Neutral Molecule Receptor Systems Using Ferrocene's "Atomic Ball Bearing" Character as the Flexible Element

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Abstract: Fourteen novel ferrocene derivatives have been designed to serve as receptors for low molecular weight diamines. The compounds that have been prepared and fully characterized possess two ferrocenedicarboxylic acid residues bridged by amide formation in their respective 1′-positions by 4,4′-benzidinyl (**15**), 3,3′-dimethoxy-4,4′-benzidinyl (**16**), 2,7-fluorenyl (**17**), 3-methoxy-2,7-fluorenyl (**18**), 4-N-piperazinoanilinyl (**19**), N,N′-4,4′-bipiperidinyl (**20**), and 4,13-diaza-18-crown-6 (**21**). In two cases, ferrocenecarboxylic acid was bridged by spacers attached using 1-methylene groups. The bridges in these cases were 4,13-diaza-18-crown-6 (**22**) and 1,5-diaminoanthraquinone (**24**). In a single case, ferrocenecarboxylic acid was bridged by 1,5-dicarbonylnaphthalene (**25**). In one additional case, the bridge was created by formation of an imine followed by hydrogenation, but both compounds (**26, 27**) proved to be relatively unstable. Attempts to increase solubility afforded the N-ethylated derivative **28** of **15** and the derivative **29** of **27** having carboxamides in the 1′-positions. A solid state structure of the diethyl ester of **20** confirms the design criteria. Complexation constants were determined in THF-d_8 or CDCl$_3$ for combinations of receptors **18**, **19**, and **20** with 4-aminopyridine, N,N,N′,N′-tetramethylethylenediamine, N,N,N′,N′-tetramethylpropylenediamine, DABCO, 3-propyladenine, and benzimidazole and were in the range 10^2–10^4. The anticipated complexation mechanism for **20** with N,N,N′,N′-tetramethylpropylenediamine was confirmed by observation of an NOE between host and guest.

Introduction

The complexation of molecular species by natural, proteinaceous receptor molecules has inspired organic and medicinal chemists for decades.[1] They have tried to understand the interactions that hold together the host and guest, and to design drugs that will mimic those interactions to an extent sufficient either to substitute for the natural substrate (ligand) or at least to compete with it. Designed molecular systems include numerous receptors intended to have specific hydrogen-bonding interactions.[2] Other examples include Lehn's phosphate binder,[3] the "molecular tweezers" of Zimmerman,[4] the pyrrole binders of Anslyn[5] and Harmata,[6] Sessler's porphyrins,[7] and the molecular boxes described by Wilcox,[8] Diederich,[9] Stoddart,[10] and many others. The greatest impetus given to this field has been the extensive effort of Rebek and co-workers[11] who employed Kemp's triacid[12] as a cornerstone for their development of "molecular clefts." We report here the development of a new family of receptor molecules based upon the ferrocene nucleus.[13] We describe the design, preparation, characterization, solid state structure, and complexation behavior of this class of molecular receptors.

Results and Discussion

Design Considerations. The extensive effort by Rebek and co-workers showed that molecular clefts can be prepared in which two polar groups (carboxyl residues in this case) can be focused toward each other and held in place on a molecular backbone. The overall aspect of such compounds is the shape of a flattened "U". The backbone of this family of molecular clefts was commonly a dimethylated aromatic diamine which formed imides at both nitrogens using two of the three available carboxyl groups of Kemp's acid. The third carboxyl group, in each case, was free to interact with hydrogen bond acceptors of appropriate length. Although substantiated by NOE experiments, this postulated inclusion arrangement was contradicted

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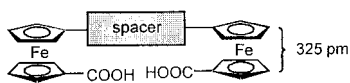
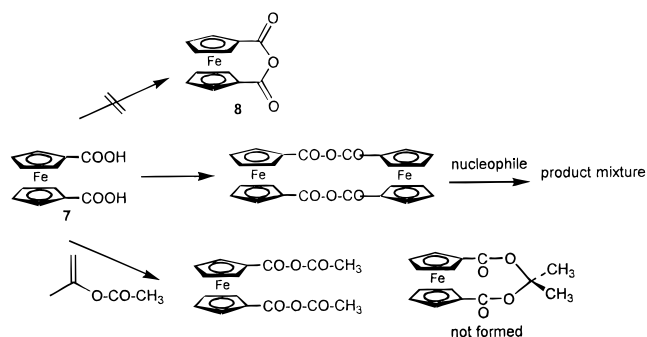**Figure 1.** Design schematic for ferrocene-based receptor molecules.

by calculations,[14] confirmed by a solid state structure determination,[15] and then confirmed by calculations.[16] The latter confusion demonstrates the importance of solution studies such as those described below.

The use of ferrocene for the pillars found at opposite ends of the molecular cleft has several advantages. First, the inter-ring spacing in ferrocene is 3.25 Å (Figure 1), or approximately two aromatic thicknesses. An architectural scheme in which two ferrocenes were connected by their respective "top" rings would leave a cleft of suitable dimension to accommodate an aromatic guest. Thus, binding could, in principle, be augmented by π,π-stacking. Second, the synthetic chemistry of ferrocene is well known and quite versatile. Third, the two cyclopentadienyl rings of ferrocene are each attached to an iron atom that constitutes a "molecular ball bearing". Rotation about the iron is hindered in ferrocene itself by a barrier of only 0.8 kcal/mol.[17]
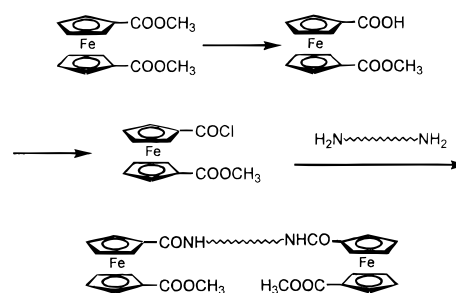
An additional consideration is that ferrocene readily undergoes oxidation. Loss of an electron affords the ferrocenium cation [$Cp_2Fe - e \rightarrow Cp_2Fe^+$]. This type of switching has been used to advantage in ferrocenyl cryptands that selectively capture and release a variety of metals.[18] It was thought that oxidation of the two ferrocene residues might permit the use of these compounds to function as anion binders, an application unrealized thus far in the present work.

The synthetic versatility of ferrocene also adds a dimension to the utility of this organometallic building block. Ferrocene readily undergoes electrophilic aromatic substitution reactions. Friedel−Crafts acylation is therefore particularly useful since it is facile and substitution of one ring normally deactivates ferrocene to further substitution. Additionally, 1,1′-ferrocenedicarboxylic acid is commercially available, and one of the two carboxyl groups can be selectively altered (see below). As a result of this versatility, a variety of spacer units can be

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Scheme 1

Scheme 2

incorporated into the molecular cleft. Although not necessarily limited to aromatic amine spacers, most of the Rebek clefts are constructed in increments of an aromatic ring.

Syntheses of Ferrocene Derivatives. For most of the receptor molecules reported here, an obvious starting material was commercially available 1,1′-ferrocenedicarboxylic acid (**7**). We attempted to differentiate the two identical carboxyl groups by formation of the intramolecular anhydride **8**. If successful, reaction of the anhydride with a nucleophile would afford the monoamide monoacid. The desired anhydride, recorded as problematic in the literature,[19] proved inaccessible. The known[20] dianhydride can react to afford monosubstituted product, but statistically, disubstituted product as well as diacid **7** may be expected. The latter approach was therefore not explored.

An alternate attempt involved reaction of 1,1′-ferrocenedicarboxylic acid into its intramolecular dicarboxylic acid acetonide by using isopropenyl acetate. In this case, only the ferrocenyl diacetyl anhydride shown in Scheme 1 was formed (70% yield). This compound presents a reactivity profile similar to that found for the dimer anhydride.

Compound **7** did, indeed, prove to be the starting material of choice. It could be readily converted into either the dimethyl (**9**) or diethyl (**10**)[21] esters (the latter is also commercially available). Partial hydrolysis of **9** was accomplished by using 5% NaOH in a mixture of MeOH/CH_2Cl_2/H_2O (1:2.5:1, v/v) at ambient temperature. Dichloromethane was present to enhance substrate solubility. The product **11** was obtained as an orange powder (mp 143−145 °C). Similar conditions were used for the partial hydrolysis of **10**. For those cases requiring it, the monoester of 1,1′-ferrocenedicarboxylic acid was converted to the monoester dichloride by using oxalyl chloride.[22] The monoester acid chloride **6** can react with diamines (incipient spacers) to form bis(amide) linkages (Scheme 2). The final step in the synthesis is mild hydrolysis of the ester groups. The

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receptors containing 4,13-diaza-18-crown-6, substituted benzidine, diaminofluorene, bipiperidine, and 1-(4-aminophenyl)-piperazine were thus synthesized.

Receptor Preparation. The preparation of the benzidinyl receptor compound **15** is typical. Monomethyl ferrocenedicarboxylate, **11** (see above), was treated with oxalyl chloride in C_5H_5N and CH_2Cl_2 to afford (88%) the red monochloride monoester **12** (mp 76–81 °C). The crude acid chloride was stirred with benzidine and Et_3N in CH_2Cl_2 for 4 h at ambient temperature. The orange diester receptor (**15**, diethyl ester) was obtained in ~60% yield (mp 245–249 °C). Hydrolysis of the ester groups was effected using 10% aqueous NaOH, and although the yield was high (>90%), the product was high melting (>440 °C) and relatively insoluble. Compounds **16**–**18** were prepared in a similar fashion.

4,4′-Diaminobiphenyl (benzidine, derivatives **15** and **16**) is a rigid diamine having a relatively long π-system, the extent of which depends on the angle between the two aromatic rings. In the limit (90°), an *ortho*-hydrogen on a ring parallel to ferrocene's axis will intrude directly into the guest cavity. Solid state structures of receptors incorporating the closely related 4,4′-bipyridyl unit[23] show that the inter-ring angle is typically about 30°.

Diaminofluorene is relatively large and flat and possesses a π-surface. Both the 2,7- and 3,7-isomers were studied. 2,7-Diaminofluorene is symmetrical and rigid (**17**). Addition of a methoxy group should enhance the π-donicity of the arene. More important, however, the methoxy group in 3,7-diamino-2-methoxyfluorene reduces the molecular symmetry: it increases the solubility of receptor **18** and permits binding to be followed by monitoring its distinctive ^1H-NMR spectrum (see below).
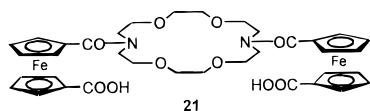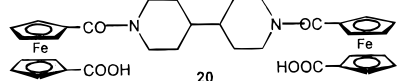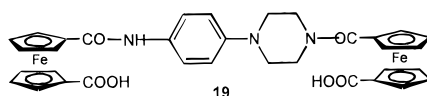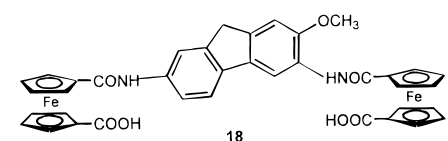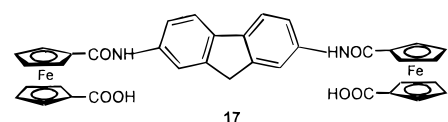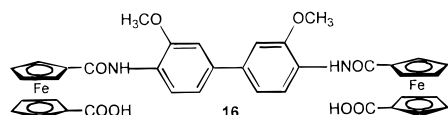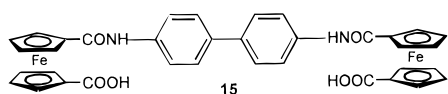
Several additional diamide receptor molecules were prepared. In contrast to **15**–**18**, compounds **19**–**21** contain partially or completely aliphatic spacer residues. Compound **19**, in which the spacer is phenylpiperazine, is a "transitional" structure in which the aromatic amide is secondary and the tertiary amide is aliphatic. 1-(4-Aminophenyl)piperazine was prepared by hydrogenation of 1-(4-nitrophenyl)piperazine. The N···N′ distance (~5.5 Å) estimated from CPK molecular models is approximately 1 Å shorter in **20** than in **19**.

4,13-Diaza-18-crown-6 differs from the other spacers described here but has qualities that commend it to this application. The N···N′ distance is known from various solid state structures[24] to be 5.2–5.8 Å depending upon conformation. Crown ethers can complex both metallic and organic cations by using the cyclic donor array. In principle, a guest might be bound on opposite sides by the carboxyl groups and, additionally, by a ring-bound, secondary guest. Indeed, we have shown that, in a related bis(crown) compound, two silver cations are simultaneously complexed.[25]

Attachment of the spacers may also be achieved by using a methylene group. The approach is illustrated for the crown analog **22** of **21**. The amide approach (to **21**) failed to afford anthraquinone derivatives. Although thin layer chromatography (TLC) suggested that the reaction of half-ester acid chloride **12** with 1,5-diaminoanthraquinone was successful, hydrolysis of the crude, presumed diester afforded an insoluble dark solid which could not be adequately characterized. Thus, 1-aminoanthraquinone was treated with methyl 1′-(chloromethyl)-ferrocenecarboxylate, **6**, to afford, after hydrolysis, **23**. Using this successful reaction as a model, bis(ferrocene) receptor **24** was prepared.
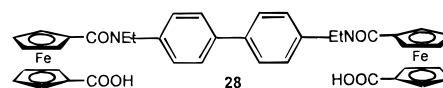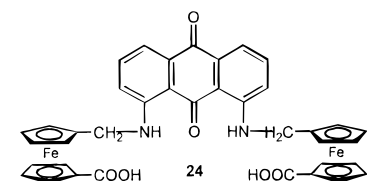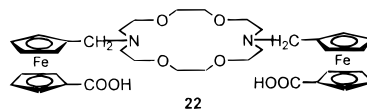
Synthetic Access by Friedel–Crafts Reaction. Ferrocene is electron rich and well known to undergo the Friedel–Crafts acylation reaction. In principle, selectivity can be achieved by use of this reaction since acylation in one ring deactivates it so that acylation in the second ring is preferred. Thus, naphthalene-2,6-dicarboxylic acid dichloride was allowed to react with methyl ferrocenecarboxylate and $AlCl_3$ in CH_2Cl_2 at ambient temperature for 30 min (Scheme 3). The red, naphthalene-bridged diester was isolated in 31% yield (mp 184–185 °C). Hydrolysis of the ester groups gave the red diacid, **25**, in 75% yield [mp 240 °C dec].

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Scheme 3
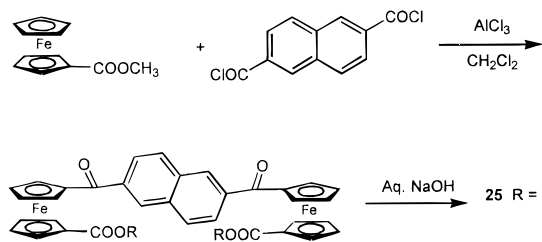
Scheme 4

Access by Imine Formation. Reaction of the formyl residue of 1-carbomethoxy-1′-formylferrocene, **4**,[26] with 1,4-phenylenediamine in CH_2Cl_2 afforded the relatively unstable bis(imine) in 31% yield (Scheme 4). Hydrogenation over Pt/C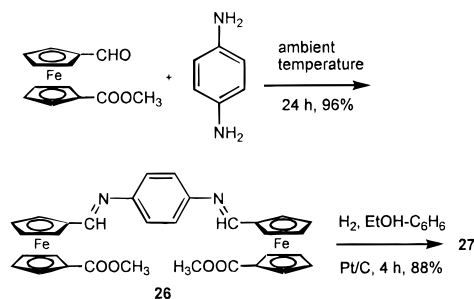 gave the yellow diester diamine **27** in 88% yield. Unfortunately, **27** decomposed on standing and could not be studied further. In principle, the precursor's C=N double bonds could be stabilized by the Diels−Alder reaction (*e.g.*, with Danishefsky's diene[27]), but this approach was not explored.

Enhancement of Receptor Solubility. Most of the compounds described in the present work are symmetrical, dicarboxylic acids having molecular weights in the range 500−1000. As a result, their solubility is poor in some cases. An attempt was made to improve solubility by converting the secondary carboxamide linkage into a tertiary *N*-ethylcarboxamide (see the Experimental Section). The conversion of the secondary into a tertiary amide has both steric and electronic implications (see below). This effort was successful to the extent that **28** was soluble enough for an assessment of binding (see Table 1).

Solid State Structure of 20. A crystal of the diethyl ester of compound **20** was obtained from a mixture of hexane/methylene chloride (1:1, v/v). Single-crystal structure analysis was conducted on a four-circle diffractometer using Mo Kα radiation. The structure obtained for diester **20** is shown in Figure 2.

The structure demonstrates several of the design features. For example, the ferrocene cyclopentadiene rings are coplanar with the amide linkage on both sides of the receptor. The resonance energies of the amide and cyclopentadiene require this planarity, but the orientation in solution of the carbonyl groups with respect to each other, *i.e., syn* or *anti*, is unknown. The *anti* arrangement balances carbonyl group dipoles and should be favored. The carboxylic acid residues are turned "inward" as envisioned for the binding conformation. The ferrocene axes are approximately parallel although the axes are oriented "*anti*" rather than "*syn*". This presumably minimizes the void space in the solid. The carboxyl groups are pointed inward as expected in the "complexing geometry".

We were unable to obtain crystals of a complex between **20** and any of the diamine substrates studied, but complex formation was confirmed in solution by the observation of a nuclear Overhauser effect between host and guest (see below).

Binding between Receptors and Substrates in Solution. Binding constants were determined for various receptors with a variety of diamines in either $CDCl_3$ or THF-d_8 by using dynamic ^{1}H-NMR methods.[28] In each case, a distinguishable proton was monitored as a function of substrate concentration. Chemical shift changes that were dependent on the substrate−receptor concentration ratio were taken as evidence for complexation. Splitting of the ferrocenyl signals (4.3−4.9 ppm) in the spectra of **18** increased with increments in substrate concentration. It is likely that if the guest locates itself within the molecular cleft, the decreased rotational freedom of the cyclopentadienyl residue would lead to increased splitting. A typical data plot, fitted logarithmically, is shown in Figure 3.

If the complexation and decomplexation rates are slow at the temperature of interest (activation energy $\Delta G^{\ddagger} \gg RT$), two distinct peaks are anticipated for an individual proton which can be distinguished in both A and A·B. However, if the rates of complexation and decomplexation are fast at the specified temperature, only one peak would be observed for the same proton in B and A·B. In all of the cases examined here ($t \approx 25$ °C), a single resonance was observed for a distinct proton in both B and A·B.

Typically, an exact amount of the receptor was dissolved in 1 mL of either $CHCl_3$ or THF-d_8 (sonication). About 800 μL of the sample was then titrated (15−20 increments) with a solution of the guest molecule. The concentration of receptor was typically ~1 mM and guest concentration was varied over a 20-fold range. A simple, 1:1 complexation model (A + B $\rightleftarrows$ A·B) was used in which A = host, B = guest, and A·B = complex.

A simple application of either Eadie−Hofstee[29] or Lineweaver−Burke[30] plots using the chemical shift change as a variable produced unsatisfactory results. The data obtained by the NMR method were thus subjected to nonlinear regression analysis. In each case, a titration curve was plotted of the proton chemical shift *vs* the concentration of substrate. Data were then fitted by a least squares calculation. Because exchange was fast on the NMR time scale, the following equation could be applied in which d is the observed chemical shift, d_B is the chemical shift of pure B and $d_{A·B}$ is the chemical shift of A·B:

$$d = \frac{[B]}{[B]\,[A·B]}d_B + \frac{[A·B]}{[B] + [A·B]}d_{AB}$$

The determinations described here are potentially prejudiced by self-association of either host or guest. No change in the chemical shift of any TMPDA proton was observed over a concentration range of 2.1−46.2 mg/mL (>20-fold). Likewise, self-association of **18** was assessed. No change was observed in the position of any aromatic proton. The chemical shifts of the amine protons changed slightly from 5.2087 ppm (0.8817 mM) to 5.2549 ppm at 91.48 mM (>100-fold concentration change). An average chemical shift value of 5.2346 was used in the appropriate calculations. It should also be noted that no chemical shift difference was observed for a solution containing varied concentrations of ferrocenecarboxylic acid and TMEDA.

Complexation studies identical to those described above were attempted using monoamines and monocarboxy "receptor"

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Table 1. Binding of Diamines by Ferrocenyl Receptors[a] (Å)

compd	substrate	distance[b]		K (M^{-1})	solvent
	Me$_2$N(CH$_2$)$_3$NMe$_2$		5.1	c	CHCl$_3$
18		7.0		c	CHCl$_3$
Fc-COOH	Me$_2$N(CH$_2$)$_2$NMe$_2$		3.8		CHCl$_3$
Fc-COOH	4-*tert*-butylpyridine				CHCl$_3$
Fc-COOH	pyrazine		2.8		CHCl$_3$
18	4-*tert*-butylpyridine	7.0			THF-d_8
18	pyrazine	7.0	2.8		THF-d_8
18	4,4′-bipyridine	7.0	7.2		THF-d_8
18	4-aminopyridine	7.0	4.2	$(3.2 \pm 0.4) \times 10^3$	THF-d_8
19	Me$_2$N(CH$_2$)$_3$NMe$_2$	8.2	5.1	3.2×10^3	CDCl$_3$
20	Me$_2$N(CH$_2$)$_2$NMe$_2$	6.8	3.8	129 ± 17	CDCl$_3$
20	Me$_2$N(CH$_2$)$_3$NMe$_2$	6.8	5.1	341 ± 32	CDCl$_3$
20	DABCO	6.8	2.5	604 ± 100	CDCl$_3$
20	3-propyladenine	6.8	4.2[d]	$(1.27 \pm 0.43) \times 10^3$	CDCl$_3$
20	benzimidazole	6.8	2.2	$K_1 = (3.9 \pm 0.6) \times 10^3$ $K_2 = 190 \pm 17$	CDCl$_3$
28	Me$_2$N(CH$_2$)$_2$NMe$_2$	9.0	3.5	61 ± 15	CDCl$_3$
28	Me$_2$N(CH$_2$)$_3$NMe$_2$	9.0	5.1	404 ± 150	CDCl$_3$
28	4,4′-bipyridine	9.0	7.2		CDCl$_3$

[a] All binding constants determined by NMR in the indicated solvent at 25 °C. [b] (See the text.) N···N distances, rounded to the nearest 0.1 Å, were measured using the computer program Sybyl and refer to the extended conformation for flexible diamines. [c] No change in chemical shift was observed for the compound under study over a 20-fold change in concentration. [d] Measurement is from the 6-amino group to N-9.
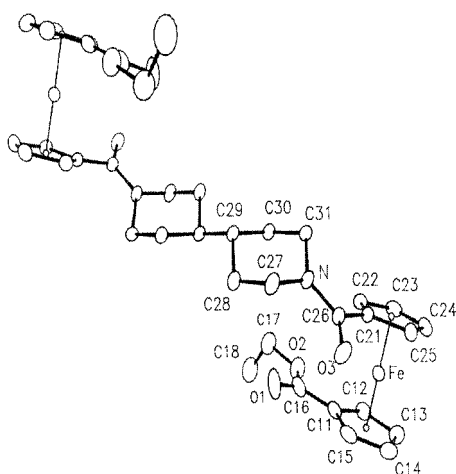
Figure 2. ORTEP plot showing the solid state structure of compound **20**.

Complexation of DABCO by 20 in CDCl$_3$
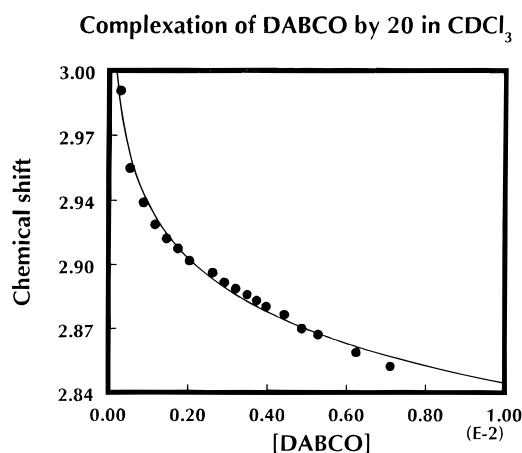
Figure 3. NMR titration curve for **20** and TMPDA.

molecules. No change in the NMR spectrum of **18** was observed during incremental addition of 4-*tert*-butylpyridine. Likewise, 1′-*N*-(morpholinocarbonyl)ferrocenecarboxylic acid[26] failed to exhibit any significant change in its NMR spectrum when incremental amounts of pyridazine were added. Binding constants are recorded in Table 1.

Binding by three of the receptor molecules with a variety of diamines proved to be successful in either THF-d_8 or CDCl$_3$

solution. The use of THF was required in the case of **18** because of its low solubility in CDCl$_3$. Among the compounds studied, **18** is unique in that its spacer unit (methoxyfluorene) is completely aromatic. In receptor **19**, the spacer is *N*′-(4-aminophenyl)piperidine; one ring is aromatic and one aliphatic. In the most studied receptor, **20**, both rings are aliphatic. In this respect, **20** differs from many of the previously reported receptor molecules.

Nitrogen−nitrogen bond distances for the potential guest molecules were calculated by the program "Sybyl". This program is not readily adaptable to sandwich complexes such as ferrocene so corresponding measurements could not be made on the guests. This was done by using CPK molecular models.[31] The distance between the two lines which bisected each carboxyl group was measured manually for each receptor in the putative binding conformation. The values obtained were as follows: **15**, 9.5 Å; **16**, 9.5 Å; **17**, 8.2 Å; **18**, 7.0 Å; **19**, 8.2 Å; **20**, 6.8 Å; **21**, 8.3 Å; **22**, 8.1 Å; **24**, 6.2 Å; **25**, 5.4 Å; **28**, 9.0 Å. An important aspect of these measurements is that they span a distance range that is not incremented by the width of an aromatic ring.

Several control experiments were conducted to establish boundary conditions for these studies. First, the NMR spectrum of Me$_2$N(CH$_2$)$_3$NMe$_2$, TMPDA, was recorded in CDCl$_3$ solution over a 100-fold concentration range. A similar, but more limited concentration range was studied for receptor **18**. In neither case was a significant chemical shift of any proton detected when the receptor or the diamine was studied in the absence of the presumed partner. Thus, self-association was ruled out as a major concern in the present studies. Similarly, equimolar concentrations of carboxyferrocene and TMEDA, 4-*tert*-butylpyridine, or pyrazine were studied by ^{1}H-NMR in CDCl$_3$. In all cases, the NMR spectra were essentially the same as the individual components despite the presumption of some proton transfer between amine and carboxylic acid.

Receptor **18**, which was soluble in THF-d_8 but not CDCl$_3$, was studied with four amines. 4-*tert*-Butylpyridine is a monoamine and, as expected, failed to alter the NMR spectrum of **18** in any ratio up to 1:1. Pyrazine is much smaller than the

(31) Molecular models of ferrocene were constructed by drilling a center hole in each five-membered aromatic ring and then connecting two rings with a bolt. This permitted rotation about the long axis, and the separation of the bisecting planes of each cyclopentadienyl ring was only slightly larger than 3.25 Å.

cavity size of **18** estimated from CPK models, and binding to it could not be detected. 4,4′-Bipyridine is estimated to be slightly larger than the cavity of **18**, but it is a rigid diamine and does not appear to fit, at least as judged from the NMR spectrum. 4-Aminopyridine is of appropriate size to fit within the cavity of **18**. Although the fit is not perfect, CPK models suggest that a relatively small adjustment of each ferrocene leads to a reasonably complementary complex. This is reflected in a binding constant of ∼3200 M^{-1}.

Receptor **19** was studied only with TMPDA, but the estimated difference in host and guest sizes is, like the **18**·4-aminopyridine case above, about 3 Å. The experimentally determined binding constant is nearly the same in both cases although binding is probably weaker for **19**·TMPDA because the latter was studied in less polar CDCl$_3$. Binding between 3-propyladenine and **20** has a similar size relationship and complexation strength. In this case, there is the added issue of π-stacking that is difficult to assess in solution studies such as these. The possibility that π-interactions are important is suggested by the fact that benzimidazole is also bound well by **20**. An alternate interpretation is that rigid substrates bind with a lower energy cost because they have fewer degrees of freedom. The fact that **20** is constructed from 4,4′-bipiperidyl, an aliphatic spacer, reinforces this possibility.

The availability of **28** permitted us to test this speculation. Measurements of the receptor and TMEDA, TMPDA, and 4,4′-bipyridine suggested that the aliphatic amines were substantially smaller than the receptor but that the latter should be an almost perfect fit and might exhibit π-stacking. Binding of TMEDA by **28** was weak, but the larger TMPDA was bound more strongly. No change in the ^{1}H-NMR spectrum of either **28** or 4,4′-bipyridyl was observed in CDCl$_3$ at any concentration studied. These data suggest that basicity may play a major role in guest binding by these compounds.

To the best of our knowledge, acidity constants have not been measured for the guests used in this study in the solvents of interest to us. Constants for several diamines in water or related diamines are, however, available in the literature: *N,N,N′,N′*-tetramethylethylenediamine (Me$_2$NCH$_2$CH$_2$NMe$_2$, TMEDA), $pK_1 = 10.7$, $pK_2 = 7.7$;[28] DABCO (diazabicyclooctane), $pK_1 = 8.2$, $pK_2 = 4.2$;[11d] 1,3-propylenediamine, $pK_2 = 10.94$, $pK_1 = 9.03$;[32] 4-aminopyridine, $pK_A = 9.11$;[29] benzimidazole, $pK_1 = 9.33$, and $pK_2 = 5.48$.[29] Obviously, pK_A values change with solvent, but related compounds normally show proportional variations.

As noted above, 4,4′-bipyridine is not bound by **28** even though it seems to be an appropriate substrate for this receptor. This suggests that basicity plays an important role. Apparently, proton transfer and salt bridge formation are required for effective host−guest association by the structures studied here. The role of π-stacking in this system remains elusive as it does in many other complexes.[33]

Structure of the Complex in Solution from NOE Results. The downfield shift of the methyl group proton in *N,N,N′,N′*-tetramethylpropylenediamine indicates that the binding involves proton transfer; the guest would be bound by double salt bridge formation in a cavity of appropriate size. The NOE (nuclear Overhauser effect) provides information about coupling which, in turn, can be related to internuclear distances and molecular motion. The NOE is proportional to the inverse of the distance between the nuclei raised to the sixth power. If the normal intensity of a resonance is I_0, a change in the intensity observed while saturating some other resonance is I and the NOE is defined as

$$\eta_i(s) = (I - I_0)/I_0$$

The 1-(4-aminophenyl)piperazine receptor (**19**) was chosen instead of the bipiperidine host (known solid state structure) for these studies because of a concern over complex stability. This receptor has a high binding constant toward TMPDA (room temperature, 1:1 ratio, [receptor]:[substrate]). Receptor **19** is less symmetrical than **20**, so its NMR spectrum is more revealing.

Upon selective irradiation of the methylene hydrogen (H$_a$) in the substrate, an NOE was observed to H$_b$ ($\eta = 13\%$) in the receptor. The structural relationship shown in Figure 4 is inferred from a CPK model of the complex between compound **19** and TMPDA. The proximity of H$_a$ in the substrate and H$_b$ of the piperidine ring, as suggested by the models, is in accord with the NOE observation. Since the NOE experiment was performed at room temperature, molecular motion precluded the observation of any other NOE.

Redox Properties of 24. An as yet unexplored dimension of these receptor molecules is their ability to change properties as a result of redox switching. Ferrocene can readily be oxidized at positive potentials, and anthraquinone can undergo two redox reactions at negative potentials. The cyclic voltammogram was determined for **24** in THF containing 0.1 M Et$_4$NPF$_6$ as supporting electrolyte. The two redox waves characteristic of anthraquinone and the clean ferrocene redox wave are all apparent. In principle, the character of these molecular receptor molecules could be substantially altered by the application of a controlled potential.

Conclusion

A family of novel molecular receptors based on the ferrocene building block were designed and synthesized. Detailed analyses, including measurements of binding constants with various substrates, the ionization constants of the functional groups (pK_A), and determination of solution NMR spectra and solid state structure, were undertaken. The synthetic schemes we have tried proved that ferrocene is a versatile subunit for the construction of molecular clefts. A series of molecular receptors bearing different functional groups and different electronic character can be readily synthesized. Single-crystal X-ray analysis of the diethyl ester of receptor **20** has provided structural details that confirm the design concept of the system.

These receptors can effectively bind small molecular substrates. The binding constants for complexation of diamines are in the range of 10^2-10^4 in either CDCl$_3$ or THF-d_8, and depend on the basicities and sizes of substrates. The correct substrate can selectively organize the receptor to the appropriate conformation, which provides an additional element of recognition. The anticipated complexation arrangement has been confirmed by NOE spectra of the complex between **19** and TMPDA. It was concluded from the NOE result that the anticipated molecular organization required for complexation was achieved. The molecular distance between the two ferrocene pillars is defined by the relatively rigid scaffold. Accessibility of the cavity is presumably enhanced by rotation of the carboxyl groups away from it during complexation. After contact, the "ball bearing" feature of ferrocene permits a low-energy conformational adjustment leading to binding. We infer that this type of flexibility is an advantage since the molecular "backbone" in this system is less rigid than other systems but the molecular cavity is presumably more accessible, leading to binding that is competitive with other systems.

Experimental Section

General Procedures. ^{1}H-NMR were recorded at 400 MHz in CDCl$_3$ solvents and are reported in parts per million (δ) downfield from internal (CH$_3$)$_4$Si unless otherwise specified. Infrared spectra were calibrated

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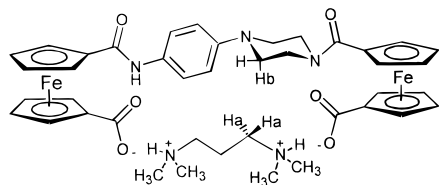(33) Hamilton, A. D. *Adv. Supramol. Chem.* **1990**, *1*, 1.

Figure 4. Complex structure for solution interaction between **19** and TMPDA inferred from NOE studies.

against the 1601 cm^{-1} band of polystyrene. Melting points were measured in open capillaries and are uncorrected. Thin layer chromatographic (TLC) analyses were performed on aluminum oxide 60F-254 neutral (type E) with a 0.2 mm layer thickness or silica gel 60F-254 plates with a 0.20 mm layer thickness. Preparative chromatography columns were packed with activated aluminum oxide (MCB 80−325 mesh, chromatographic grade, AX611) or with Kieselgel 60 (70−230 mesh).

All reactions were conducted under dry N_2 unless otherwise stated. All reagents were the best (non-LC) grade commercially available and were distilled, recrystallized, or used without further purification, as appropriate. Molecular distillation temperatures refer to the oven temperature of a Kugelrohr apparatus. Combustion analyses were conducted by Atlantic Microlab Inc., Atlanta, GA, and are reported as percents. Values given for molecular weights were determined by fast atom bombardment mass spectrometric analysis and are reported in daltons to the nearest integer.

X-ray Crystal Study. The crystal was prepared by dissolving it in a mixture of hexane and methylene chloride (1:1, v/v) and permitting slow evaporation of the solvent. The crystals were capillary mounted and the reflections recorded using a graphite monochrometer, radiation used was Mo Kα ($m = 9.20$ cm^{-1}). Crystal data: $C_{34}H_{36}N_2O_6Fe_2$, FW = 680.36, crystal system monoclinic, space group $P2_1/n$, $a = 10.204(1)$ Å, $b = 10.124(1)$ Å, $c = 16.614(1)$ Å, $\beta = 103.204(7)°$, $V = 1671$ Å^3, $z = 2$, $d_c = 1.469$ g cm^{-1}, Mo Kα ($m = 9.20$ cm^{-1}), $R = 0.0352$ for 2113 unique reflections with $I > 3\sigma(I)$ (of 2817 unique data) measured by an Enraf-Nonius CAD4 X-ray spectrometer by $\theta - 22$ scans, $2° < 22 < 48°$. All non-hydrogen atoms were refined with anisotropic thermal parameters.

Ferrocene (1), ferrocenecarboxylic acid (2), and methyl ferrocenecarboxylate (3) were obtained commercially, purified by standard methods, or used as received as appropriate.

1′-Carbomethoxy-1-formylferrocene (4), 1′-carbomethoxy-1-(hydroxymethyl)ferrocene (5), and 1′-carbomethoxy-1-(chloromethyl)ferrocene (6) were prepared as recently described.[26] **1,1′-Dicarboxyferrocene, 7,** was obtained commercially and used as received.

Attempted Preparation of 1,1′-Dicarboxyferrocene Anhydride, 8. A solution of 1,1′-ferrocenedicarboxylic acid (0.10 g, 0.37 mmol) in 10 mL of dry THF was sonicated (bath) for 2 min to afford a finely suspended mixture. To this was added dropwise a solution of *N,N′*-dicyclohexylcarbodiimide (DCC, 0.075 g, 0.37 mmol). The reaction was stirred (ambient temperature) overnight, diluted with Et₂O, quenched with H_2O, extracted with Et₂O, washed with brine, dried (MgSO₄), filtered, and concentrated *in vacuo* to afford a thick, dark yellow oil. Purification was attempted by column chromatography (silica, 50% EtOAc/hexanes, EtOAc, and finally 50% 2-PrOH/EtOAc), but the product decomposed on the column. When the reaction was attempted using Et₂O or CH₂Cl₂ as solvent, no product was obtained due to the low solubilities of the stating materials.

An attempt was also made to convert 1,1′-ferrocenedicarboxylic acid into the anhydride by using triphenylphosphine and diethyl azodicarboxylate. Numerous new spots were observed in the reaction mixture, and no further purification was undertaken.

Dimethyl 1,1′-ferrocenedicarboxylate, 9, was obtained commercially and used as received.

1′-Carbomethoxy-1-carboxyferrocene (11) and 1′-carbomethoxy-1-(chlorocarbonyl)ferrocene (12) were prepared as recently described.[26]

1-Carboxy-1′-carbethoxyferrocene, 13. To diethyl 1,1′-ferrocenedicarboxylate (**10**, 3.79 g, 12.5 mmol) was added a solution containing EtOH (200 mL), 5% aqueous NaOH (100 mL), and CH₂Cl₂ (100 mL). The reaction mixture was stirred at ambient temperature for 4 h and

then acidified (3 N HCl, pH 2). Water (500 mL) was added, and the reaction mixture was extracted (CH₂Cl₂, 2 × 200 mL) and dried (MgSO₄), the solvent was evaporated, and the resulting oil was chromatographed (silica, 5% MeOH/CH₂Cl₂ as eluent) to give **13** (1.5 g, 30%) as an orange solid. Its structure was confirmed only by ¹H-NMR: 1.37 (t, 6H), 4.28 (q, 4H); 4.40 (s, 4H); 4.48 (s, 4H); 4.56 (t, 4H), 4.65 (s, 4H) ppm.

1-Carbethoxy-1′-(chlorocarbonyl)ferrocene, 14. To a mixture of 1-carboxy-1′-carbethoxyferrocene (1.0 g, 3.5 mmol), CH₂Cl₂ (10 mL), and pyridine (~40 mg) was added oxalyl chloride (8 mL). The reaction was stirred for 4 h (ambient temperature), the solvent was evaporated, and the residue was dissolved in Et₂O (50 mL) and filtered. Evaporation *in vacuo* of the solvent gave the acid chloride (0.88 g, 88%) as a dark red solid which was used without further purification.

Preparation of *N,N′*-Bis[1-carbonyl-1′-carbomethoxyferrocenyl]-benzidine, 15. Preparation of the Dimethyl Ester of 15. To benzidine (300 mg, 1.6 mmol) in CH₂Cl₂ 50 mL) containing Et₃N (1 mL) was added dropwise during 30 min a solution of 1-(chlorocarbonyl)-1′-carbomethoxyferrocene (**12**, 1.0 g, 3.3 mmol) in CH₂Cl₂ (25 mL). The mixture was stirred at ambient temperature for 4 h, the solvent was evaporated, and the crude material was chromatographed over silica (1:32 MeOH/CH₂Cl₂) to afford the diester of **15** (720 mg, 62%) as an orange powder, mp 245−249 °C dec. IR: 3330 (w), 1750−1550 (s), 1500 (s), 1280 (s), 1130 (s) cm^{-1}. ¹H-NMR: 8.24 (s, 2H), 7.83 (d, $J = 8$ Hz, 4H), 7.62 (d, $J = 8$ Hz, 4H), 4.82 (d, $J = 1.7$ Hz, 4H), 4.66 (d, $J = 1.5$ Hz, 4H), 4.52 (t, $J_1 = 1$ Hz, $J_2 = 0.6$Hz, 4H), 4.48 (d, $J = 0.8$ Hz, 4H), 3.86 (s, 6H) ppm. Anal. Calcd for $C_{38}H_{32}N_2O_6Fe_2$: C, 63.00; H, 4.45%. Found: C, 63.12; H, 4.74.

Hydrolysis To Afford 15. To a solution of the dimethyl ester (0.5 g, 0.7 mmol) in dimethoxyethane (DME, 20 mL) was added a solution of LiOH (2.0 g) in H_2O (20 mL). The reaction mixture was heated under reflux for 12 h, diluted with 10% aqueous NaOH (50 mL), and then extracted with CH₂Cl₂ (2 × 50 mL). The aqueous phase was acidified to pH 2 with 3 N HCl, and the solution was filtered to afford **15** (448 mg, 93%) as a brown powder, mp >440 °C. IR: 3680−2120 (s), 1630 (s), 1480 (s), 1270 (s), 810 (m) cm^{-1}. ¹H-NMR (DMSO-d_6): 9.54 (s, 2H), 7.80 (d, $J = 8$ Hz, 4H), 7.65 (d, $J = 9$ Hz, 4H), 5.04 (s, 4H), 4.71 (s, 4H), 4.46 (s, 8H) ppm. Anal. Calcd for $C_{36}H_{28}N_2O_6Fe_2$: C, 62.10; H, 4.05. Found: C, 61.72; H, 4.16.

Preparation of *N,N′*-Bis[1-carbonyl-1′-carbomethoxyferrocene]-3,3′-dimethoxybenzidine, 16. Preparation of the Dimethyl Ester of 16. To a solution of 3,3′-dimethoxybenzidine (398 mg, 1.6 mmol) in CH₂Cl₂ (50 mL) containing Et₃N (1 mL) was added dropwise (130 min) a solution of 1-(chlorocarbonyl)-1′-carbomethoxyferrocene (**12**, 1.0 g, 3.3 mmol) in CH₂Cl₂ (25 mL). The mixture was stirred at ambient temperature for 5 h, the solvent was then evaporated *in vacuo*, and the residue was chromatographed over silica (1:32 MeOH/CH₂Cl₂ as eluent) to afford the dimethyl ester of **16** (572 mg, 46%) as an orange powder, mp 200−205 °C. IR: 3400 (w), 2950 (w), 1680 (s), 1480 (s), 1370 (s), 1140 (s), 1020 (s), 820 (m) cm^{-1}. ¹H-NMR: 8.49 (d, $J = 8$ Hz, 2H), 8.16 (s, 2H), 7.24 (q, $J_1 = 1.7$ Hz, $J_2 = 6.6$ Hz, 2H), 7.14 (d, $J = 1.7$ Hz, 2H), 4.90 (d, $J = 1.5$ Hz, 4H), 4.81 (d, $J = 7.5$ Hz, 4H), 4.48 (d, $J = 1.5$ Hz, 4H), 4.45 (d, $J = 1.5$ Hz, 4H), 4.06 (s, 6H), 3.75 (s, 6H). DCI mass spectrum, *m/z* (relative intensity): 785 (38, M + 1), 784 (15, M⁺), 753 (4), 515 (17), 271 (8), 125 (100), 93(51). Anal. Calcd for $C_{40}H_{36}N_2O_8Fe_2$: C, 61.25; H, 4.63. Found: C, 60.99; H, 4.70.

Hydrolysis of the Diester To Afford 16. To a solution of the diester (0.5 g, 0.64 mmol) in DME (20 mL) was added a solution of aqueous LiOH (2.0 g, 20 mL of H_2O). The reaction was heated under reflux for 10 h, and the mixture was diluted with 50 mL of 10% aqueous NaOH solution, acidified to pH 2 with 3 N HCl, and filtered to afford **16** (440 mg, 91%) as a pale brown solid, mp 171 °C dec. IR: 3670−2300 (s), 1660 (s), 1510 (s), 1250 (s), 820 (m) cm^{-1}. ¹H-NMR (DMSO-d_6): 8.82 (s, 2H), 7.82 (d,$J = 8$ Hz, 2H), 7.39 (s, 2H), 7.30 (d, $J = 8$Hz, 2H), 4.98 (s, 4H), 4.78 (s, 4H), 4.52 (s, 4H), 4.47 (s, 4H), 4.01 (s, 6H) ppm. Anal. Calcd for $C_{38}H_{32}N_2O_8Fe_2$: C, 60.34; H, 4.26. Found: C, 60.23; H, 4.30.

2,6-Bis(1′-carboxy-1-(carbonylamino)ferrocenyl)fluorene, 17. Preparation of the Diester of 17. To a solution of 1′-carbomethoxyferrocenecarboxylic acid chloride (1.78 g, 5.8 mmol) in CH₂Cl₂ (100 mL) were added 2,6-diaminofluorene (0.57 g, 2.9 mmol) and Et₃N (0.65 g, 6.4 mmol). The reaction mixture was magnetically stirred at ambient

temperature for 8 h, and aqueous HCl (1 N, 200 mL) was added. The mixture was extracted (CH_2Cl_2, 500 mL) and dried ($MgSO_4$), the solvent was removed *in vacuo*, and the residue was chromatographed over alumina (3% MeOH in CH_2Cl_2 as eluent) to give the diester (1.0 g, 47%) as an orange solid, mp 225–227 °C. ^{1}H-NMR: 3.86 (s, 6H); 3.97 (s, 2H); 4.48 (t, 4H); 4.53 (t, 4H); 4.68 (t, 4H); 4.84 (t, 4H); 7.65 (d, 2H); 7.71 (d, 2H); 8.06 (s, 2H); 8.26 (s, 2H). FAB/MS molecular weight calcd for $C_{39}H_{32}N_2O_6Fe_2$: 736.4, found 736.

Hydrolysis To Afford 17. A solution of 2,6-bis[[1′-(carbomethoxyferrocenyl)carbonyl]amino]fluorene (0.8 g, 1.1 mmol) in a mixed solvent (5% NaOH, H_2O/MeOH/CH_2Cl_2, 2:5:2, 500 mL) was stirred at ambient temperature under N_2 for 10 h, CH_2Cl_2 and MeOH were evaporated *in vacuo*, the aqueous solution was acidified (0.3 N HCl), and the precipitate was filtered and washed with H_2O and then CH_3-OH (3×). The product was dried *in vacuo* (ambient temperature) to give **17** (0.76 g, 80%) as an orange solid, mp >300 °C. ^{1}H-NMR (DMSO-d_6): 3.92 (s, 2H); 4.46 (s, 8H); 4.74 (s, 4H); 5.06 (s, 4H); 7.64 (d, 2H); 7.74 (d, 2H); 7.95 (s, 2H); 9.52 (s, 2H). Anal. Calcd for $C_{37}H_{28}N_2O_6Fe_2$: C, 62.74, H, 3.98, N, 3.95. Found: C, 62.53, H, 4.02, N, 3.94.

2-Methoxy-3,7-bis[[1′-(carboxyferrocen-1-yl)carbonyl]amino]-fluorene, 18. Preparation of the Dimethyl Ester of 18. To 368 mg (1.6 mmol) of 2-methoxy-3,7-diaminofluorene dissolved in CH_2Cl_2 (50 mL) and Et$_3$N (1 mL) at ambient temperature was added dropwise (20 min) a solution of 1-(chlorocarbonyl)-1′-(methoxycarbonyl)ferrocene (1.0 g, 3.3 mmol). The mixture was stirred for 3 h, the solvent was evaporated, and the crude product was chromatographed over silica using 1:32 MeOH/CH_2Cl_2 to afford the diester of **18** (623 mg, 51%) as an orange powder, mp 134–136 °C. ^{1}H-NMR: 8.82 (s, 1H), 8.23 (s, 1H), 8.21 (s, 1H), 8.1 (s, 1H), 7.72 (d, *J* = 8 Hz, 1H), 7.56 (d, *J* = 8 Hz, 1H), 7.13 (s, 1H), 4.90 (t, *J* = 2 Hz, 2H), 4.83 (quintuplet, 4H), 4.68 (s, 2H), 4.51 (t, *J* = 2 Hz, 2H), 4,49 (t, *J* = 2 Hz, 2H), 4.45 (s, 4H), 4.03 (s, 3H), 3.88 (s, 2H), 3.85 (s, 3H), 3.73 (s, 3H) ppm. IR: 3360 (br, m), 2900 (w), 1670 (br, s), 1460 (s), 1280 (s) cm^{-1}. DCI mass spectrum, *m/z* (relative intensity): 767 (1, M + H$^+$), 766 (<1, M$^+$), 271 (5), 214 (4), 125 (100). Anal. Calcd for $C_{40}H_{34}N_2O_7Fe_2$: C, 62.69; H, 4.47. Found: C, 62.60; H, 4.70.

Hydrolysis To Give N,N′-Bis[1-carbonyl-1′-carboxyferrocenyl]-3-methoxy-2,7-diaminofluorene, 18. To a solution of 0.5 g (0.65 mmol) of N,N′-bis[1-carbonyl-1′-carbomethoxyferrocenyl]-2-methoxy-3,7-diaminofluorene in DME (20 mL) was added a solution of 2 g of LiOH in 20 mL of H_2O (20 mL). The reaction was heated at reflux temperature (12 h), diluted with 50 mL of 10% NaOH, and extracted 2× with CH_2Cl_2. The aqueous solution was acidified to pH 2 with 3N HCl and filtered to afford an orange-brown powder (412 mg, 86%), mp 196–200 °C. IR: 3570–2110 (s), 1610 (s), 1460 (s), 1260 (s), 1020 (m), 820 (m) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 9.53 (s, 1H), 8.90 (s, 1H), 8.10 (s, 1H), 8.01 (s, 2H), 7.72 (s, 1H), 7.66 (s, 1H), 7.36 (s, 1H), 5.05 (s, 2H), 4.98 (s, 2H), 4.79 (s, 2H), 4.74 (s, 2H), 4.54 (s, 2H), 4.47 (s, 6H), 3.94 (s, 3H), 3.42 (s, 2H) ppm. Anal. Calcd for $C_{38}H_{30}N_2O_7Fe_2$: C, 61.82; H, 4.10. Found: C, 62.02; H, 4.24.

1,4′-Bis[(1′-carboxyferrocenyl)carbonyl](4-aminophenyl)pipera-zine, 19. Preparation of the Dimethyl Ester of 19. To a solution of 1′-(carbomethoxy)ferrocenecarboxylic acid chloride (1.80 g, 5.9 mmol) in CH_2Cl_2 (100 mL) were added 4-aminophenylpiperazine (0.50 g, 2.8 mmol, prepared by hydrogenation of 4-piperidinylnitrobenzene, mmol) and Et$_3$N (0.65 g, 6.4 mmol). The reaction mixture was magnetically stirred at ambient temperature for 8 h. Aqueous HCl solution (0.1 N, 200 mL) was added, and then the product was extracted by CH_2Cl_2 (200 mL) twice. The combined organic phase was dried over $MgSO_4$. The solvent was removed *in vacuo,* and the residue was chromatographed over alumina (3% MeOH in CH_2Cl_2 as eluent) to give an orange solid (1.33 g, 68%), mp 181–184 °C. ^{1}H-NMR: 3.16 (t, 4H); 3.80 (s, 6H); 3.84 (t, 4H); 4.34 (t, 2H); 4.40 (t, 2H); 4.50 (t,2H); 4.52 (t, 2H); 4.60 (t, 2H); 4.68 (t, 2H); 4.78 (t, 2H); 4.85 (t, 2H); 6.92 (d, 2H); 7.65 (d, 2H); 8.18 (s, 1H) ppm. Anal. Calcd for $C_{36}H_{35}N_3O_6Fe_2$: C, 60.27; H, 4.92; N, 5.86. Found: C, 60.14; H, 4.98; N, 5.82.

Hydrolysis of the Diester To Afford 19. To the mixed solvent of 5% NaOH in H_2O/MeOH/CH_2Cl_2 (200 mL, 40:100:40 (v/v)) was added bis[1-(carbonylmethoxy)ferrocenyl]-(4-aminophenyl)piperazine (0.5 g, 0.70 mmol). The reaction mixture was stirred at ambient temperature for 10 h. Aqueous HCl (0.3 N, 100 mL) was added. The mixture was extracted with CH_2Cl_2 (2 × 250 mL). The combined organic phase

was dried over $MgSO_4$. The solvent was removed *in vacuo* to afford a yellow solid, mp 126–128 °C. ^{1}H-NMR: 3.15 (t, 4H); 3.82 (t, 4H); 4.38 (s, 2H); 4.40 (s, 2H); 4.44 (s, 2H); 4.50 (s, 2H); 4.55 (s, 2H); 4.64 (s, 2H); 4.70 (s, 2H); 6.90 (d, 2H); 7.70 (d, 2H); 8.10 (s, 1H) ppm. Anal. Calcd for $C_{34}H_{31}N_3O_6Fe_2$·H_2O: C, 57.74; H, 4.70; N, 5.94. Found: C, 57.93; H, 4.67; N; 5.87.

4,4′-Bis[(1′-carbomethoxyferrocenyl)carbonyl]bipiperidine, 20. Preparation of the Dimethyl Ester of 20. To a solution of **12** (0.35 g, 1.1 mmol) in CH_2Cl_2 (25 mL) was added 4,4′-bipiperidine (85 mg, 0.51 mmol) followed by addition of Et$_3$N (1.0 g, mmol). The reaction mixture was stirred at ambient temperature for 10 h. Water (200 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 200 mL). The organic phase was dried ($MgSO_4$), the solvent was evaporated, and the resulting oil was chromatographed (alumina, 1% MeOH/CH_2-Cl_2 as eluent) to give the dimethyl ester of **20** (0.16 g, 46%) as an orange solid, mp 181–184 °C. ^{1}H-NMR: 1.21 (m, 4H); 1.37 (m, 2H). 1.68 (s, 4H); 1.76 (d, 4H); 2.80 (br, 4H); 3.81 (s, 6H); 4.31 (t, 4H); 4.50 (d, 4H); 4.57 (d, 4H); 4.86 (t, 4H) ppm. IR: 3100 (m), 2860– 2960 (m); 1710 (s); 1605 (s); 1455 (s); 1420 (s); 1284 (s); 1150 (s) cm^{-1}. Anal. Calcd for $C_{36}H_{40}N_2O_6Fe_2$: C, 61.04; H, 5.69; N, 3.95. Found: C, 61.25; H, 5.96; N, 3.76.

Preparation of the Diethyl Ester of 20. The title compound was prepared by a procedure similar to that described above. The product (59%) was obtained as an orange powder, mp 133–136 °C. ^{1}H-NMR: 1.20 (m, 4H); 1.36 (t, 6H); 1.74 (m, 8H); 2.78 (m, 2H); 4.28 (q, 4H); 4.30 (s, 4H); 4.49 (4H); 4.57 (s, 4H); 4.87 (s, 4H) ppm. Anal. Calcd for $C_{38}H_{44}N_2O_6Fe_2$: C, 61.98; H, 6.02; N, 3.80. Found: C, 62.04; H, 6.03; N, 3.79.

4,4′-Bis[(1′-carbomethoxyferrocenyl)carbonyl]bipiperidine, 20. Hydrolysis of the Dimethyl Ester. To a suspension of 0.80 g (1.2 mmol) of N,N′-bis[1-carbonyl-1′-carbomethoxyferrocenyl]-4,4′-bipiperidine in 75 mL of EtOH was added a solution of 5 g of NaOH in 75 mL of H_2O. The reaction was allowed to stir at 45 °C for 48 h, the mixture was acidified with 1 N HCl and extracted with CH_2Cl_2, the organic layer was dried over $MgSO_4$, the solvent was evaporated, and the crude material was chromatographed over aluminum oxide (absolute EtOH) to afford the diacid (0.15 g, 19%) as an orange solid, mp 230 °C dec. Anal. Calcd for $C_{34}H_{36}N_2O_6Fe_2$ (MW 680.36): C, 60.02; H, 5.30; N, 4.12. Found: C, 60.06; H, 5.36; N, 4.07.

4,13-Bis[(1′-carboxyferrocenyl)carbonyl]diaza-18-crown-6, 21. Preparation of 21. To a solution of 1′-carbomethoxy-ferrocenecarboxylic acid chloride (0.68 g, 2.2 mmol) in CH_2Cl_2 (100 mL) were added 4,13-diaza-18-crown-6 (0.29 g, 1.1 mmol) and Et$_3$N (0.5 g, 4.9 mmol). The reaction mixture was stirred at ambient temperature for 8 h. Water (200 mL) was added, and the mixture was extracted twice with CH_2Cl_2 (100 mL). The combined organic phase was dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and the residue was chromatographed over alumina (3% MeOH in CH_2Cl_2 as eluent). The product (0.56 g, 68%) was obtained as an orange solid, mp 161–163 °C. ^{1}H-NMR: 3.55 (t, 8H); 3.59 (s, 8H); 3.75 (t, 8H); 3.83 (s, 6H); 4.48 (t, 4H); 4.53 (t, 4H); 4.68 (t, 4H); 4.84 (t, 4H) ppm. DCI mass spectrum, *m/z* (relative intensity): 803 (3, M + 1), 679 (1), 271 (10), 125 (100), 92(49). Anal. Calcd for $C_{38}H_{46}N_2O_{10}Fe_2$: C, 56.88; H 5.78. Found: C, 56.86; H, 5.82.

Hydrolysis To Give 21. The solution of 4,13-bis[(1′-carbomethoxyferrocenyl)carbonyl]diaza-18-crown-6 (0.56 g, 0.62 mmol) in the mixed solvent (50 mL, 5% NaOH (aq)/MeOH/CH_2Cl_2, 40:100:40) was stirred at ambient temperature for 10 h. The mixture was evaporated *in vacuo* to remove solvent. The aqueous phase was acidified with 0.3 N HCl-(aq) to pH = 2. The product was extracted with CH_2Cl_2 (200 mL) three times. The combined organic phase was dried over $MgSO_4$. The solvent was evaporated *in vacuo*. The residual was washed by ethyl ether (∼20 mL) and dried under vacuum at ambient temperature. The product was obtained (0.23 g, 43%) as a yellow solid, mp 205 °C dec. ^{1}H-NMR: 3.92 (s, 2H); 4.46 (s, 8H); 4.74 (s, 4H); 5.06 (s, 4H); 7.64 (d, 2H); 7.74 (d, 2H); 7.95 (s, 2H); 9.52 (s, 2H) ppm. Anal. Calcd for $C_{36}H_{42}N_2O_{10}Fe_2$: C, 55.83; H, 5.47; N, 3.62. Found: C, 55.81; H, 5.69; N, 3.67.

N,N′-Bis[(1′-carbomethoxyferrocenyl)methyl]-4,13-diaza-18-crown-6, 22. To a mixture of diaza-18-crown-6 (0.54 g, 2.06 mmol) and 1.06 g of Na_2CO_3 in THF (20 mL) was added dropwise a solution of 1-carbomethoxy-1′-(chloromethyl)ferrocene (from 2.74 g of **5**). The solvent was removed *in vacuo*, and dry MeCN (50 mL) was added.

The reaction mixture was heated at reflux for 6 h, allowed to cool, and filtered. The filtrate was concentrated *in vacuo*. Water (200 mL) was added, and the residue was extracted with CH_2Cl_2 (2 × 100 mL). The solvent was evaporated *in vacuo*. The resulting material was chromatographed over alumina (5% $MeOH/CH_2Cl_2$ as eluent) to give **22** (1.84 g, 51%) as an orange solid, mp 91−93 °C. NMR: 4.73 (t, 2H); 4.34 (t, 2H); 4.16 (s, 2H); 4.13 (s, 2H); 3.84 (s, 3H); 3.59 (s, 4H); 3.55 (t, 4H); 3.47 (s, 2H); 2.68 (t, 4H) ppm. FAB/MS molecular ion determination: calcd for $C_{38}H_{50}N_2O_8Fe_2$ 774.5, found 774.

N-1-[(1′-Carbomethoxylferrocenyl)methyl]-1-aminoanthra-quinone, 23. Sodium hydride (0.48 g) was added to a stirred solution of 1-aminoanthraquinone (2.04 g, 9.1 mmol) in DMF (40 mL). 1-Carbomethoxy-1′-(chloromethyl)ferrocene (from 2.50 g of the alcohol, 9.1 mmol) in THF (100 mL) was then added dropwise, and the mixture was heated to reflux temperature for 48 h. The mixture was allowed to cool to ambient temperature. The reaction was quenched by addition of water (200 mL) and extracted with CH_2Cl_2 (3 × 150 mL), the combined organic phase was dried over Na_2SO_4, and the solvent was removed *in vacuo*. The residue was chromatographed over silica (3% $MeOH/CH_2Cl_2$ as eluent), and the product was obtained (0.25 g, 5.6%) as red leaflets, mp 170-172 °C. ^{1}H-NMR: 3.78 (s, 3H); 4.17 (d, 2H); 4.24 (s, 2H); 4.36 (s, 2H); 4.56 (s, 2H); 4.90 (s, 2H); 7.08 (d, 1H); 7.56 (t, 1H); 7.62 (d, 1H); 7.69 (t, 1H); 7.77 (t, 1H); 8.24 (d, 1H); 8.34 (d, 1H); 9.97 (t, 1H) ppm. Anal. Calcd for $C_{27}H_{21}NO_4Fe$: C, 67.66; H, 4.42; N, 2.92. Found: C, 67.57; H, 4.47; N, 2.83.

N,N′-Bis[(1′-carbomethoxyferrocenyl)methyl]-1,5-diaminoan-thraquinone, 24. Sodium hydride (0.33 g, 8.25 mmol) was added to a stirred solution of 1,5-diaminoanthraquinone (0.7 g, 2.9 mmol) in THF (50 mL). A solution of 1-carbomethoxy-1′-(chloromethyl)-ferrocene (from 2.14 g of 1-carbomethoxy-1-hydroxyferrocene, 7.8 mmol) in THF (100 mL) was added dropwise, and the reaction mixture was heated under reflux for 48 h. The reaction mixture was allowed to cool to ambient temperature and quenched (H_2O, 5 mL), the solvent was removed *in vacuo*, and the residual oil was chromatographed over silica. The product was obtained (1.18 g, 53%) as purple needles, mp 183−185 °C. ^{1}H-NMR: 7.65 (d, 2H); 7.56 (t, 2H); 7.02 (d, 2H); 4.90 (t, 4H); 4.58 (t, 4H); 4.35 (t,4H); 4.24 (s, 4H); 4.18 (d, 4H); 3.8 (s, 6H) ppm. Anal. Calcd for $C_{40}H_{34}N_2O_6Fe_2$: C, 64.02; H, 4.57; N: 3.73. Found: C, 63.75, H, 4.66; N, 3.50.

N,N′-Bis[(1′-carboxyferrocenyl)methyl]-1,5-diaminoanthra-quinone, 24. Sodium hydroxide (10 g) was added to a solution of 1,5-bis[[(1′-carbomethoxyferrocene)methyl]amino]anthraquinone (1.07 g, 1.4 mmol) in a mixed solvent of CH_2Cl_2, MeOH, and H_2O (40:50: 15). The reaction mixture was stirred mechanically and heated to reflux for 48 h, then the mixture was allowed to cool to room temperature, and the organic solvent was removed *in vacuo*. HCl solution (3 N, 50 mL) was added to precipitate the product. The mixture was filtered and the solid was washed by distilled water (3 × 50 mL). THF (~25 mL) was used to wash away the small amount of nonhydrolyzed ester. The product was dried under vacuum to give **24** (0.64 g, 63%) as a red solid, mp 230 °C dec. ^{1}H-NMR (DMSO-d_6): 7.64 (t, 2H); 7.46 (d, 2H); 4.88 (s, 4H); 4.35 (s, 4H); 4.20 (s, 8H). Anal. Calcd for $C_{38}H_{30}N_2O_6Fe_2 \cdot H_2O$: C, 61.65, H, 4.36, N, 3.78. Found: C, 61.65; H, 4.43; N, 3.79.

2,6-Bis[(1′-carboxyferrocenyl)carbonyl]naphthalene, 25. Prepa-ration of the Dimethyl Ester of 25. To a solution of methyl ester of ferrocenecarboxylic acid (9.66 g, 39.6 mmol) and 2,6-naphthalenedi-carboxylic acid chloride (4.57 g, 18.1 mmol) in CH_2Cl_2 (75 mL) was added anhydrous $AlCl_3$ (12 g, 90 mmol) in portions. After the addition, the reaction was carried at ambient temperature for another 0.5 h. Water (~100 mL) was added to quench the reaction. The organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (200 mL). The combined organic phase was dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. The residual was chromatographed over silica (3% $MeOH/CH_2Cl_2$ as eluent). The product (3.7 g, 31%) was a red solid, mp 184−185 °C. ^{1}H-NMR: 3.64 (s, 6H); 4.44 (s, 4H); 4.64 (s, 4H); 4.85 (s, 4H); 5.02 (s, 4H); 8.04 (d, 2H); 8.10 (d, 2H); 8.48 (s, 2H) ppm.

Hydrolysis To Afford 25. The solution of 2,6-bis[(1′-carbometh-oxyferrocenyl)carbonyl]naphthalene (0.65 g, 1.0 mmol) in the mixed solvent of 5% NaOH, $H_2O/MeOH/CH_2Cl_2$ (2:5:2, 50 mL) was stirred at ambient temperature for 10 h. The organic solvent was evaporated *in vacuo*, and the remaining aqueous solution was acidified with 0.3 N

HCl(aq) solution to pH 2. The precipitate was filtered and washed three times with water. The product was dried under vacuum at ambient temperature to give **25** (0.47 g, 75%) as a red solid, mp 240 °C dec. ^{1}H-NMR (DMSO-d_6): 4.55 (s, 4H); 4.78 (s, 8H); 4.96 (s, 4H); 8.00 (d, 2H); 8.32 (d, 2H); 8.60 (s, 2H) ppm. Anal. Calcd for $C_{34}H_{24}O_6$-Fe_2: C, 63.78; H, 3.78. Found: C, 63.60; H, 3.81.

1,4-Bis[(1′-carbomethoxyferrocenyl)formylidene]phenylene-diamine, 26. To the solution of 1-carbomethoxy-1′-formylferrocene (**4**, 1.0 g, 3.67 mmol) in CH_2Cl_2 (50 mL) was added 1,4-phenylene-diamine (0.2 g, 1.85 mmol). The reaction mixture was stirred overnight at ambient temperature. The solvent was removed *in vacuo*, and the residue was washed with Et_2O to give **26** (1.1 g, 96%) as a red solid, mp 160−165 °C. ^{1}H-NMR: 3.71 (s, 6H); 4.46 (s, 4H); 4.51 (s, 4H); 4.84 (s, 4H); 4.90 (s, 4H); 7.25 (s, 4H); 8.33 (s, 2H) ppm. It was found by TLC that the product was unstable on either silica or alumina.

1,4-Bis[(1′-carbomethoxyferrocenyl)methyl]phenylenediamine, 27. 1,4-Bis[(1′-carbomethoxyferrocenyl)formylidine]phenylenediamine (**26**) (0.95 g, 1.5 mmol) was dissolved in EtOH (50 mL) and benzene (100 mL). Pt/C (0.2 g) was added, and the mixture was hydrogenated using a Parr Shaker for 4 h. The reaction mixture was filtered over diatomaceous earth. The solvent was removed *in vacuo*. The residual was chromatographed on silica (1% MeOH in CH_2Cl_2 as eluent to give a yellow solid (0.84 g, 88%), mp 148−151 °C. ^{1}H-NMR: 3.80 (s, 6H); 3.88 (s, 4H); 4.16 (s, 4H); 4.21 (s, 4H); 4.39 (s, 4H); 4.77 (s, 4H); 6.66 (s, 4H) ppm. The product proved too unstable for further characterization.

4,4′-Bis[[[(1′-carboxyferrocenyl)carboxy]amino]ethyl]biphenyl, 28. 4,4′-Diaminobiphenyl (16.10 g, 0.0875 mol) was dissolved in EtOH (absolute, 80 mL), and Raney nickel catalyst (15 g) was added. The solution was refluxed for 15 h, cooled, and filtered through Celite to give, after evaporation, *N,N′*-diethylbenzidine (11.45 g, 54%) as a colorless solid. *N,N′*-Diethylbenzidine (1.00 g, 4.16 mmol) was added to a 100 mL round-bottomed flask containing dry THF (50 mL). To this solution was added Et_3N (1.00 g, 9.90 mmol). 1-(Chloromethyl)-1′-(methoxycarbonyl)ferrocene (2.55 g, 8.32 mmol), dissolved in THF (25 mL), was added dropwise to the reaction mixture. This solution was stirred overnight, the solvent was evaporated *in vacuo*, and the product was chromatographed over alumina to afford the yellow methyl ester of **28** (1.65 g, 53% yield).

This compound was hydrolyzed as described above to afford **28** (mp 260 °C (soften), >300 °C dec). ^{1}H-NMR: $CDCl_3$ 1.19−1.26 (t, 6H), 3.84−4.24 (m,12H), 4.41 (s, 4H), 4.69 (s, 4H), 7.17−7.21 (d, 4H), 7.52−7.6 (d, 4H) ppm. High-resolution mass spectrum calcd for $C_{40}H_{36}N_2O_6Fe_2$: 752.4500, found 752.4500.

Attempted Complexation with 4,4′-Bipyridyl. A solution of 0.0043 M (in $CDCl_3$) was made by adding 3.24 mg of the host molecule. A 0.6 mL sample of this solution was pipetted into an NMR tube. To this mixture was added (in 10 mL aliquots) a 0.1 M solution of 4,4′-bipyridyl in $CDCl_3$. An NMR spectrum was taken after each addition of the guest solution. The *o*-pyridyl proton observed at 8.74 ppm did not shift from its uncomplexed position.

Determination of Binding Constant by NMR Titration. General Experimental Procedure. Accurately weigh approximately 1 mg of receptors into a 5 mL vial and transfer 1.0 mL of $CDCl_3$ (or THF-d_8) into the vial with a 1000 μL syringe. The sample was sonicated to dissolve the solid. Then 0.8 mL of the solution was transferred into a 5 mm NMR tube and titrated by adding an aliquot (usually 10 μL) of the solution of substrate with a 50 μL syringe. The concentration of substrate in $CDCl_3$ (or THF-d_8) is usually 100 times the concentration of the receptor's solution in $CDCl_3$ (or THF-d_8). ^{1}H-NMR spectra were recorded after each addition. The TMS or solvent signal ($CHCl_3$ or THF) was used as reference peak. The chemical shift (δ) of the indicated proton(s) of substrates was used for calculating binding constants.

Binding Constant Calculation. Complexation is assumed to involve the equilibrium receptor + substrate ⇌ complex. When the equilibrium is fast on the NMR time scale, the equation

$$d = \frac{[B]}{[B]+[C]}d_b + \frac{[C]}{[B]+[C]}d_c$$

is valid, in which d = the observed chemical shift, d_b = chemical shift of pure substrate, d_c = chemical shift of the complex, [B] = equilibrium

concentration of substrate, $[C]$ = equilibrium concentration of the complex, and $[A]$ = equilibrium concentration of receptor. The data fit was accomplished by a least squares calculation. The stability constants were obtained by using the commercial computer program "Minsq" (MicroMath, Inc., Salt Lake City, UT, Version 3.12). The model for calculating K and d_c is as follows in which K is the stability constant and C_A and C_B are the initial concentrations of receptor and substrate, respectively: independent variables, C_A, C_B; dependent variable, d; parameters, d_c, K; if $BR = C_A + C_B + 1/K$; $RR = BR^2 - 4(CA)(CB)$; $X = 0.5(BR - RR^{1/2})$; $d = Xd_c + (1 - X)d_B$.

Preparation of Solution A. Accurately weigh 45.2 mg of **20** into a 25 mL volumetric flask, add ∼15 mL of CDCl$_3$, and sonicate to dissolve the solid. Dilute to volume with CDCl$_3$.

Preparation of Solution B. Accurately weigh 35.5 mg of *N*,*N*,*N*′,*N*′-tetramethylpropylenediamine into a 10 mL volumetric flask and dilute to volume with CDCl$_3$.

Transfer 1.0 mL of solution A into a 5 mm NMR tube through an air tight syringe (1000 μL). The solution was titrated by adding an aliquot (usually 10 μL each time) of the solution of substrate with a 50 μL syringe. The NMR spectrum was recorded after each addition. The bold−underlined proton was used to calculate the binding constant.

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