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Bispyrrolylbenzene Anion Receptor: From Supramolecular Switch to Molecular Logic Gate

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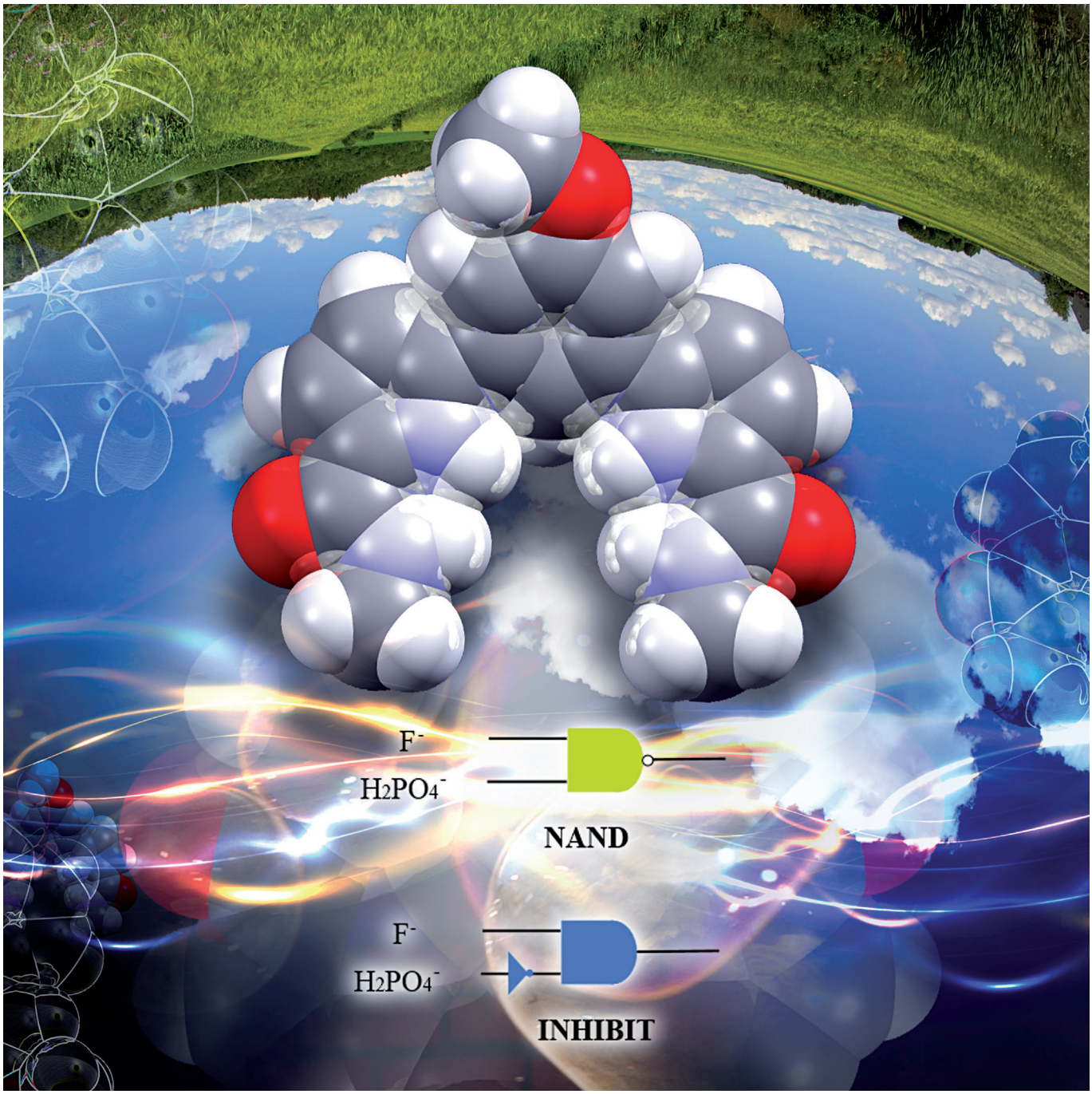


Abstract: We have designed anion receptor **4** based on a conformationally labile bispyrrolylbenzene framework, the conformation of which can be changed by appropriate anionic stimuli. In the absence of fluoride anion, the pyrrole moieties rotate freely at room temperature. However, when the concentration of fluoride anion exceeds 2 equivalents, the rotation of the pyrrole units slows down and the conformation of the receptor changes to *anti-anti*. DFT calculations have shown that this change is due to binding of a third fluoride anion through C–H interaction. Anion receptor **4** can also serve as a molecular logic gate. Anionic inputs such as fluoride and dihydrogenphosphate allow the realization of INHIBIT and NAND logic gate functions with absorption and fluorescence as readouts, respectively.

Introduction

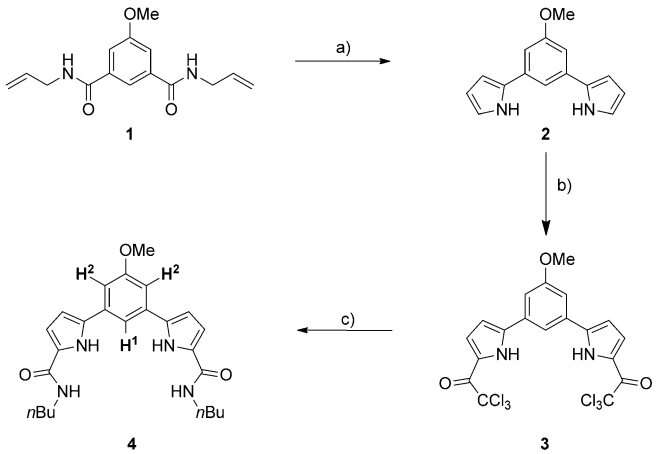
Recently, many attempts have been made to produce synthetic molecules that can change conformation upon the application of various external stimuli, such as temperature,[1] light,[2] pH,[3] or guest molecules.[4] Molecules that can change conformation are expected to find a broad range of applications in molecular machines,[5] information processing at the molecular level,[6] catalysis,[7] sensing,[8] and so on. Many cellular processes are controlled by receptors, which, after binding an appropriate guest, undergo a conformational change, triggering a cascade of biochemical processes. A typical example can be found in the growth hormone receptor.[9] A conformational change is also crucial in the induced-fit model of enzyme–substrate interaction.[10] In this model, the initially weakly bound substrate causes a conformational change of the enzyme, strengthening its binding until the substrate is completely bound, thus stabilizing the transition state of the catalyzed reaction. This differs from the typical mechanism of guest-induced conformational switching, in which the binding event causes the conformational change, and the degree of conformational change depends on the guest concentration. Moreover, several enzymes are activated in similar ways by binding additional small molecules (cofactors).[11]

Switches that can operate by reversible hydrogen binding of an anionic stimulus seem to be particularly interesting in this regard, owing to the importance of anions in Nature.[12] A common anion-binding motif consists of hydrogen-bond donors, such as amide, urea, pyrrole, or indole.[13] It has previously been shown that for diphenylacetylenes with both intramolecularly hydrogen-bonded urea and carbonyl groups, the addition of chloride anion resulted in cleavage of the intramolecular hydrogen bond and a change in the conformation of the receptor.[14] Gale and co-workers[15] investigated 2,7-disubstituted indole-based receptors, which, after the addition of anionic guests, underwent a conformational change such that the hydrogen-bond donors became cooperatively directed towards the anion. A similar mechanism was observed for boron complexes of dipyrrolyldiketones.[16]

Motivated by the above considerations, we decided to design a new conformationally labile anion-binding platform, the conformation of which could be switched by appropriate anionic stimuli. We anticipated that further functionalization of the previously reported bispyrrolylbenzene building block[17] with two additional hydrogen-bond donors (two amide groups) would provide a flexible functional unit showing guest-dependent conformation. Moreover, due to the four hydrogen-bond donors capable of switching, this system should be effective even in a demanding solvent such as DMSO.

Results and Discussion

The bispyrrolylbenzene anion receptor **4** is readily available by a short reaction sequence from commercially available 5-methoxyisophthalic acid (Scheme 1). In the first step, the acid dichloride was generated from 5-methoxyisophthalic acid by treatment with thionyl chloride; reaction of this acid dichloride with allylamine yielded diamide **1** in 91% overall yield. Compound **1** was then reacted with phosgene, and the product was immediately treated with potassium *tert*-butylate to afford the bispyrrolylbenzene derivative **2** in 49% yield. Compound **2** was acylated with trichloroacetyl chloride to form compound



a) i) $COCl_2$, toluene 24h, ii) *t*BuOK, THF, 49%; b) CCl_3COCl, $CHCl_3$, 2,6-lutidine, 38%; c) $BuNH_2$, MeCN, reflux, 88%.

Scheme 1. Synthesis of bispyrrolylbenzene anion receptor **4**.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201403116: Details of the experimental procedures and spectral data for new compounds, including images of ^1H and ^{13}C NMR spectra, titration experiments and Job plots, and conformational studies in solution.

3. The anion receptor **4** was synthesized in 88% yield from **3** by simple treatment with *n*-butylamine.

In the next part of our study, the binding properties of receptor **4** were studied under ^{1}H NMR controlled titration at constant concentration of the receptor (ca. 1×10^{-2} M). In all cases, binding affinities were measured by complexation-induced resonance shift changes of the amide and pyrrole NH protons upon addition of anionic guests in the form of tetrabutylammonium salts.

Binding constants were obtained by nonlinear regression of the experimental data using the software HypNMR.[18] Binding stoichiometry was confirmed by Job plots (see the Supporting Information). The titration of receptor **4** with a set of standard anions (Table 1) showed that all anions other than fluoride were bound with a 1:1 host–guest stoichiometry.

Table 1. Binding constants of anion receptor **4** determined by ^{1}H NMR titrations in [D$_6$]DMSO + 0.5% H$_2$O.

Entry	Anion[a]	K_a [M^{-1}]	Stoich. (H:G)	$\Delta\delta_{max}$[b] pyrrole [ppm]	$\Delta\delta_{max}$[b] amide [ppm]
1	F^-	66 ± 25 1456 ± 121	1:1 1:2	5.24	3.01
2	Cl^-	6.0 ± 1	1:1	1.41	1.71
3	AcO^-	297 ± 9	1:1	1.54	1.35
4	$PhCOO^-$	47.5 ± 1	1:1	1.84	0.87
5	$H_2PO_4^-$	1037 ± 94	1:1	2.44	1.81

[a] Added as tetrabutylammonium salts. [b] Asymptotic change in chemical shifts obtained by nonlinear curve-fitting.

The representative carboxylates, acetate and benzoate, were bound with binding constants of 297 and 47.5 M^{-1}, respectively. The much less basic chloride anion was bound with a smaller binding constant (6 M^{-1}). It seems that bromide anion was too large to fit the cavity of receptor **4**. The addition of bromide did not cause any noticeable chemical shift changes of the protons of host molecule **4**. The tetrahedral dihydrogenphosphate showed a binding constant of 1037 M^{-1}. The binding constants of receptor **4** are relatively small compared to those of receptors based on dipyrrolylmethanes[19] and diindolylmethanes[20] (each possessing four hydrogen-bond donors). Receptor **4** appears to have an anion-binding pocket of appropriate size and shape for accommodating most anions in a *syn-syn* conformation. However, the binding isotherm for fluoride anion clearly indicates a 1:2 host–guest stoichiometry, and the second binding constant $K_{ass2:1}$ was much larger (1456 M^{-1}) than the first ($K_{ass1:1}=66$ M^{-1}).[21] More detailed analysis of the binding isotherms for the aromatic protons and the methyl group revealed some interesting features of this binding event (Figure 1).

After addition of the first equivalent of fluoride anion, the signals of protons H^1 and H^2 were both downfield shifted, which may be associated with a predominant *syn-syn* conformation of the anion receptor **4**. On the other hand, the signals of the methyl protons were upfield shifted, which may be explained in terms of the fluoride anion increasing the electron density in the ring. Further tracking of the binding isotherm

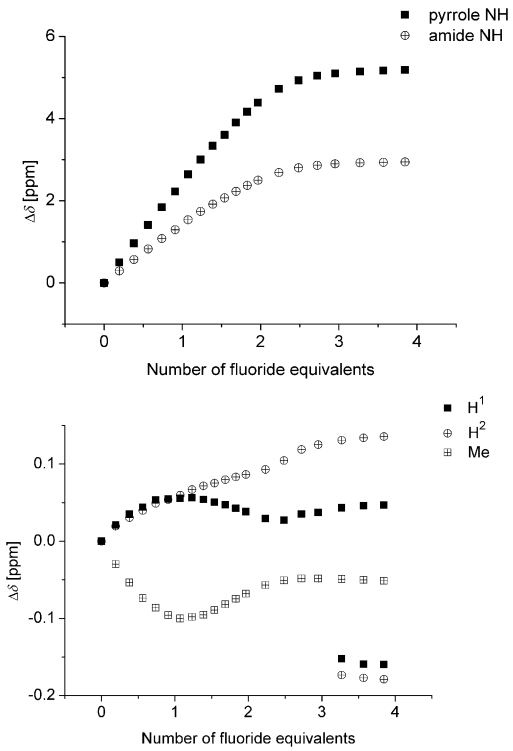


Figure 1. Chemical shift changes of protons of receptor **4** upon addition of fluoride anion.

for proton H^1 showed that increasing the fluoride concentration (to two equiv) caused it to exhibit the opposite behavior, namely an upfield shift. The best interpretation of these data is that a hydrogen bond between the bound fluoride and H^1 was weakened. This may be associated with a conformational change (to a *syn-anti* conformation) of anion receptor **4** in order to accommodate two fluoride anions. The pyrrole and amide NH proton signals were saturated at this point and further increase in the fluoride anion concentration did not result in significant changes in their chemical shifts. However, addition of a further equivalent of fluoride anion resulted in a noticeable chemical shift change for protons H^2, and induced slow equilibrium on the NMR time scale (Figure 2).[22] Only the CH protons of the benzene and pyrrole rings showed this type of slow equilibrium, which can be associated with rotation of the pyrrole moieties relative to the benzene ring.

The rationale for this would seem to be that the anion receptor **4** can accommodate an additional fluoride anion, which forces it to change its conformation to *anti-anti*, and this binding event is slow on the NMR time scale. Increasing the fluoride anion content to four equivalents caused further switching of the receptor **4** population to the *anti-anti* conformation. The suggested binding mechanism is shown in Scheme 2.

The reversibility of this slow conformational equilibrium was also confirmed by the addition of free ligand to a solution of receptor **4** containing four equivalents of fluoride anion, which resulted in a broadening and coalescence of the proton signals of the benzene ring.

The validity of fluoride-induced slow conformational equilibrium was also confirmed by molecular modeling.[23] It showed

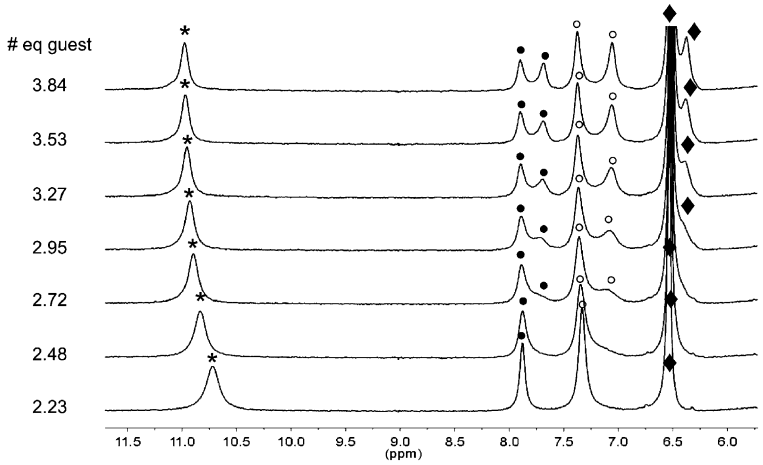
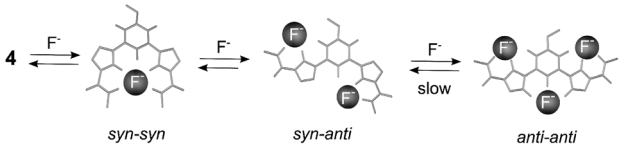


Figure 2. An excerpt from stacked plots of ^{1}H NMR spectra during titration of receptor **4** with fluoride anion. Fluoride induced slow conformational equilibrium of anion receptor **4** on the NMR time scale (* amide NH protons, ● H^1, ○ H^2, ◆ pyrrole Ar-H).



Scheme 2. Proposed mechanism of fluoride binding by anion receptor **4**.

that anion receptor **4** in an *anti-anti* conformation can bind additional fluoride anion. This conformation has the appropriate geometry of hydrogen-bond donors (CH protons of benzene and pyrrole rings) to accommodate the small fluoride anion. It has previously been shown that anions can be bound through C–H interactions.[24] The distances between the fluoride anion and benzene and pyrrole C-H atoms were found to be 2.013 and 2.127 Å, respectively. The structure of the complex of anion receptor **4**⊂3 F^- is shown in Figure 3.

The switching ability of anion receptor **4** was also determined through competitive titrations using three different anions, which formed complexes of different stoichiometry (acetate and dihydrogenphosphate (1:1) and fluoride anion (1:2)). Upon the addition of acetate anion (2 equiv), the conformation of the anion receptor **4** changed to *syn-syn* due to the formation of a 1:1 complex with all hydrogen-bond donors pointing cooperatively towards the anion. Subsequent addition of fluoride anion led to the formation of a 1:2 complex with *syn-anti* conformation. Addition of dihydrogenphosphate to the latter solution resulted in reversion to a *syn-syn* conformation (the basic fluoride anion was presumably able to deprotonate dihydrogenphosphate, and the resulting multiply-charged phosphate was able to displace the fluoride anion). Evidence for this behavior is provided by chemical shift changes for protons H^1 and H^2, which may form hydrogen bonds with the anion when **4** is in an appropriate conformation. H^1 prefers to form a hydrogen bond with the anion when **4** is in the *syn-syn* conformation, H^2 when it is in the *syn-anti* conformation. Chemical shift changes for protons H^1 and H^2 during competitive titration are shown in Figure 4.

Unfortunately, ROESY and NOESY experiments on the interaction of receptor **4** with fluoride anion in [D$_6$]DMSO + 0.5 % H_2O as well as in CD_3CN did not afford any additional information about the nature of the anion-bound conformation, owing to signal broadening after addition of the guest. We therefore turned our attention to chloride anion in

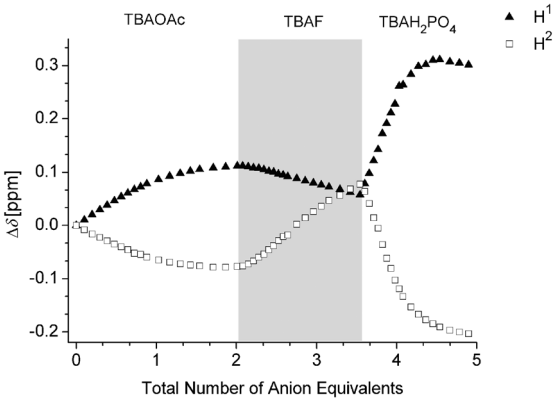


Figure 4. Chemical shift changes of selected protons of receptor **4**, as first AcO^-, then F^-, and then $H_2PO_4^-$ anions are added during competitive titration.

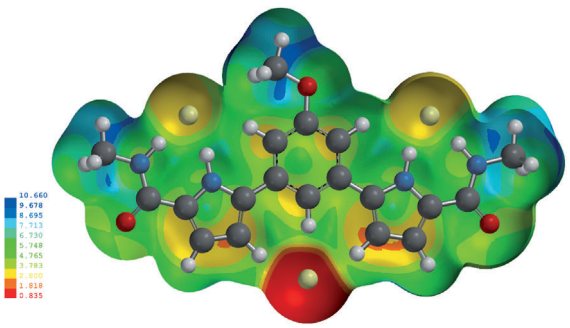


Figure 3. View of an electrostatic potential surface (EPS) obtained by DFT (ωB97X-D/6-311 + + G**) for the optimized structure of the fluoride complex with receptor **4**. For simplicity, butyl groups are replaced by methyl groups.

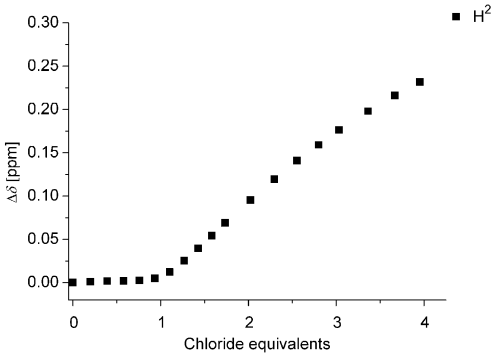


Figure 5. Chemical shift changes of the signal of proton H^2 during titration of anion receptor **4** in CD_3CN with chloride anion ($K_{ass1:1}$ = 11 590 ± 3940 M^{-1}, $K_{ass2:1}$ = 27 ± 12 M^{-1}).

CD_3CN. The trends in the chemical shift changes for the aromatic protons (H^1 and H^2) after chloride addition indicated a possible conformational change. For instance, the chemical shift of proton H^2 did not change until one equivalent of anion had been added (Figure 5).

Analysis of 1D NOESY spectra of anion receptor **4** showed that in the absence of any anions, the distribution of conformers is almost statistical (Figure 6). After the initial addition of one equivalent of chloride anion, the anion receptor changed its conformation to *syn-syn*. Further addition of chloride anion caused a change to the *syn-anti* conformation, which was characterized by a chemical shift change of proton H^2 associated with hydrogen-bond formation. The binding constants $K_{ass1:1}$ and $K_{ass2:1}$ were $11\,590 \pm 3940\ M^{-1}$ and $27 \pm 12\ M^{-1}$, respectively. The trends in the changes of the chemical shifts of receptor **4** during titration with chloride anion are consistent with those observed for 0–2 equivalents of fluoride anion.

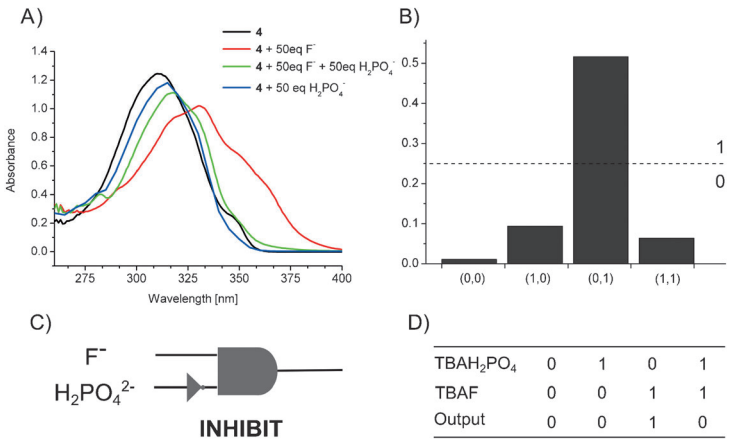


Figure 7. Performance of anion receptor **4** as an INHIBIT logic gate, with F^- and $H_2PO_4^-$ as inputs and UV/Vis absorbance as readout. A) UV/Vis spectra for combinations of the inputs in DMSO. B) Bar graph showing the experimental absorbance at 360 nm; the dashed line represents a hypothetical threshold for readout processes. C) Equivalent electronic circuit for the INHIBIT gate. D) Truth table for this logic gate.

The above-mentioned results suggest that anion receptor **4** may act as a molecular logic gate.[25] Therefore, we decided to use dihydrogenphosphate and fluoride anions as inputs and UV/Vis absorption or fluorescence as readout. The presence of anion was defined as input 1 and its absence as input 0, respectively (Figure 7).

Figure 7A shows the measured UV/Vis spectra for receptor **4**, following different combinations of inputs. Evidently, only the presence of the fluoride anion (0,1) caused the pronounced red shift of the absorbance maximum. Accordingly, anion receptor **4** can perform the function of an INHIBIT logic gate. The INHIBIT gate can be considered as an AND gate with one of the inputs inverted by a NOT function (Figure 7C). Figure 7B shows the absorbances measured at 360 nm. Clearly, it is easy to distinguish between the "on" and "off" states of receptor **4**, and the outputs follow the truth table for an INHIBIT gate shown in Figure 7D.

On the other hand, the fluorescence readout of the receptor **4** state revealed that it can perform the function of a different logic gate when compared with the UV/Vis absorbance readout (Figure 8). Figure 8A shows the fluorescence spectra of anion receptor **4** in the presence of different combinations of anionic inputs. Only when both inputs were present was a substantial quenching of the fluorescence at 390 nm observed. In other cases, the fluorescence intensities were above the readout threshold. Analysis of changes in the fluorescence spectra of anion receptor **4** showed that it can act as a NAND logic gate, which may be viewed as an AND logic gate with output inverted by a NOT function (Figure 8C). The outputs are in agreement with the truth table for a NAND gate (Figure 8D). It is noteworthy that anion receptor **4** can also function as an AND logic gate when monitoring the fluorescence intensity at 470 nm.

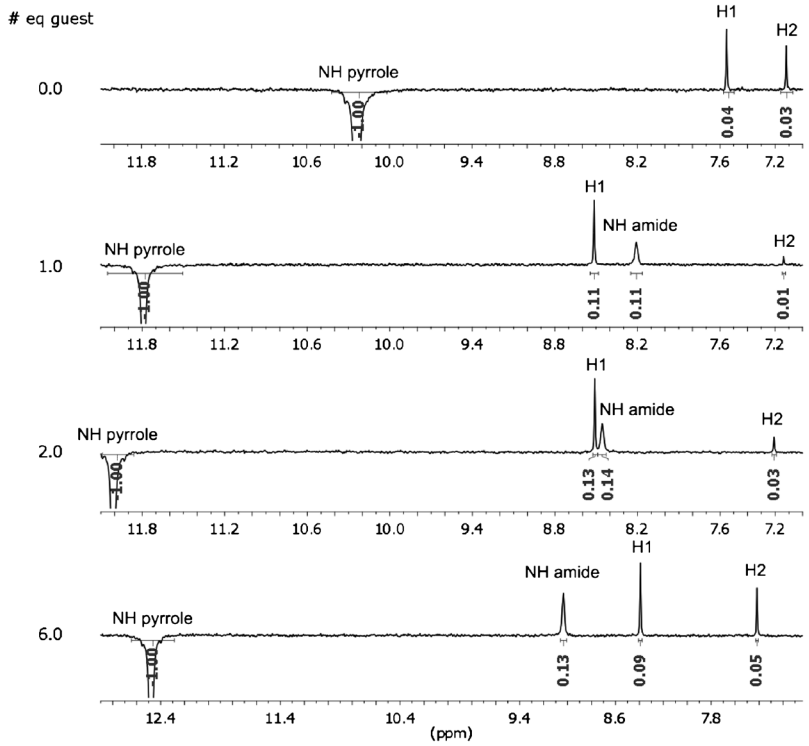


Figure 6. 1D NOESY spectra of receptor **4** after addition of chloride anion in CD_3CN.

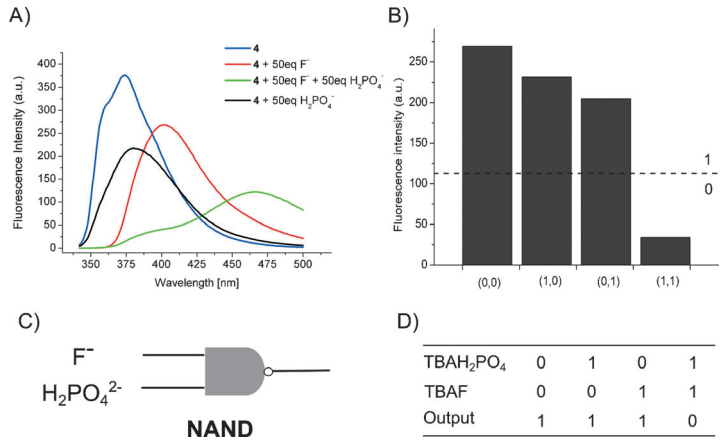


Figure 8. Performance of anion receptor **4** as a NAND logic gate, with F^- and $H_2PO_4^-$ as inputs and fluorescence as readout. A) Emission spectra for combinations of the inputs with excitation at 330 nm. B) Bar graph showing the experimental fluorescence at 390 nm upon excitation at 330 nm; the dashed line represents the hypothetical threshold for readout processes. C) Equivalent electronic circuit for the NAND logic gate. D) Truth table for the NAND logic gate.

Conclusion

We have synthesized the bispyrrolylbenzene anion receptor **4** and have investigated its binding properties in [D_6]DMSO + 0.5% H_2O. All anions other than fluoride showed a 1:1 binding stoichiometry and thus preference for a *syn-syn* conformation. The conformation of the anion receptor can be selectively switched by fluoride anion, and the barrier to rotation about the $C_{benzene}$–$C_{pyrrole}$ bond can be controlled by the fluoride ion concentration. Additionally, we have shown that compound **4** can act as a molecular logic gate as well as a supramolecular switch, its conformation being changed by acetate, fluoride, and dihydrogenphosphate anions.

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Keywords: anions · host–guest systems · molecular devices · receptors · supramolecular chemistry

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[21] The binding constants of the receptor with fluoride anion were calculated by standard regression of experimental data. They were calculated with the assumption that the first two binding constants are much larger than the third. Additionally, we assumed that the conformation of receptor **4** would not affect the binding of fluoride anion by NH protons. The 1:2 stoichiometry was also confirmed by a Job plot.
[22] Addition of a strong base such as tetrabutylammonium hydroxide did not result in this type of slow conformational equilibrium. For details, see the Supporting Information.
[23] All calculations were performed by using Spartan'10 for Windows (Wavefunction Inc., California, USA, 2011).
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