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Self-Assembly of Dimeric Tetrathiafulvalene-Calix[4]pyrrole: Receptor for 1,3,5-Trinitrobenzene

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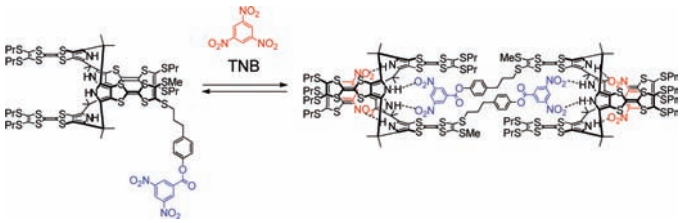
ABSTRACT



The synthesis and binding properties of a tetrathiafulvalene (TTF)-calix[4]pyrrole receptor 2 appended with one 3,5-dinitrobenzoate guest moiety are reported. The preliminary studies revealed that the receptor is self-complexing into a dimer receptor 2•2. The self-complexation of the receptor leads to preorganization—in its 1,3-alternate conformation—and as a result hereof, the dimer receptor 2•2 is displaying a 2 order higher binding affinity toward analytes (e.g., 1,3,5-trinitrobenzene) than the model tetrathiafulvalene (TTF)-calix[4]pyrrole receptor 3.

The design of novel synthetic receptors that mimic the binding processes in biological systems has recently attracted considerable interest. In many biological systems, change in activity is affected by self-assembly of identical, or nearly identical, subunits into larger aggregates.[1] These aggregates often show enhanced binding properties or formation of catalytically active sites as a result of self-assembly.[1,2] Although there are numerous examples of synthetic systems that self-assemble into dimers or larger aggregates, such as cyclodextrins,[3] porphyrins,[4] and encapsulation complexes,[5] we are unaware of any examples where self-assembly of two identical receptors into a novel dimer receptor has been exploited to demonstrate an enhanced binding response to a nitroaromatic analyte.

The motivation for the present work was the finding that TTF[6]-substituted calix[4]pyrrole[7] showed positive homotropic allosteric binding of electron-deficient guests[8] (e.g., 1,3,5-trinitrobenzene, TNB). After binding of the first TNB guest, the flexible TTF-calix[4]pyrrole receptor was

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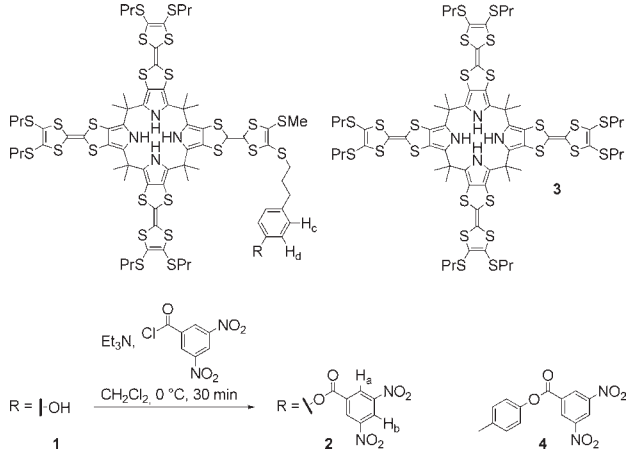
forced to adopt a more rigidified 1,3-alternate conformation, thereby providing a preorganized framework for the subsequent binding of the second TNB guest. This resulted in weak binding of the first TNB and stronger binding of the second TNB guest. The purpose of the present study was to design a TTF-calix[4]pyrrole receptor that is preorganized in the 1,3-alternate conformation, thus eliminating the inherent low binding of the first TNB guest, and to show that this receptor displays an enhanced binding for our test substrate TNB. If the TTF-calix[4]pyrrole receptor could be modified by covalently linking it to one nitroaromatic guest (Scheme 1), the resulting receptor might preorganize itself into the 1,3-alternate conformation, through intra/intermolecular host–guest complexation and at the same time present the "second" and strongest binding site for TNB complexation, resulting in enhanced binding.

Scheme 1. Chemical Structure of the Receptors **1**, **2**, and **3** and the Model Compound **4**, and Synthesis of the Receptor **2**



The receptor **2** was synthesized as outlined in Scheme 1. Reaction of the asymmetric TTF-calix[4]pyrrole receptor **1**[8a] appended with one phenol moiety and 3,5-dinitrobenzoyl chloride in a CH_2Cl_2 solution in the presence of Et_3N afforded the desired asymmetric TTF-calix[4]pyrrole receptor **2** in 70% yield after aqueous workup and column chromatographic purification. The asymmetry of receptor **2** is clearly evident from the ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298 K). The spectrum (Figure S1 in Supporting Information) shows three singlets resonating at δ = 7.80, 7.74, and 7.69 ppm—integrating to 1 H, 2 H, and 1 H, respectively—which can be assigned to the chemically nonequivalent NH protons. Multiplets corresponding to the six thiopropyl and eight *meso*-methyl groups (Figure S1) are observed to resonate in the aliphatic part of the spectrum.

Initial evidence for the interactions between the host part (calix[4]pyrrole) and the guest part (3,5-dinitrobenzoate) of receptor **2** came from absorption spectroscopy. The resulting spectra (Figure S13) revealed a charge transfer (CT) band centered around λ = 560 nm, which is characteristic[8] for the interactions between TTF-calix[4]pyrrole receptors and nitroaromatic guests. Further, support for the interaction

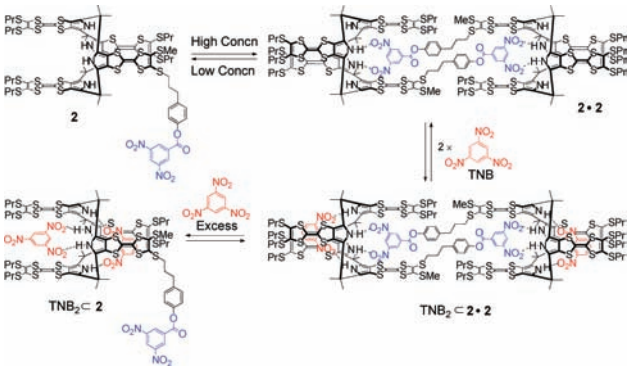


Figure 1. Schematic illustration of dimer receptor **2•2** formation and the following complexation with TNB.

came by comparing the ^{1}H NMR spectrum of receptor **2** (20.0 mM, Figure S6) with the spectra of receptor **1** and the model compound *p*-methylphenyl-3,5-dinitrobenzoate (**4**).[9] In the spectrum of receptor **2** (Figure S6), the signals corresponding to the resonances of the NH protons are downfield shifted $\Delta\delta$ = 0.51–0.59 ppm, relative to that of receptor **1** as a result of the hydrogen bonding taking place between the NH protons of the host part of receptor **2** and the nitro groups of the guest part of receptor **2**. The aromatic protons of the guest part of receptor **2** are found to be upfield shifted $\Delta\delta$ = 0.09–0.32 ppm, relative to that of the model compound **4**, as a consequence of being sandwiched between two shielding TTF subunits.[8d] Due to the covalent link between the guest part and the host part of receptor **2**, the receptor might form intra-[10] or intermolecular[11] complexes. To establish whether the complexation between the host part and guest part of receptor **2** were intra-[10] or intermolecular[11] in nature, a dilution experiment was carried out employing ^{1}H NMR spectroscopy (Figure 2 and Figure S7). Upon dilution of a concentrated solution of receptor **2** (44.0–0.15 mM), significant peak shifts were observed throughout the spectrum. In particular, the peaks corresponding to the NH protons shifted upfield $\Delta\delta$ = 0.49–0.55 ppm and the aromatic protons from the guest part shifted downfield $\Delta\delta$ = 0.13–0.41 ppm. These results indicate that receptor **2** forms intermolecular aggregates in solution. To determine if the intermolecular aggregates are dimers,

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(12) The rational for formation of inter- rather than intramolecular complexation was found in the rather rigid linker connecting the host part and guest part of receptor **2**. A Corey–Pauling–Koltun (CPK) model analysis showed that the geometry of the guest part (*p*-alkylphenyl-3,5-dinitrobenzoate) of receptor **2** makes it unfavorable to form intramolecular complexation.

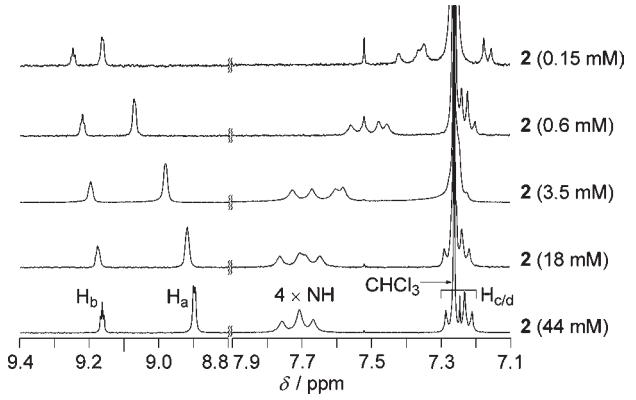
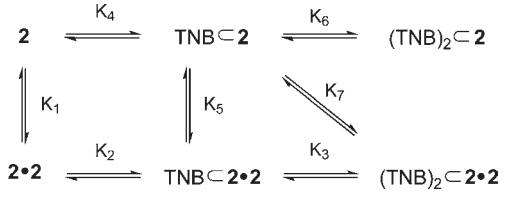


Figure 2. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of receptor **2** at various concentrations (44.0−0.15 mM).

Scheme 2. Complexes and Equilibria Taken into Account for the Data Analysis



oligomers, or polymers, the equilibrium expressed by eqs 1a and 1b was considered with $q = 0$. From the dilution experiment and the equilibrium (eqs 1a and 1b), the number of units in the aggregate was determined to be $p \sim 1.9-2.1$, indicating dimer[12] (**2•2**, Figure 1) rather than oligomer or polymer formation.[13] By fitting the data (Figure S10), assuming a monomer to dimer equilibrium, a dimerization constant $K_D = 1950\ M^{-1}$ (K_1 in Scheme 2 and Table 1) was obtained.

$$pH + qG \rightleftharpoons H_pG_q \quad (1a)$$

$$\begin{cases} [H]^0 = \sum_{p,q} p[H_pG_q] \\ [G]^0 = \sum_{p,q} q[H_pG_q] \end{cases} \quad (1b)$$

$$\delta = \sum_{p,q} \frac{[H_pG_q]}{[H]^o} p\delta_{pq} = \delta_H + \sum_{p,q\neq\{1,0\}} \frac{[H_pG_q]}{[H]^o} p\Delta_{pq} \quad (2)$$

The complexation between the dimer receptor **2•2**, preorganized in the 1,3-alternate conformation, and the analyte TNB was studied in $CDCl_3$ solution using ^{1}H NMR spectroscopy and in CH_2Cl_2 solution using absorption spectroscopy.

(13) It was not possible to rule out polymer formation; however, under the condition studied, dimer formation was favored, probably as a consequence of the two host−guest complexations leading to dimer **2•2** formation, rather than only one host−guest complexation leading to polymer formation.

Table 1. Dimerization Constant (K_1) of Receptor **2** and Binding Constants (K_a) for Guest Complexes of Receptor **2** and **3**[8d] with the Analyte 1,3,5-Trinitrobenzene Determined by ^{1}H NMR Spectroscopy in $CDCl_3$ at 298 K

receptor	K_1 (M^{-1})	K_2 (M^{-1})	K_3 (M^{-1})	K_4 (M^{-1})	K_6 (M^{-1})
2	1950	3500	3500	660	3100
3		20			900

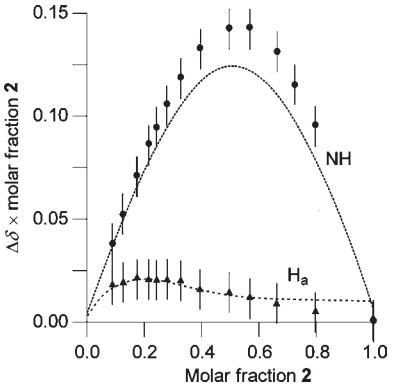


Figure 3. Job plot for the NH and H_a protons ([**2**] + [TNB] = 2.0 mM). The data points (● for NH and ▲ for H_a) are obtained from the Job plot experiment, whereas the curves are predicted from known association constants and chemical shifts (Table 1 and Table S1 in Supporting Information).

First, a Job's[14] plot analysis (Figure 3) was carried out in order to determine the stoichiometry between the dimer receptor **2•2** and TNB. The analysis showed 1:1 stoichiometry for the NH protons, indicating that the dimer receptor **2•2** is complexing two TNB guests (Figure 1). However, the H_a protons showed a maximum in the area between 0.2 and 0.3 indicating that more complexes are involved in the equlibria.[15] ^{1}H NMR spectroscopic titration methods were used to determine the binding constants (K_a) corresponding to the interaction between the dimer receptor **2•2** and TNB. As expected, addition of TNB to a solution of the dimer receptor **2•2** (0.78 mM) did cause a large downfield shift ($\Delta\delta = 0.53-0.59$ ppm) for the NH protons of the host part of receptor **2** (Figure 4a). The aromatic signals from the guest part of receptor **2** experienced a downfield shift ($\Delta\delta = 0.06-0.12$ ppm). Analyses of the NMR data were carried out by considering the equilibria shown in Scheme 2, and for each equilibrium, the set of eqs 1a, 1b, and 2 was considered.[16] In the fast exchange regime, each complex

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(15) The NH proton is describing the situation (TNB_2⊂**2•2**) where two TNB molecules are complexed by the dimer receptor **2•2** (1:1 stoichiometry). However, excess TNB is needed to expel the guest part (H_a) from the host part of receptor **2** (Figure 1) leading to formation of the TNB_2⊂**2** complex and therefore is a maximum in the area between 0.2 and 0.3 observed for the H_a proton.

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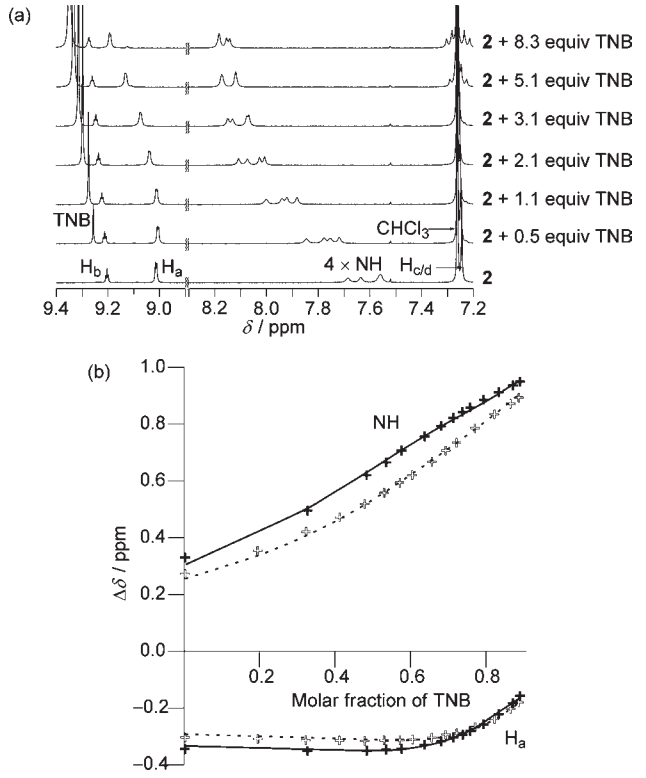

Figure 4. (a) Partial ^{1}H NMR spectra (400 MHz, 298 K) of the dimer receptor **2•2** ([**2**] = 0.78 mM) titrated with increasing amounts of TNB in $CDCl_3$. (b) Binding curves of the NH and H_a protons obtained from two different titration experiments (1.5 mM (solid line) and (0.78 mM, dotted line) of receptor **2**.

contributes to the average chemical shift, and therefore, the chemical shifts of the complexes are expressed by $\delta_{pq} = \delta_H + \Delta_{pq}$ and the average chemical shift (δ) can be expressed by eq 2, where the summation is over all relevant complexes (see Supporting Information). The chemical shift changes were fitted using a downhill simplex method[17] with a least-squares metric, while we limit ourselves to the NH proton with the largest chemical shift change and to H_a.

Two titration experiments were subsequently used to fit the association constants (K_a) for the equilibria expressed by K_2, K_3, K_4, and K_6, and this gave the K_a values listed in Table 1. From Table 1, it can be seen that the binding of the TNB substrates to the dimer receptor **2•2** (K_2 and K_3) is around 2 orders higher than the first binding (K_2) of TNB to the parent TTF-calix[4]pyrrole receptor **3** (Table 1), studied under nearly[8d] identical conditions. This enhancement is believed to arise from the preorganization of the receptor **2** into a dimer receptor **2•2**. In the preorganization step, the guest part of the receptor **2** is complexed (recognized) by the first binding site of the host part of receptor **2**, thereby exposing the second binding site with a higher binding affinity for the analyte in quest (TNB). In order to check the robustness of the fitting procedures, the Job plots were predicted using the equilibrium constants and changes in chemical shift as fitted above. The resulting curves are depicted in Figure 3 and describe the experimental data for the H_a proton very well and for the NH proton reasonably well.

The interactions between the dimer receptor **2•2** and TNB were also investigated in CH_2Cl_2 at 298 K using absorption spectroscopy. The TNB guest did not give rise to any notable absorption bands at $\lambda > 500$ nm. However, the dimer receptor **2•2** showed a charge transfer (CT) absorption band centered at $\lambda = 560$ nm. Upon addition of TNB to a solution of the dimer receptor **2•2**, an increase in intensity (Figure S13) and a shift of the CT band ($\lambda = 633$ nm) were observed,[10] signaling that complexation between the dimer receptor **2•2** and the TNB guests has occurred.

In summary, we have synthesized an asymmetric TTF-calix[4]pyrrole receptor appended with one 3,5-dinitrobenzoate guest and investigated its self-complexation into a dimer receptor **2•2**. The dimer receptor **2•2** showed an increased binding for the analyte TNB, as a consequence of preorganization of the receptor in its 1,3-alternate conformation. This work serves to illustrate how self-complexation of two identical synthetic receptors—into a novel dimer receptor—may be used to enhance the recognition ability toward analytes.

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Supporting Information Available. Supporting figures, experimental and fitting details. This material is available free of charge via the Internet at http://pubs.acs.org.