(aromatic and olefinic C, 2 equiv), 79.3 (COH), 65.6 (CHO_2C), 43.4, 37.7 (COCHCHCO), 23.9, 22.6, 22.1, 20.4 ($CH_2C{=}C$, 4 CH_3, 1 equiv). CI MS (m/e): 376.1784 $(M + NH_4)^+$, calcd for $C_{20}H_{26}NO_6$ 376.1760. The stereochemistry of **19c** was determined by X-ray analysis (Figure 5).

Cycloaddition of 5e with 1,4-Benzoquinone. Diels-Alder reactions in toluene and dimethylformamide gave diastereomeric ratios **18d**:**19d** of 6:94 and 21:79, respectively, determined by HPLC (reverse-phase, 70:30 methanol-water, t_R (min) = 5.65 for **18d**, 6.83 for **19d**). The crude product from toluene was recrystallized from hexanes-EtOAc to yield colorless needles of **19d** (114.4 mg, 72%, ≥97% diastereomerically pure). Mp: 159-160 °C. IR ($CHCl_3$): 3540 (br), 3010, 2925, 1735, 1705, 1680, 1610 (w), 1420, 1110, 1015 (br), 750 (br) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.77 (s, 2 H, aromatic H), 6.0 (m, 3 H, COCH=CHCO, $CH_2CH{=}CHCH$), 5.88 (dd, J = 10.2, 0.8, 1 H, $COCH{=}CHCO$), 5.25 (dd, J = 4.0, 3.5, 1 H, CHO_2C), 3.24 (m, 1 H, $COCHCHO_2C$), 3.15 (dd, J = 7.4, 6.7, 1 H, $COCHCH_2$), 3.01 (br dd, J = 19.0, 1.1, 1 H, $CH_aH_bC{=}C$), 2.9 (br s, 1 H, OH), 2.22 (s, 9 H, 3 $ArCH_3$), 2.08 (br dd, J = 19.3, 7.6, 1 H, $CH_aH_bC{=}C$), 1.66 (s, 3 H, CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 197.9, 196.5 (C=O), 175.9 (CO_2), 140.7, 138.9, 137.3, 136.7, 134.2, 132.3, 131.6, 121.7 (aromatic and olefinic C, 2 equiv), 77.9 (COH), 68.5 (CHO_2C), 48.9, 41.9 (COCH-CHCO), 28.7, 22.8, 21.3, 20.4 ($CH_2C{=}C$, 4 CH_3, 1 equiv). CI MS (m/e): 386.1963 $(M + NH_4)^+$, calcd for $C_{22}H_{28}NO_5$ 386.1967. The stereochemistry of the major product **19d** was determined by X-ray analysis (Figure 6).

Cycloaddition of 5e with 1,4-Naphthoquinone. Diels-Alder reactions in toluene and dimethylformamide gave diastereomeric ratios **18e**:**19e** of 10:90 and 19:81, respectively, determined by HPLC (reverse-phase, 70:30 methanol-water, t_R (min) = 19.82 for **13e**, 14.77 for **19e**). The crude product mixture from toluene was recrystallized from methanol to yield pale yellow needles of **19e** (59 mg, 70%, ≥98% diastereomerically pure). Mp: 192-193 °C. The crystals were not suitable for X-ray analysis. IR ($CHCl_3$): 3580, 3040, 1740, 1700 (br), 1590, 1430, 1335, 1255, 1255, 1210, 1110 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.94 (dd, J = 8.6, 0.5, 1 H, benzo H), 7.6 (m, 1 H, benzo H), 7.53 (d, J = 3.9, 2 H, benzo H), 6.58 (s, 2 H, ArH), 6.15 and 6.13 (AB pattern with additional splitting, $J_{AB} \approx 10.5$, 2 H, $CH{=}CH$), 5.46 (br s, 1 H, CHO_2C), 3.51 (dd, J = 6.1, 4.5, 1 H, $COCHCHO_2C$), 3.51 (dd (appears as t), J = 6.5, 6.4, 1 H, $COCHCH_2$), 3.9 (br d, J = 17.9, 1 H, $CH_aH_bC{=}C$), 2.21 (m overlapping s, 4 H, $ArCH_3$ and $CH_aH_bC{=}C$), 1.95 (s, 6 H, 2 $ArCH_3$), 1.65 (br s, 1 H, OH), 1.24 (s, 3 H, CCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 195.7, 194.8 (C=O), 173.8 (CO_2), 136.3, 136.0, 135.2, 134.8, 134.3, 133.1, 132.5, 131.2, 126.2, 125.9, 122.2, 106.6 (aromatic and olefinic C, 2 equiv), 78.7 (COH), 68.9 (CHO_2C), 49.7, 42.5 (COCHC-HCO), 24.1, 22.0, 20.5 ($CH_2C{=}C$ and 4 CH_3, 2 equiv). CI MS (m/e): 436.2083 $(M + NH_4)^+$, calcd for $C_{26}H_{30}NO_5$ 436.2124. The stereochemistry for **19e** was assigned by correlation with another naphthoquinone adduct.[11]

Cycloaddition of 5e with Tetracyanoethylene. Diels-Alder reaction in toluene gave a diastereomeric ratio **20**:**21** of 25:75, determined by HPLC (reverse-phase, 70:30 methanol-water, t_R (min) = 12.96 for **20**, and 14.51 for **21**). In dimethylformamide, there was virtually no reaction after stirring for 4 days. The crude product from toluene was recrystallized from methanol to yield pure white needles of **21** (32.7 mg, 63%, ≥99% diastereomerically pure). Mp: 213-214 °C. IR ($CHCl_3$): 3580, 3025, 2985, 2950, 1755, 1445, 1430, 1375, 1325, 1135, 1120, 995 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.80 (s, 2 H, aromatic H), 6.08 (ddd, J = 10.6, 3.7, 1.5, 1 H, one of $CH{=}CH$), 5.99 (ddd, J = 4.8, 1.7, 1.7, 1 H, CHO_2C), 5.95 (ddd, J = 10.6, 2.1, 1.0, 1 H, one of $CH{=}CH$), 3.22 and 3.15 (AB pattern of 2 dm, J = 18.8, 2 H, $CH_aH_bC{=}C$), 2.65 (s, 1 H, OH), 2.34 (s, 6 H, 2 $ArCH_3$), 2.21 (s, 3 H, $ArCH_3$), 1.54 (s, 3 H, CCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 172.3 (ester C=O), 137.1, 135.1, 134.8, 131.6, 125.2, 122.6, 110.0, 109.9, 108.5, 107.8 (aromatic, cyano, and olefinic C, 2 equiv), 79.6 (COH), 67.4 (CHO_2C), 42.3, 36.8, 32.3, 24.7, 22.4, 20.4, (NCCHCHCN, $CH_2C{=}C$ and 4 CH_3, 1 equiv). CI MS (m/e): 406.1908, $(M + NH_4)^+$, calcd for $C_{22}H_{24}N_5O_3$ 406.1879. The stereochemistry of **21** was determined by X-ray analysis (Figure 7).

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Supplementary Material Available: Crystal structure determination summaries and tables of refined atomic positional and thermal parameters and bond distances and angles for the six Diels-Alder adducts **8a**, **16a**, **17a**, **19c**, **19d**, and **21** (64 pages). Ordering information is given on any current masthead page.

Hydrogen Bonding and Molecular Recognition: Synthetic, Complexation, and Structural Studies on Barbiturate Binding to an Artificial Receptor

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Abstract: A series of synthetic receptors with strong selectivity for the barbiturate family of drugs has been prepared. The receptor design is based on two 2,6-diaminopyridine groups linked through an isophthalic acid spacer. X-ray crystallographic, ^1H NMR spectroscopic, and substrate binding studies confirm that six hydrogen bonds are formed between the receptor and its substrate. The strongest binding ($K_a \approx 10^5$ M^{-1}) is seen to those substrates containing the complementary barbituric acid core. Systematic deletion of hydrogen-bonding sites from the receptor and substrate allows an assessment of the contribution of individual binding sites to complexation.

Introduction

The development of *artificial receptors* for neutral molecules is an important challenge in modern bio-organic chemistry.[1] In addition to a compatibility of shape and size, effective molecular recognition requires a precise alignment of binding groups on the receptor with complementary regions on the substrate. In several recent reports,[2,3] one or more hydrogen-bonding sites have been incorporated into artificial receptors to provide both orientation

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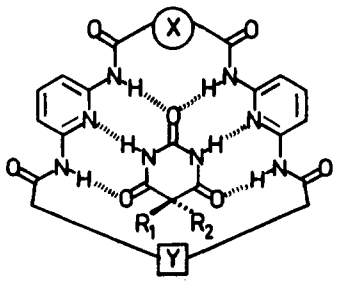
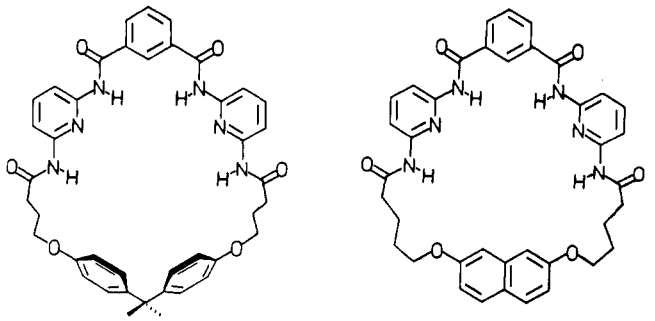


Figure 1. Schematic of a barbiturate binding site.

and selective complexation of the substrate. However, crucial for the further development of this field is an understanding and characterization of the precise role of hydrogen bonding in the molecular recognition process. In this paper, we report our approach to the design and synthesis of a new series of receptors for barbiturate derivatives.[4] We also report their complexation properties with a range of barbiturates and related substrates as well as crystal structure determinations on a representative receptor and its complex.

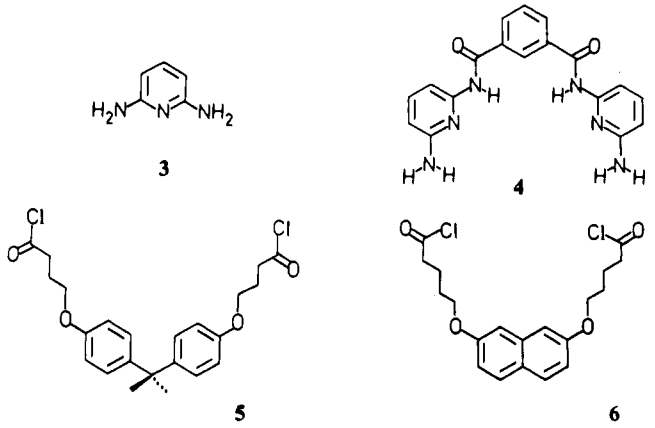
The widespread use of barbiturates as sedatives and anticonvulsants[5] makes them attractive targets for molecular recognition studies. They are small, rigid substrates with a well-defined functional-group structure that will permit a systematic investigation of the role of hydrogen bonding in molecular recognition. Of further interest is the possible application of artificial receptors both in the analysis of the drug and in its removal from biological solutions.[6] The barbituric acid framework contains eight potential hydrogen-bonding sites: two imide NHs and six carbonyl oxygen lone pairs. Since most of the clinically important barbiturates have alkyl or aryl substituents in the 5,5-positions, the two lower lone pairs on the 4- and 6-CO groups are sterically prevented from hydrogen bonding. Inspection of CPK models and subsequent molecular modelling[7] suggested that the remaining six hydrogen-bonding groups would be complexed by two 2,6-diaminopyridine units (Figure 1) linked by suitable spacer groups (X and Y) within a macrocyclic cavity. The choice of spacer X is critical since it must provide a cavity of the correct shape and size for barbiturate encapsulation, sufficient rigidity to prevent intramolecular hydrogen bonding across the cavity, and simplicity in the synthetic plan for many modifications of the basic receptor. These criteria are fulfilled by the isophthalic acid group, which can be easily functionalized as its diacid chloride to barbiturate receptors such as **1** and **2**. The lower spacer Y is much more variable within the design, although it was expected that some secondary recognition of the 5,5-dialkyl substituents of the barbiturate substrates might be achieved in this region.



1 **2**

Synthesis

The synthesis of the barbiturate receptors is remarkably direct, involving only two steps from 2,6-diaminopyridine **3**. Reaction of an excess of **3** with isophthaloyl dichloride in THF gave, after column chromatography on alumina (CH_2Cl_2, THF eluant), diamine **4** in 79% yield. This forms the key hydrogen-bonding part of the receptors. The diacid component is more readily varied, and two examples based on diphenylmethane or naphthalene spacers are reported here. Diacid chloride **5** was prepared from 4,4′-isopropylidenediphenol via alkylation with ethyl 4-bromobutyrate ($tBuO^-K^+$, DMSO), hydrolysis of the two ester groups (aqueous NaOH, EtOH), and treatment with oxalyl chloride (THF). Similarly, diacid chloride **6** was formed from 2,7-dihydroxynaphthalene by sequential alkylation with ethyl 5-bromovalerate (K_2CO_3, acetone), hydrolysis (NaOH, EtOH), and acid chloride formation ($(COCl)_2$, CH_2Cl_2).[2a] The target receptors **1** and **2** were prepared by the high-dilution coupling of diamine **4** with diacid chlorides **5** or **6** in THF and triethylamine (2 equiv) in 12% and 14% yields, respectively.



3 **4**

5 **6**

Modifications of the hydrogen-bonding groups can be readily made. For example, substitution of a hydrogen-bond donor (pyr-2-NHCO) by a hydrogen-bond acceptor (pyr-2-OCH_2) in **7** was achieved in 14% yield via the high-dilution coupling of diamine **8** with isophthaloyl dichloride. The key diamine **8** was, in turn, prepared from the reaction of diol **9**[8] and 2-bromo-6-aminopyridine in a sealed tube at 190 °C.[9] A modified macrocycle, **10**, in which the isophthaloyl group of **2** is replaced by a pyridine-2,6-dicarboxamide, could not be prepared by an analogous route due to the insolubility of the intermediate diamine derivative. Instead, 2,6-diaminopyridine was reacted with **6** to form diamine **11**, which was cyclized under high-dilution conditions with pyridine-2,6-dicarbonyl chloride to form **10** in 33% yield.

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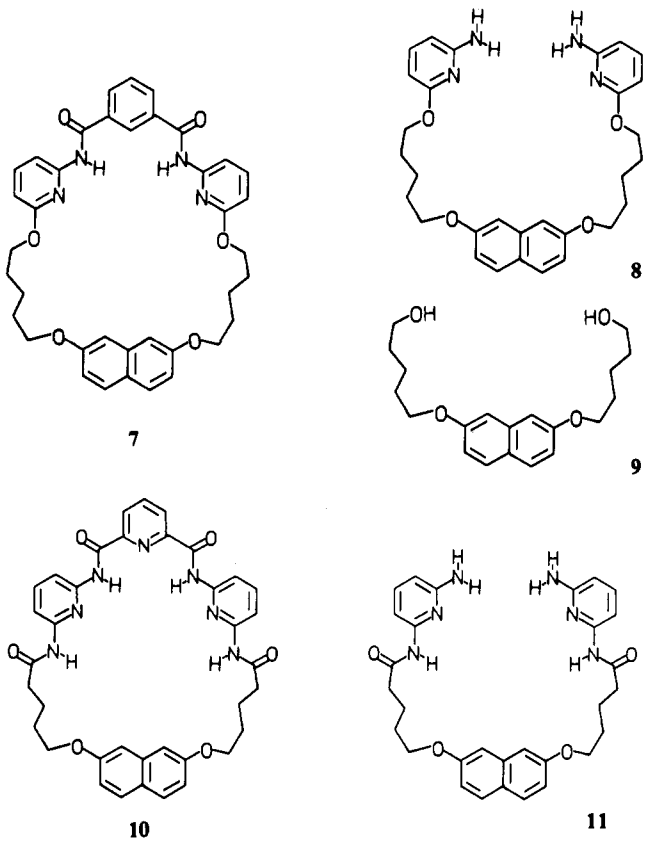


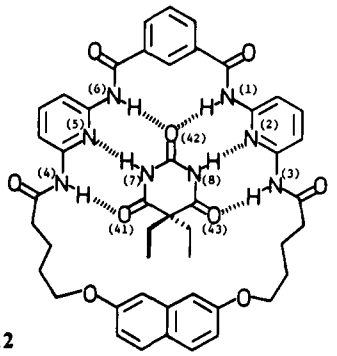
7 8 9 10 11

Structure of Receptor 2

Naphthalene receptor **2** crystallized from a THF/heptane mixture as small triclinic crystals. X-ray analysis showed an open structure for the macrocycle with all six hydrogen-bonding groups directed into its center (Figure 2). The cavity is occupied by a THF molecule of crystallization, which forms a hydrogen bond to one of the amide NHs. There is a considerable degree of preorganization in this structure. The distances between the pairs of H-bonding groups are 7.25 Å for the pyridine N's, 4.06 Å for the upper amide NHs, and 7.12 Å for the lower amide NHs. Modelling studies[7] indicate that these distances should be suitable for complexation of barbiturates into a planar conformation of the hydrogen-bonding cavity. The primary deviation from this preorganization, however, is found in the nonplanarity of the binding site, which takes up a twisted structure with an angle between the pyridine planes of approximately 44°. This solid state conformation is most likely due to nonbonded interactions between the two isophthalamide NHs and the isophthalic acid 2-H, which are positioned 2.26 and 1.98 Å apart from each other.

Substrate Binding Properties

The complexation properties of the receptors were followed by ^{1}H NMR spectroscopy. Titration experiments in $CDCl_3$ between the receptor and complementary barbiturate substrates led to characteristic changes in the ^{1}H NMR spectra of both the receptor and substrate that were consistent with the formation of a hexa-hydrogen-bonded complex of type **12**. The primary H-bonding



12

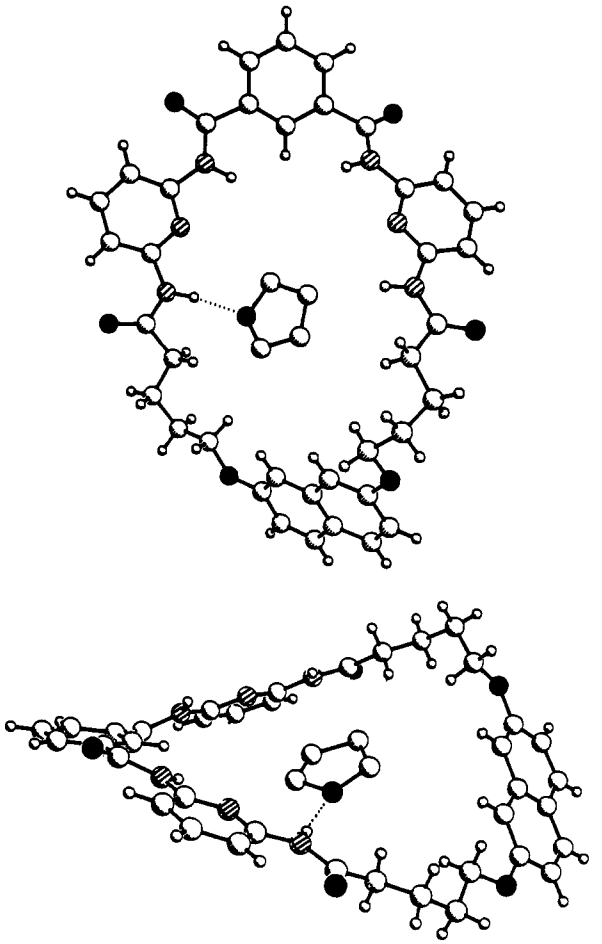


Figure 2. Front and side views of the X-ray structure of **2**.

Table I. Association Constants for the Different Receptors with a Range of Substrates

solvent	receptor	substrate	K_a (M^{-1})
CH_2Cl_2	**1**	barbital **13**	$(6.0 \pm 1.4) \times 10^5$
CH_2Cl_2	**2**	barbital **13**	$(2.5 \pm 0.7) \times 10^5$
CH_2Cl_2	**10**	barbital **13**	$(4.1 \pm 0.3) \times 10^4$
$CDCl_3$	**2**	cyclic urea **14**	$(4.0 \pm 1.1) \times 10^2$
$CDCl_3$	**7**	barbital **13**	$(3.1 \pm 0.8) \times 10^2$
$CDCl_3$	**1**	mephobarbitol **16**	$(6.8 \pm 1.2) \times 10^2$
$CDCl_3$	**2**	mephobarbitol **16**	$(4.9 \pm 1.1) \times 10^2$
$CDCl_3$	**2**	DL-glutethimide **17**	$(8.7 \pm 1.8) \times 10^2$
$CDCl_3$	**2**	thiobarbital **18**	$(7.4 \pm 1.5) \times 10^2$

Table II. Lengths and Bond Angles of Hydrogen Bonds in **12**

H bond	A–B, length (Å)	A–H–B angle (deg)
N(3)–O(43)	2.92	169.1
N(4)–O(41)	2.87	147.7
N(2)–N(8)	3.00	161.3
N(5)–N(7)	2.95	161.7
N(1)–O(42)	3.23	177.5
N(6)–O(42)	3.18	175.1

recognition between **1** and barbital **13** is seen in the large downfield shifts of the host amide (1.65 and 1.63 ppm) and guest imide (4.38 ppm) resonances. Further confirmation of the position of the substrate within the cavity is shown by the upfield shifts of the CH_2 and CH_3 resonances of the barbital ethyl groups (0.25 and 0.23 ppm) that fit into the cleft formed by the diphenylmethane unit. Also the 2-proton of the isophthalic acid spacer, which is positioned close to the 2-CO of the barbiturate, becomes sharper and shifts downfield by 0.4 ppm. Monitoring the chemical shift changes of the amide NH or isophthaloyl 2-H resonances as a function of barbital concentration led to a titration curve that showed a sharp saturation point at a 1:1 stoichiometry of host and

guest. These results are consistent with the formation of a very strong complex but preclude the use of ^{1}H NMR data for determination of association constants. Deranleau[10a] and Wilcox have discussed[10b] the limitations of the NMR method for measuring strong binding interactions and the importance of working at concentrations that allow a saturation range (Weber's p value) of between 20 and 80%.

The binding between **1** or **2** and barbital **13** can be conveniently followed by either fluorescence or UV–visible spectroscopy, thus providing titration data at concentrations between 10^{-4} and 10^{-6} M. The fluorescence titration exploited a binding-induced increase in fluorescence emission at 460 nm (excitation wavelength 304 nm), while in the UV–vis titration an increase in intensity of the absorption at 303 nm was monitored. In both cases, the titration curve was analyzed with use of the nonlinear regression program, Hostest-II,[10b,11] and the calculated association constants are collected in Table I.[12]

Complex Structure

The nature of the hexahydrogen-bonding interaction between **2** and **13** was confirmed by X-ray crystallography. Figure 3 shows the structure of the complex with barbital in the center of the macrocycle forming three hydrogen bonds to each diamidopyridine unit. The bond lengths and angles of the six hydrogen bonds are collected in Table II. These fall into three pairs corresponding to short [2.9 Å, N(4,3) to O(41,43)], medium [3.0 Å, N(5,2) to N(7,8)], and long [3.2 Å, N(6,1) to O(4,2)] hydrogen bonds.[13] By comparison to the structure of uncomplexed **2** (see Figure 2), a conformational change has occurred in the receptor on binding to place all six hydrogen-bonding groups in the same plane; for example, the distance between the upper phthalamide NH groups changes from 4.06 Å in **2** to 3.44 Å in **2**:**13**. However, the barbital itself is not coplanar to the macrocycle but lies at a 27° angle relative to the plane of the pyridine rings. Such nonplanar arrangements of hydrogen-bonding groups are common in nucleic acid chemistry[14] where propeller twists of up to 30° are seen. In this case, the deviation from planarity is most probably due to the shape of the binding cavity, which is too narrow to completely encircle the barbiturate. In order to achieve hydrogen bonds of reasonable length (2.87 and 2.92 Å), the 4- and 6-carbonyl groups on the barbiturate must take up positions below the binding plane. Also, the isophthaloyl 2-proton projects into the cavity toward the barbital 2-carbonyl group, with phthaloyl 2-C···O and CH···O distances of 3.08 and 2.21 Å, respectively. The key structural element determining both the shape and width of the cavity is the isophthalic acid group, and this must be modified to overcome these problems.

Hydrogen Bonding in Molecular Recognition

The solution- and solid-state properties of **1** and **2** prompt several key questions concerning the barbiturate recognition process. First, what are the strengths of individual hydrogen bonds within the overall binding free energy of the complex? The selective removal of H-bonding groups from either the substrate or receptor has been an important strategy[15] for assessing the apparent[16,17] contribution of individual interactions to binding. Cyclic urea **14**[18] lacks two of the six H-bonding sites in barbital **13** and, consequently, forms a weaker complex with receptor **2** (K_s = 400 M^{-1}). The ^{1}H NMR peak of the amide N(3,4)Hs in **2** shows no strong downfield shift on titration with **14**, confirming that they are not involved in hydrogen bonding and that the tetradentate binding site for **14** is formed by N(2,5) and N(1,6)H (as in **15**). An important comparison to complex **15** is provided by macrocycle **7** in which the H-bond-donating amides [N(3,4)] in **2** have been replaced by H-bond-acceptor ether groups. This receptor should form a complex with **13**, in which the same two hydrogen bonds [N(3)-O(43), N(4)-O(41)] as in **15** had been eliminated. The association constant for **7**:**13** was found (using ^{1}H NMR) to be 310 M^{-1}. H-bond deletion studies of this type must be treated with caution as other changes in the molecular properties, such as basicity (in **14** and **7**) and conformation (in **7**), may contribute to the differences in binding free energy.[16,17] Nonetheless, the similar drop in K_s seen for **2**:**14** and **7**:**13** compared to **12** indicates that the two lower (and shortest in Figure 3) hydrogen bonds [N(3)-O(43), N(4)-O(41)] are each con-

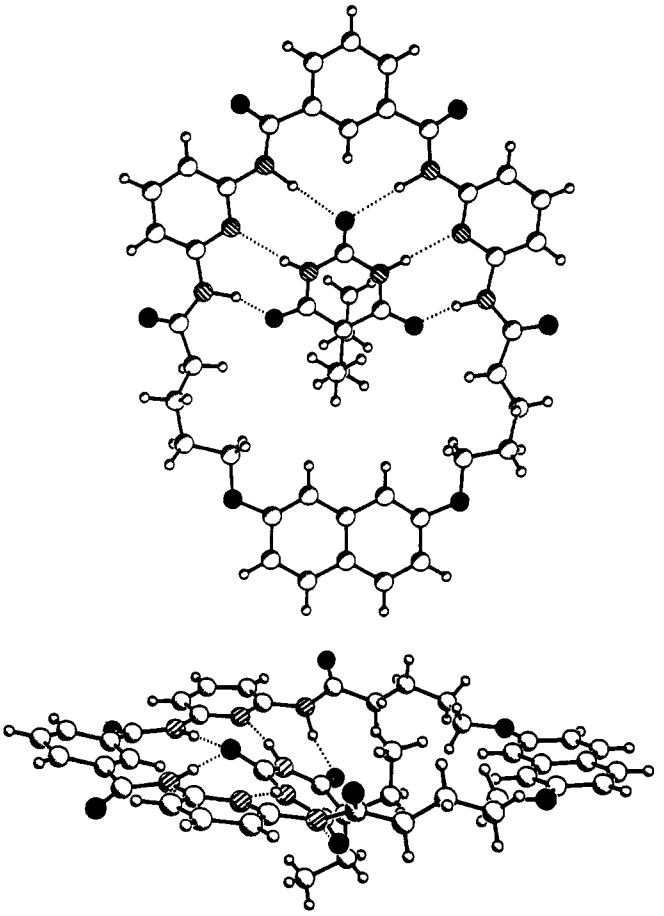
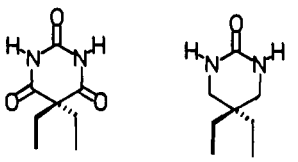


Figure 3. Front and side views of the X-ray structure of **2**:**13** (**12**).



13 **14**

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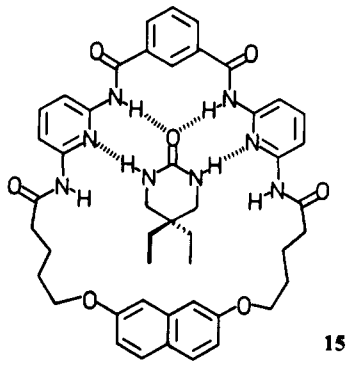
tributing ~1.8 kcal mol^{-1} to the overall binding free energy.



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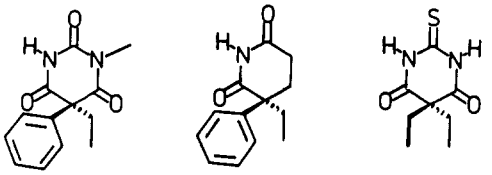

16 17 18

Second, what is the role of the isophthaloyl 2-proton in binding? The X-ray structure of **12** (Figure 3) shows this proton projecting into the cavity and positioned 2.21 Å from the barbital 2-CO. Such close proximity may indicate a favorable interaction between the isophthaloyl 2-H and the barbital 2-CO. Etter[19a] and Leiserowitz[19b] have identified related intra- and intermolecular CH···O hydrogen bonds in the solid state. The electron-withdrawing carboxamide substituents should increase the acidity of the isophthaloyl 2-H, and its downfield shift on substrate complexation (0.4 ppm) is consistent with a hydrogen bond to the barbital 2-CO. In order to investigate this possibility, we synthesized receptor **10** in which the isophthaloyl 2-H is replaced by a pyridine N. Fluorescence titration studies were carried out with barbital **13**, and a binding constant of 4.0×10^4 M^{-1} was measured. This corresponds to a 10-fold drop in binding and may be partially due to the loss of a CH···O hydrogen bond. However, the structural change from **2** to **10** also introduces a lone pair (from the pyridine dicarboxamide) into the cavity, which may lead to a repulsive interaction with the barbital 2-carbonyl oxygen. The relative contributions of these attractive and repulsive effects awaits further study.[20]

A third question concerns the overall selectivity of the receptors. The association constants for the complexes between **1** or **2** and a range of barbiturate and urea substrates are collected in Table I. These show a strong selectivity for the six hydrogen bonding barbituric acid core. Binding constants of ~10^5 M^{-1} are seen for barbital and receptors **1** and **2**. Alkylation of one imide N, as in mephobarbital **16**, leads to a blocking of 3–4 H-bonding interactions and a drop in K_a of ~10^3 M^{-1}. Similarly, glutethimide **17**, with only four possible H-bonding sites binds 290-fold less strongly than barbital. An interesting selectivity was observed between barbital **13** and thiobarbital **18**. All six necessary H-bonding sites are present in **18**, yet binding is almost 350-fold weaker. This is consistent with the weaker H-bond-accepting characteristics of sulfur (compared to oxygen) as well as its larger size inhibiting binding into the cavity.[22]

In summary, we have shown that the careful positioning of inwardly facing hydrogen-bonding groups into a semirigid receptor can lead to strong and selective complexation of those substrates with complementary shape and hydrogen-bonding characteristics. A combination of X-ray structural and synthetic modification studies can provide valuable insights into the nature of individual interactions in the molecular recognition process.

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(20) Fersht[15a] and Kollman[21] have discussed a related problem concerning the introduction of repulsive interactions with transition-state analogues of thermolysin.

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Experimental Section

1,3-Bis[[(6-aminopyrid-2-yl)amino]carbonyl]benzene (4). To a solution of 2,6-diaminopyridine (2.18 g, 20 mmol) and triethylamine (0.40 g, 4 mmol) in THF (100 mL) was added dropwise a THF solution (20 mL) of isophthaloyl dichloride (0.406 g, 2 mmol) at room temperature under an inert atmosphere. The reaction mixture was stirred for 3 h, and then the solvent was removed under reduced pressure. The residue was treated with water, and the resulting precipitate was filtered and washed with more water to remove excess unreacted diamine and triethylamine hydrochloride. The crude product was purified by column chromatography on alumina (CH_2Cl_2/THF mixture as eluant). Further purification was achieved by recrystallization from THF/heptane mixture to yield 0.547 g of **4** as a faintly yellow crystalline solid: 79% yield; mp 201–202 °C; ^{1}H NMR ($CDCl_3$) δ 8.42 (1 H, s, isophth-2H), 8.33 (2 H, br s, CONH), 8.08 (2 H, d of d, J = 8 Hz, isophth-4,6H), 7.70 (2 H, d, J = 8 Hz, pyr-5H), 7.61 (1 H, t, J = 8 Hz, isophth-5H), 7.51 (2 H, t, J = 8 Hz, pyr-4H), 6.30 (2 H, d, J = 8 Hz, pyr-3H), 4.33 (4 H, s, NH_2); exact mass M$^+$ 348.1323 $C_{18}H_{16}N_6O_2$, requires 348.1335. Anal. Calcd for $C_{18}H_{16}N_6O_2$: C, 62.06; H, 4.63; N, 24.12. Found: C, 61.73; H, 4.59; N, 23.74.

2,7-Bis[[4-(chlorocarbonyl)butyl]oxy]naphthalene (6). A mixture of 2,7-naphthalenediol (2.0 g, 12.5 mmol), K_2CO_3 (3.6 g, 26 mmol), and ethyl 5-bromovalerate (4.0 mL, 25 mmol) in acetone (100 mL) was refluxed overnight under an inert atmosphere. The reaction mixture was evaporated to dryness, dissolved in water, and extracted into CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4. After evaporation, the crude product was purified by alumina chromatography (eluant CH_2Cl_2). The resultant amber colored oil solidified on standing and was recrystallized from a CH_2Cl_2/heptane mixture to give 2,7-bis-[[4-(ethoxycarbonyl)butyl]oxy]naphthalene as white crystals: 4.3 g, 83% yield; mp 82–84 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (2 H, d of d, J = 8.5, 2.2 Hz, naph-4,5H), 7.02–6.89 (4 H, m, naph-1,8H, naph-3,6H), 4.13 (4 H, q, J = 7 Hz, CH_2CH_3), 4.06 (4 H, t, J = 5.5 Hz, OCH_2), 2.39 (4 H, t, J = 7 Hz, CH_2CO), 1.87–1.84 (8 H, m, $OCH_2CH_2CH_2$), 1.25 (6 H, t, J = 7.0 Hz, CH_2CH_3). The diester (4.3 g, 10.3 mmol) was dissolved in a mixture of 10% aqueous NaOH solution and EtOH (1:1) and heated under reflux for 24 h. The reaction mixture was evaporated to dryness and the residue was dissolved in water. Acidification with HCl yielded a white precipitate, which was filtered and then purified by recrystallization from acetone to give 2,7-bis[[4-(hydroxycarbonyl)butyl]oxy]-naphthalene: 3.6 g, 98% yield mp 167–168.5 °C; ^{1}H NMR (CD_3COCD_3) δ 10.60 (2 H, br s, CO_2H), 7.67 (2 H, d, J = 9 Hz, naph-4,5H), 7.17 (2 H, d, J = 2 Hz, naph-1,8H), 6.95 (2 H, dd, J = 9, 2 Hz, naph-3,6H), 4.10 (4 H, t, J = 6.1 Hz, OCH_2), 2.39 (4 H, t, J = 7.0 Hz, $COCH_2$), 1.76–1.89 (8 H, m, $OCH_2CH_2CH_2$). Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.67; H, 6.74.

The diacid (0.36 g, 1 mmol) was suspended in dry CH_2Cl_2 (50 mL), and oxalyl chloride (0.5 mL) and DMF (1 drop) were added. The reaction mixture was stirred at room temperature for 2 h, after which time all the starting material had gone into solution. The volatile materials were removed on a rotary evaporator and the residue was dried under high vacuum for 3 h. Diacid chloride **6** was used without further purification.

2,2-Bis[4-[[3-(chlorocarbonyl)propyl]oxy]phenyl]propane (5). To a solution of 4,4-isopropylidenediphenol (2.28 g, 10 mmol) in DMSO was added potassium *tert*-butoxide (2.91 g, 26 mmol) under an argon atmosphere. The reaction mixture was stirred at room temperature for 1 h, after which time ethyl 4-bromobutyrate (5.85 g, 26 mmol) was added and the solution was heated at 100 °C for 10 h. Extraction of the reaction mixture with CH_2Cl_2 followed by removal of the volatile materials on a rotary evaporator afforded a pale yellow oil. This was purified by passage through a short column of silica gel (CH_2Cl_2 eluant) to give 2,2-bis[4-[[3-(ethoxycarbonyl)propyl]oxy]phenyl]propane as an oil (3.6 g, 79%): ^{1}H NMR ($CDCl_3$) δ 7.12 (4 H, d, J = 8.7 Hz, phenol-3,5H), 6.77 (4 H, d, J = 8.7 Hz, phenol-2,6H), 4.13 (4 H, q, J = 7.1 Hz, CH_2CH_3), 3.97 (4 H, t, J = 6.1 Hz, OCH_2CH_2), 2.50 (4 H, t, J = 7.3 Hz, $COCH_2$), 2.06–2.10 (4 H, m, OCH_2CH_2), 1.64 (6 H, s, $C(CH_3)_2$), 1.25 (6 H, t, J = 7.2 Hz, CH_2CH_3); exact mass M$^+$ 456.2516 $C_{27}H_{36}O_6$, requires 456.2512.

The diester (3.6 g, 7.9 mmol) was dissolved in EtOH (20 mL), treated with aqueous NaOH (10%, 20 mL), and heated under reflux for 24 h. After removal of the EtOH by evaporation, the reaction mixture was acidified with concentrated hydrochloric acid and the resulting white precipitate was separated by filtration. Recrystallization from MeOH/H_2O gave 2,2-bis[4-[[3-(hydroxycarbonyl)propyl]oxy]phenyl]-

propane (3.0 g, 95%): mp 167–170 °C; ^{1}H NMR ($CDCl_3$) δ 7.10 (4 H, d, J = 9 Hz, phenol-3,5H), 6.78 (4 H, d, J = 9 Hz, phenol-2,6H), 3.97 (4 H, t, J = 6 Hz, OCH_2), 2.56 (4 H, t, J = 7 Hz, $COCH_2$), 2.04–2.11 (4 H, m, OCH_2CH_2), 1.61 (6 H, s, $C(CH_3)_2$). Anal. Calcd for $C_{23}H_{28}O_6 \cdot {}^1/_3H_2O$: C, 67.96; H, 7.11. Found: C, 67.91; H, 6.80. The diacid (0.3 g, 0.75 mmol) was suspended in dry CH_2Cl_2 (50 mL), and oxalyl chloride (0.5 mL) and DMF (1 drop) were added. The reaction mixture was stirred at room temperature for 4 h, during which time all the diacid went into solution. The volatile materials were removed on a rotary evaporator, and the solid residue was dried under high vacuum for 4 h. The product diacid chloride **5** was used without further purification.

Naphthalene Macrocycle 2. Into a three-necked, 250-mL flask was added dry THF (40 mL) and the apparatus was flushed with nitrogen. A solution of diamine **4** (174 mg, 0.5 mmol) and triethylamine (61 mg, 0.6 mmol) in dry THF (50 mL) was added dropwise simultaneously with a solution of diacid chloride **6** (198 mg, 0.5 mmol) in dry THF (50 mL) over a period of 3 h at room temperature and with vigorous stirring. The reaction mixture was stirred for an additional 3 h, after which time the volatiles were removed by rotary evaporation. The solid residue was redissolved in CH_2Cl_2 and the solution was washed with aqueous $KHCO_3$ (5%), dried over Na_2SO_4, and evaporated to dryness. The crude mixture was purified by preparative layer chromatography on alumina (CH_2Cl_2/MeOH, 50:1 eluant) to give macrocycle **2**, which was crystallized from THF/heptane as fine needles (48 mg, 14% yield): mp 299.5–301 °C; ^{1}H NMR ($CDCl_3$) δ 8.19 (2 H, s, isophth-CONH), 8.19 (2 H, d, J = 8 Hz, pyr-3H), 8.06 (1 H, br s, isophth-2H), 8.01 (2 H, d, J = 8 Hz, isophth-4,6H), 7.99 (2 H, d, J = 8 Hz, pyr-5H), 7.76 (2 H, t, J = 8 Hz, pyr-4H), 7.70 (2 H, s, CH_2CONH), 7.68 (1 H, t, J = 8 Hz, isophth-5H), 7.57 (2 H, d, J = 9 Hz, naph-4,5H), 6.98 (2 H, d, J = 2 Hz, naph-1,8H), 6.97 (2 H, dd, J = 9, 2 Hz, naph-3,6H), 4.13 (4 H, m, OCH_2), 2.46 (4 H, m, $COCH_2$), 1.96 (8 H, m, $OCH_2CH_2CH_2$); exact mass M^+ 672.2696 $C_{38}H_{36}N_6O_6$, requires 672.2696. Anal. Calcd for $C_{38}H_{36}N_6O_6$: C, 67.84; H, 5.39; N, 12.49. Found: C, 67.36; H, 5.28; N, 12.34.

Diphenylmethane Macrocycle 1. The synthesis of **1** was accomplished by a similar procedure to that for **2**. This involved high-dilution mixing of a mixture of **4** (174 mg) and triethylamine (120 mg) in THF (50 mL) with diacid chloride **5** in THF (50 mL) at room temperature to give, after workup and crystallization from THF/heptane, macrocycle **1** as white microcrystals (39 mg, 12% yield): mp 172–175 °C; ^{1}H NMR ($CDCl_3$) δ 8.18 (2 H, s, isophth-CONH), 8.09 (3 H, m, pyr-3H, isophth-2H), 7.92 (6 H, m, pyr-5H, CH_2CONH, isophth-4,6H), 7.76 (2 H, t, J = 8 Hz, pyr-4H), 7.64 (1 H, m, isophth-5H), 7.02 (4 H, d, J = 9 Hz, phenol-3,5H), 6.71 (4 H, d, J = 9 Hz, phenol-2,6H), 4.03 (4 H, t, J = 5.5 Hz, CH_2O), 2.57 (4 H, m, CH_2CO), 2.19 (4 H, m, CH_2CH_2O), 1.54 (6 H, s, CH_3); exact mass M^+ 712.3028 $C_{41}H_{40}N_6O_6$, requires 712.3009.

2,7-Bis[[5-[(6-aminopyrid-2-yl)oxy]pentyl]oxy]naphthalene (8). 2,7-Bis[(5-hydroxypentyl)oxy]naphthalene (0.92 g, 2.77 mmol) was heated in a sealed tube with 2-amino-6-bromopyridine (0.95 g, 5.5 mmol) and NaH (0.135 g, 5.62 mmol) in dry dimethoxyethane (7 mL) for 19 h at 190 °C. The tube was cooled and opened carefully. [Caution: An internal pressure of H_2 builds up and opening should be carried out behind a screen.] The supernatant was removed and concentrated to give a crude product mixture, which was chromatographed on alumina (CH_2Cl/MeOH, 100:1 eluant) to yield the product as a yellow oil (0.28 g, 21% yield): ^{1}H NMR ($CDCl_3$) δ 7.63 (2 H, d, J = 9 Hz, naph-4,5H), 7.33 (2 H, t, J = 8 Hz, pyr-4H), 7.03 (2 H, d, J = 2 Hz, naph-1,8H), 6.98 (2 H, dd, J = 9, 2 Hz, naph-3,6H), 6.08, 6.05 (4 H, 2d, J = 8 Hz, pyr-3,5H), 4.3 (4 H, br s, NH_2), 4.21 (4 H, t, J = 6.5 Hz, CH_2O-naph), 4.08 (4 H, t, J = 6.5 Hz, CH_2O-pyr), 1.90 (8 H, m, CH_2CH_2O), 1.70 (4 H, m, $CH_2(CH_2)_2O$).

Oxypyridine Macrocycle 7. The synthesis of **7** was accomplished by a similar high-dilution coupling to that of **2**. A solution of diamine **8** (74 mg, 0.143 mmol) and triethylamine (0.048 mL) in CH_2Cl_2 (20 mL) was added simultaneously with a solution of isophthaloyl dichloride (29 mg, 0.143 mmol) in CH_2Cl_2 (20 mL) to vigorously stirred CH_2Cl_2 (10 mL) at room temperature over a period of 4 h. Workup and purification via alumina chromatography (CH_2Cl_2/MeOH, 100:1 eluant) gave macrocycle **7** as a white powder (12.6 mg, 13.6% yield): mp 242–243 °C; ^{1}H NMR ($CDCl_3$) δ 8.14 (2 H, s, CONH), 8.02 (1 H, s, isophth-2H), 7.97 (2 H, dd, J = 2, 8 Hz, pyr-3H), 7.86 (2 H, d, J = 8 Hz, isophth-4,6H), 7.65 (2 H, t, J = 8 Hz, pyr-4H), 7.51 (1 H, t, J = 8 Hz, isophth-5H), 7.40 (2 H, d, J = 9 Hz, naph-4,5H), 6.85 (2 H, d, J = 2 Hz, naph-1,8H), 6.73 (2 H, dd, J = 2, 9 Hz, naph-3,6H), 6.53 (2 H, d, J = 8 Hz, pyr-5H), 4.38 (4 H, t, J = 6 Hz, CH_2O-pyr), 4.04 (4 H, t, J = 7 Hz, CH_2O-naphth), 1.90 (8 H, m, CH_2CH_2O), 1.59 (4 H, m, $CH_2(CH_2)_2O$); exact mass M^+ 646.2809 $C_{38}H_{38}N_4O_6$, requires 646.2791.

2,7-Bis[[4-[[(6-aminopyrid-2-yl)amino]carbonyl]butyl]oxy]naphthalene (11). To a solution of 2,6-diaminopyridine (2.18 g, 20 mmol) in 50 mL of THF was added dropwise a solution of diacid chloride **6** (0.4 g, 1 mmol) in 10 mL of THF. The reaction mixture was evaporated to dryness and the solid residue was washed several times with water. Purification by column chromatography on alumina (THF/CH_2Cl_2 eluant) gave diamine **11** (225 mg, 42%) which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.83 (2 H, s, CONH), 7.62 (2 H, d, J = 8 Hz, naph-4,5H), 7.53 (2 H, d, J = 7.4 Hz, pyr-3H), 7.41 (2 H, m, pyr-4H), 6.95–7.0 (4 H, m, naph-1,3,6,8H), 6.22 (2 H, d, J = 8 Hz, pyr-5H), 4.30 (4 H, s, NH_2), 4.06 (4 H, m, OCH_2), 2.43 (4 H, m, $COCH_2$), 1.91 (8 H, br m, $OCH_2CH_2CH_2$); exact mass M^+ 542.2633 $C_{30}H_{34}N_6O_4$, requires 542.2641.

Trispyridyl Macrocycle 10. A solution of diamine **11** (136 mg, 0.25 mmol) in THF (30 mL) and triethylamine (70 μL) was added simultaneously with a solution 2,6-bis(chlorocarbonyl)pyridine (51 mg, 0.25 mmol) in THF (30 mL) to a stirred solution of THF (30 mL) at room temperature over a period of 3 h. The reaction mixture was evaporated to dryness and purified by column chromatography on alumina (CH_2Cl_2/MeOH, 50:1 eluant). Crystallization from $CHCl_3$/MeOH (1:1) afforded the product macrocycle **10** (56 mg, 33%): mp 320–325 °C dec; ^{1}H NMR ($CDCl_3$) δ 9.50 (2 H, s, pyr-CONH), 8.49 (2 H, d, J = 8 Hz, pyr-3,5H), 8.14 (1 H, t, J = 8 Hz, pyr-4H), 8.07 (2 H, d, J = 8.5 Hz, amino-pyr-3H), 8.03 (2 H, d, J = 8 Hz, amino-pyr-5H), 7.79 (2 H, m, amino-pyr-4H), 7.6–7.65 (4 H, m, naph-4,5H,RCONH), 6.9–7.0 (4 H, m, naph-1,8H, naph-3,6H), 4.20 (4 H, m, OCH_2), 2.45 (4 H, m, CH_2CO), 1.8–1.95 (8 H, m, $OCH_2CH_2CH_2$); exact mass 673.2618 $C_{37}H_{35}N_7O_6$, requires 673.2649. Anal. Calcd for $C_{37}N_{35}N_7O_6 \cdot H_2O$: C, 64.24; H, 5.39; N, 14.17. Found: C, 64.51; H, 5.08; N, 13.95.

Determination of Association Constants. A. Fluorescence Method. The receptor ($1–10 \times 10^{-6}$ M in 2.5 mL of CH_2Cl_2) was titrated with a solution of guest ($4–40 \times 10^{-4}$ M) dissolved in the same receptor solution. The concentrations were adjusted according to the estimated K_a value to maintain 'p' values close to the 0.2–0.8 range.[10] The increase in fluorescence emission at 461 nm (466 nm in the case of **10**) was monitored as a function of guest concentration with an excitation wavelength of 303 nm. The titration curve was fitted by using nonlinear regression methods on the Hostest-II program.[11]

B. UV–Vis Methods. A similar protocol to A was followed. The increase in absorbance at 303 nm was monitored.

C. NMR Method. The receptor ($1–10 \times 10^{-3}$ M) in 0.5 mL of $CDCl_3$ was titrated with a solution of guest (1×10^{-2} M) dissolved in the same receptor solution. The downfield shifts of the receptor amide NH and isophthloyl 2-H protons were monitored as a function of guest concentration. Addition was continued through 8–15 equiv. The resultant titration curve was analyzed either by using nonlinear regression methods[11] or by linearization via the Scatchard equation.[23]

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Registry No. 1, 135043-43-5; **2**, 123402-43-7; **4**, 112817-57-9; **5**, 123402-42-6; **6**, 122603-65-0; **7**, 135043-44-6; **8**, 135043-45-7; **10**, 135043-46-8; **11**, 135043-47-9; **13**, 57-44-3; **14**, 5454-56-8; **16**, 115-38-8; **17**, 18389-24-7; **18**, 77-32-7; 2,6-diaminopyridine, 141-86-6; isophthaloyl dichloride, 99-63-8; 2,7-naphthalenediol, 582-17-2; ethyl 5-bromovalerate, 14660-52-7; 2,7-bis[[4-(ethoxycarbonyl)butyl]oxy]naphthalene, 122603-64-9; 2,7-bis[[4-(hydroxycarbonyl)butyl]oxy]naphthalene, 135043-48-0; 4,4-isopropylidenediphenol, 80-05-7; ethyl 4-bromobutyrate, 2969-81-5; 2,2-bis[4-[[3-(ethoxycarbonyl)propyl]oxy]phenyl]propane, 135043-49-1; 2,2-bis[4-[[3-(hydroxycarbonyl)propyl]oxy]phenyl]propane, 135043-50-4; 2,7-bis[(5-hydroxypentyl)oxy]naphthalene, 135043-51-5; 2-amino-6-bromopyridine, 19798-81-3; 2,6-bis(chlorocarbonyl)pyridine, 3739-94-4.

Supplementary Material Available: Crystallographic details for **2** and **12**, including tables of atomic coordinates, thermal parameters, bond angles, and bond lengths (25 pages). Ordering information is given on any current masthead page.

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