The weak solvation of the hydrogen bonding sites leads to a strongly enthalpic driving force for binding ($\Delta H = -7.9$ kcal mol^{-1}, $\Delta S = -14$ cal mol^{-1} K^{-1}) with a substantially negative entropy term due to the loss of translational and rotational motion inherent in bimolecular association and also the freezing of bond rotations in the complex (Adrian & Wilcox 1991; Williams *et al.* 1991). Addition of dimethylsulfoxide to **12**: glutaric acid leads to strong solvation of the hydrogen bond donor sites and an almost complete disruption of the binding (Fan *et al.* 1993).

Table 1. *Thermodynamic parameters for binding of bis-urea receptors to carboxylates in d_6-DMSO*

receptor	substrate	K_a at 293 K M^{-1}	ΔG_{293} kcal mol^{-1}	ΔH kcal mol^{-1}	ΔS cal mol^{-1} K^{-1}
19[a]	glutarate[b]	$6.4 \pm 0.4 \times 10^2$	-3.7	-3.8	-0.1
20[c]	adipate[b]	$3.3 \pm 0.3 \times 10^2$	-3.4	-2.8	$+2.1$
21[c]	glutarate[b]	$6.5 \pm 0.2 \times 10^2$	-3.8	-4.8	-3.5
DiMeUrea[d]	acetate[e]	45 ± 3	-2.2	-2.7	-1.7

[a] [Receptor] $= 8.0 \times 10^{-4}$ M; [acid] $= 8.0 \times 10^{-4}$–2.0×10^{-2} M. [b] Used as bis-tetrabutylammonium salt. [c] [Receptor] $= 6.0 \times 10^{-4}$ M; [acid] $= 6.0 \times 10^{-4}$–1.0×10^{-2} M. [d] [Receptor] $= 1.0 \times 10^{-2}$ M; [acid] $= 1.0 \times 10^{-2}$–1.0×10^{-1} M. [e] Used as tetramethylammonium salt.
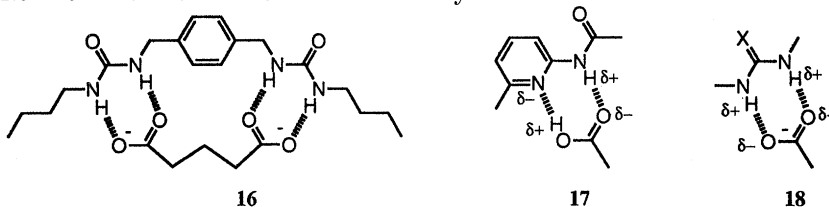
The binding site disposition in **12** can be improved by placing both hydrogen bond donors on the host to create a bis-urea receptor for dicarboxylate derivatives, as in **16**. This has the advantage of creating four favourable secondary hydrogen bonding interactions (Jorgensen & Pranata 1990; Murray & Zimmerman 1992) in **18** (as opposed to four unfavourable in **17**) and of increasing the strength of the primary interaction through the use of charged hydrogen bond acceptors (Fersht 1987). The simple receptor **19** can be prepared in one step by reaction of 1,4-bis(aminomethyl)benzene with butyl isocyanate, followed by treatment with aqueous HCl to remove unreacted starting materials (77% yield). Analogous routes have allowed the synthesis of a range of bis-urea receptors, **19**–**21**, with different spacings between the binding sites.
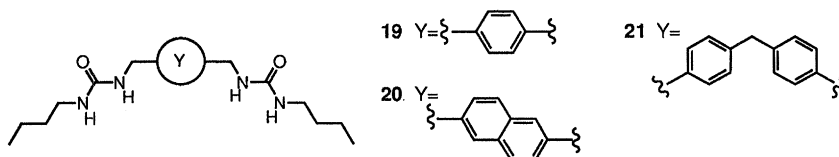
All the receptors were soluble in d_6-DMSO and their interaction with the bis-tetrabutylammonium salts (TBA) of dicarboxylic acids was conveniently followed by ^{1}H NMR. Addition of one equivalent of glutarate (TBA) to a DMSO solution of **19** (1.0×10^{-2} M) gave large downfield shifts of both the inner and outer urea-NH resonances (1.1 and 1.2 ppm), consistent with the formation of a tetrahydrogen bonded complex, as in **16**. A Job's plot gave a maximum at mole ratio 0.5 confirming the 1:1 stoichiometry of the complex (Connors 1987). Similar results were obtained with hosts **20** and **21**. Association constants were measured by nonlinear regression analysis of the binding curves (Wilcox 1990) and are collected in table 1. In contrast to the bis-amide complex of **12**:glutaric acid, efficient binding is seen between the bis-urea receptors and dicarboxylates in DMSO. The presence of two binding sites is critical as seen by the weak association between N,N′-dimethylurea and tetramethylammonium acetate.

Insights into the origins of binding came from variable temperature measurements of thermodynamic parameters (table 1). The binding enthalpy (ΔH) for **16** in DMSO
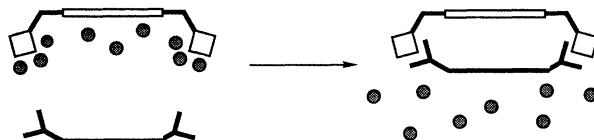
Figure 1. A schematic of solvent displacement on binding a substrate.

is reduced (compared with **12**:glutaric acid in 5% THF/CDCl$_3$) due to increased solvation, but is still significant enough to drive association. This underlines the advantage of positioning H-bond donor sites close together in the host where, for steric reasons, they are less effectively solvated than when widely spaced. This effect is clearly seen in the shift of the NH resonances, on going from CDCl$_3$ to d$_6$-DMSO, which is smaller for the ureas (1.65 ppm) than for the 2-acylaminopyridines (2.33 ppm). The entropy of association (ΔS) for **16** in DMSO is close to zero despite the inherent entropic cost of bimolecular association and the greater flexibility of the xylylene spacer, compared with the terephthaloyl group in **12**. Binding must therefore involve an entropically favourable component to counterbalance these unfavourable factors. This may derive from two sources. The first is displacement by the dicarboxylate substrate of the two or more DMSO molecules solvating the urea-NH sites (as shown schematically in figure 1). The resultant randomization of solvent would lead to an increase in entropy and similar effects have been seen with aqueous solvation of H-bonding sites (Adrian & Wilcox 1991; Williams *et al.* 1991). The second, related factor concerns the substrate which may be present as an associated ion pair in DMSO. Binding of the dicarboxylate dianion into the bis-urea cavity will lead to the entropically favourable dissociation of the two tetrabutylammonium cations (Stauffer *et al.* 1990).

Further gains in binding energy can be achieved by increasing the acidity of the H-bond donor sites in the receptor (Hamilton & Little 1990; Neder & Whitlock 1990). Thiourea (pK_a = 21.0) is more acidic than urea (pK_a = 26.9) (Bordwell *et al.* 1988) and reaction of 1,4-bis(aminomethyl)benzene with butyl isothiocyanate readily provides a bis-thiourea receptor capable of binding to glutarate, as in **22**. All NMR evidence is consistent with a complex of structure **22** and the K_a in d$_6$-DMSO ($1.0 \pm 0.2 \times 10^4$ M^{-1}) shows a 15-fold increase over **16**.

Alkylguanidinium groups are even more acidic (p$K_a \approx 14$) and provide additional electrostatic stabilization from the complementary charge in the hydrogen bonding sites. Reaction of 1,4-bis(aminomethyl)benzene with methyl ethylenethiouronium iodide gave a bis-alkylguanidinium receptor **23** which can bind to glutarate, as in **24** (Dietrich *et al.* 1979; Müller *et al.* 1988; Ariga & Anslyn 1992). Binding was monitored by following the upfield shifts of the benzylic proton resonances and was further supported by the observation of an NOE between the aromatic and glutarate protons. The association constant for the complex between **23** (as its bis-iodide salt) and glutarate-TBA in d$_6$-DMSO was too large ($K_a > 5 \times 10^4$ M^{-1}) to be measured by ^{1}H NMR. Addition of D$_2$O to the DMSO solution led to the expected decrease in K_a, due to increased solvation of the carboxylate groups. However, binding was still clearly observable at 12% D$_2$O/DMSO ($K_a = 8.5 \pm 1.5 \times 10^3$ M^{-1}) and even 25% D$_2$O/DMSO ($K_a = 4.8 \pm 2.5 \times 10^2$ M^{-1}). This strategy of manipulation of both the location and charge of hydrogen bonding sites can convert a synthetic receptor that functioned only in non-polar solvents into one that binds its substrate strongly in highly competitive solvents.
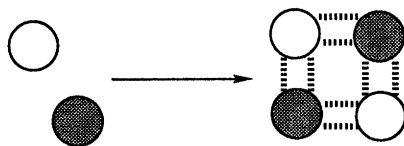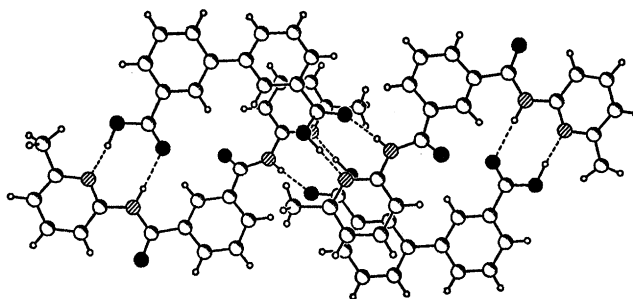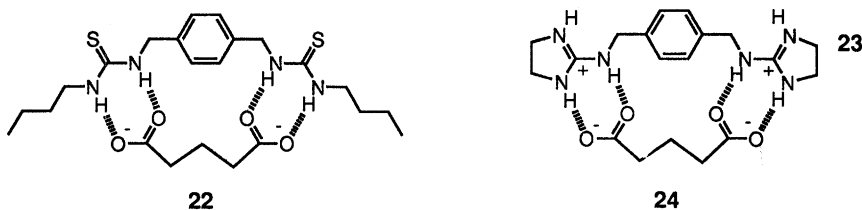
Figure 2.

Figure 3. Top view of the X-ray structure of the complex **28a**.

4. Controlled aggregation

The above studies have been directed at the formation of discrete 1:1 complexes. However, the bidentate interaction between carboxylic acids and 2-acylamino-pyridines provides a strong and versatile binding motif for the formation of both cyclic (Garcia-Tellado *et al.* 1990) or polymeric (Garcia-Tellado *et al.* 1991) hydrogen bonded aggregates. Careful choice of rigid or semi-rigid spacers between the binding groups can lead to cyclic 2+2 (as in figure 2), as opposed to 1:1 aggregates (Zimmerman 1992). Complexes of this type fall into the little-studied intermediate molecular mass region $(1-20 \times 10^3 \text{ Da})$ between small molecule and polymeric supramolecular structures that is of much importance in the development of nanometer scale structures (Lindsey 1991; Whitesides *et al.* 1992). Isophthaloyl receptor **25** is unable to form a 1:1 complex with biphenyl-3,3′-dicarboxylic acid **26a** due to the conformational restrictions of the two components. Instead the 1:1 complex **27** contains open carboxylic acid and acylaminopyridine sites that point in the same direction and can dimerize to 2+2 aggregate **28a**. Crystallization of an equimolar mixture of **25** and biphenyl-3,3′-dicarboxylic acid **26a** from a THF/hexanes solution showed the formation of a 2+2 aggregate (figure 3) made up of a cyclic arrangement of alternating diacid-diamide units linked by eight hydrogen bonds (N···O distances, 2.70–2.93 Å). The overall shape is that of a figure-of-eight with the outwardly directed aminopyridine–carboxylic-acid region stacking at a distance of *ca.* 3.5 Å to the corresponding region on the opposite side of the macrocycle.
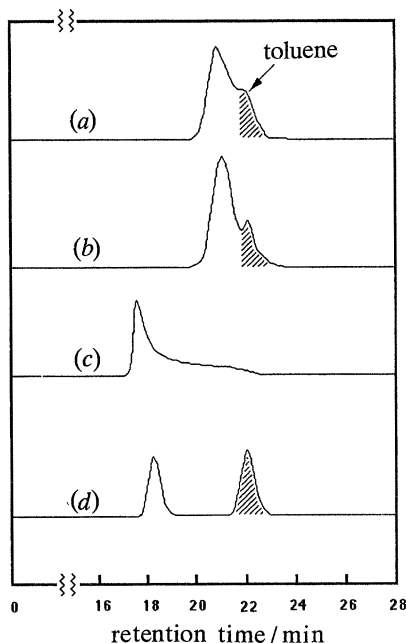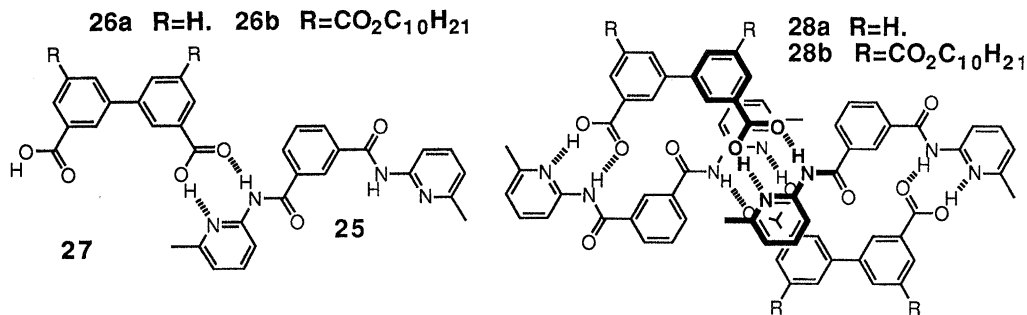
Figure 4. Gel permeation chromatograms with CH_2Cl_2 as eluent and toluene as standard for (*a*) **26b** (3 mm), (*b*) **25** (30 mm), (*c*) **25:26b** (1:1, 30 mm) and (*d*) reference triple porphyrin (0.1 mm).

The stability of the $2+2$ complex in solution was studied by gel permeation chromatography (Seto & Whitesides 1993). The individual components **25** (MW = 346) and **26b** (a more soluble derivative, MW = 611) show sharp peaks with long retention times (21.0 and 20.4 min; figure 4*a*, *b*), while an equimolar mixture of **25** and **26b** (at 30 mm) gives a peak with a shorter retention time (17.6 min; figure 4*c*), as expected for a larger aggregate. The sharpness of this peak indicates the formation of a well-defined structure in solution with some dissociation of the aggregate on the column, as evidenced by the tailing visible in figure 4*c*. The molecular mass of the aggregate was estimated, by comparison to a series of standards, to be 1970 ± 100, which is close to that calculated for the $2+2$ aggregate **28b** (MW = 1914). Figure 4*d* shows as an example the chromatogram of a similarly-sized triple decker porphyrin (MW = 1704).

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