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Indole-based macrocycles and oligomers binding anions*

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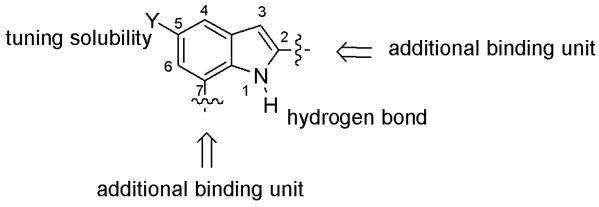
Abstract: Indole-based synthetic receptors which bind anions by multiple hydrogen bonds in organic solvents have been prepared. The biindole scaffold bearing two good hydrogen bond donors of indole NHs has been used as a molecular building block to construct the receptors. Incorporation of more hydrogen bond donors or acceptors increases the binding strength and selectivity toward a specific ion. Two macrocycles having different sizes of the internal cavities have been also synthesized, and their binding properties have been compared. Two macrocycles display distinct binding modes with polyatomic anions such as azide, as unequivocally proven by X-ray crystal structures. Finally, a series of oligoindoles containing four, six, and eight indoles have been prepared by Sonogashira reactions. The oligoindoles fold into helical structures upon binding with chloride. The binding affinities of the oligoindoles with chloride increase with increasing of the chain length, which provides an additional evidence for helical folding of the complexes.

Keywords: anion receptors; indoles; hydrogen bonds; macrocycles; foldamers.

INTRODUCTION

Anions are abundant in Nature and are involved in most biological and environmental processes. Indole, a key component of tryptophan, has been known as a hydrogen bond donor for binding anions in biological systems. Examples are found in sulfate-binding protein [1] and in the active site of haloalkane dehalogenase [2]. It is, however, surprising that indole had not been utilized for the synthesis of anion receptors until the first example was independently reported by us [3,4] and by Beer's group [5] in 2005.



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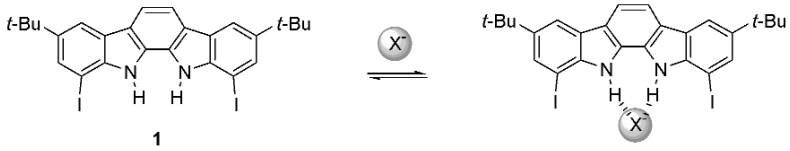
For the construction of anion receptors [6–11], we have been interested in indole as a molecular building block [11,12] for the following reasons. First, indole has a good hydrogen bond donor NH. The pK_a of the indole NH is 21 in dimethyl sulfoxide, which is slightly lower than those of amide (pK_a = 21–26), urea (pK_a = 27), and pyrrole (pK_a = 23) [12]. Second, indole can be functionalized at 2- and 7-positions to produce anion receptors with multiple hydrogen bond donors, which probably leads to increasing the binding affinity and selectivity. Finally, the solubility is a critical factor to quantitatively analyze the binding properties of receptors in solution. This latent problem can be solved by introducing an appropriate group at the 5-position of indole, which is distant from the NH and therefore may not hinder the binding process. Taking advantage of these features, a variety of indole-based anion receptors have been reported over the last two years [13–18], and herein we summarize our own studies.

RESULTS AND DISCUSSION

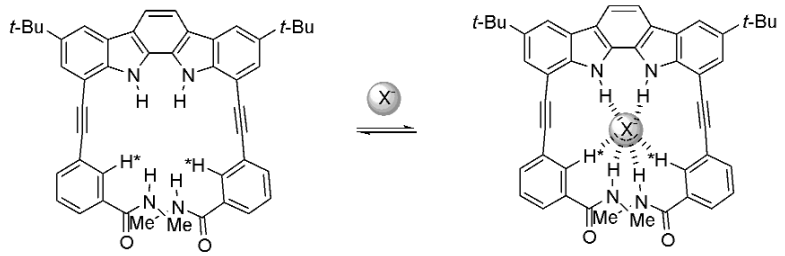
Anion receptors with biindole scaffold

A biindole derivative **1**, prepared from *p*-substituted aniline [3,4], has been used as the actual building block for the preparation of indole-based receptors. Compound **1** possesses two indole NHs in a convergent manner, thus capable of binding anions by two hydrogen bonds. The association constant of **1** with tetrabutylammonium chloride was found to be 900 M^{-1} in acetonitrile (containing ~0.1 % water) at 22 ± 1 °C, which corresponds to the free energy of ΔG = 4.0 kcal mol^{-1}, indicative of strong hydrogen bonds. Starting from this biindole scaffold, we prepared two different receptors, **2** and **3**, described below.



1

First, two benzamide units have been introduced in order to synthesize receptor **2** with two additional hydrogen bond donors of amide NHs [19]. The association constant of **2** with chloride is 110 000 M^{-1} in acetonitrile, which is two orders of magnitude higher than that (900 M^{-1}) of **1**. As summarized in Table 1, the binding affinities are greatly enhanced and the binding selectivity between halides also increases. The enhancements are ascribed not only to the additional NH (amide)···X hydrogen bonds but also to the CH···X^- hydrogen bonds. In the ^{1}H NMR spectra, the CH* signal was significantly downfield-shifted by approximately 1 ppm upon addition of tetrabutylammonium chloride.

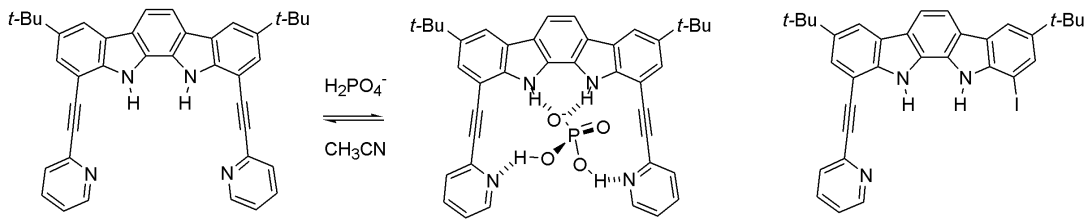


2

Table 1 Association constants (K_a ± 20 %, M^{-1}) of **1** and **2** with tetrabutylammonium halides in acetonitrile (containing ~0.1 % water) at 22 ± 1 °C.

Halide	**1**	**2**	Ratio **2/1**
Cl^-	900	110 000	122
Br^-	160	8700	54
I^-	12	180	15

Second, phosphates are the most abundant anions in the biological system and exist in different forms, depending on the pH of the solution. In a weakly acidic or neutral condition, dihydrogen phosphate ($H_2PO_4^-$, pK_a = 7.21) is predominant while hydrogen phosphate (HPO_4^{2-}, pK_a = 12.67) is prevailing in a basic solution. In order to selectively bind dihydrogen phosphate, receptor **3** was prepared which contains both hydrogen bond donors (indole NHs) and acceptors (pyridyl nitrogen) [20]. Here, the rigid rod-like ethynyl group was chosen as the linker to prevent possible intramolecular hydrogen bonds between donors and acceptors. The association constant (K_a ± 20 %) of **3** with $H_2PO_4^-$ was determined to be 1.1×10^5 M^{-1} in CH_3CN at 22 ± 1 °C. The binding constants of biindole **1** and monopyridyl receptor **4** with $H_2PO_4^-$ were found to be 500 and 6800 M^{-1}, respectively. These results suggest that each hydrogen bond between the phosphate hydroxyl group and the pyridyl nitrogen atom stabilizes the complex by $\Delta\Delta G$ = 1.6 kcal mol^{-1}. For comparison, the association constants with other anions are 5000 M^{-1} (Cl^-), 560 M^{-1} (Br^-), 40 M^{-1} (I^-), 1600 M^{-1} (HSO_4^-), 2100 M^{-1} (CN^-), and 22 000 M^{-1} ($CH_3CO_2^-$).



3 **4**

Ion pair receptors

Ion pair receptors should contain both cation- and anion-binding sites with the right geometry and distance able to achieve contact ion pair. Otherwise, high unfavorable energy is required for the charge separation, which decreases the binding affinity. Ion pair receptor **5** was prepared by incorporating a diazacrown ether to the biindole scaffold [21]. The binding properties of **5** with salts were revealed by ^1H NMR spectroscopy in a highly polar medium, 10 % (v/v) d_6-DMSO/CD_3CN at 24 ± 1 °C. For binding studies, anions are used as tetrabutylammonium salts and alkali metal cations as perchlorate (ClO_4^-) or hexafluorophosphate (PF_6^-) because these counterions bind negligibly under the conditions. Receptor **5** weakly binds a chloride with the association constant (K_a) of 7 (± 2) M^{-1}. However, the association constant significantly increases up to 2000-fold in the presence of an alkali metal cation (1 equiv) as summarized in Table 2. Among alkali metal cations, sodium ion shows the largest cooperative effect on the binding strength of halides. The enhancement of the binding affinity stems from electrostatic interactions between the bound halide and alkali metal cation, which depends on the charge density as well as the inter-ionic distance. In receptor **5**, the interaction seems to be optimal when sodium ion is present at the crown ether site.

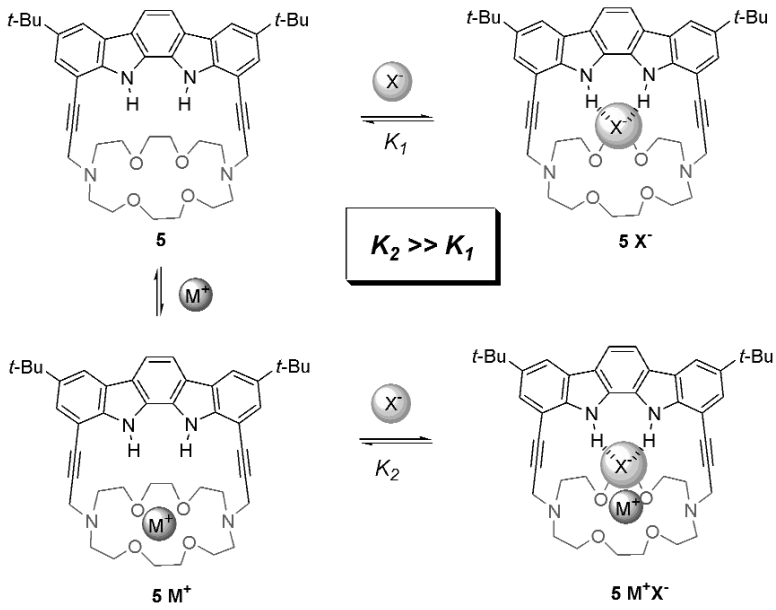


Table 2 Association constants (K_a, M^{-1})[a] between ion pair receptor **5** and halides in the presence of alkali metal salts (1 equiv) in 10 % (v/v) d_6-DMSO/CD_3CN at 24 ± 1 °C.

Halide			
Additive	Cl^-	Br^-	I^-
none	7	_[b]	_[b]
Li^+ClO_4	120	24	9
Na^+ClO_4	14 000	600	61
K^+PF_6	6200	200	45

[a]The association constants were analyzed in the ^1H NMR spectroscopy based on the downfield shifts of the indole NH signals. Errors in the association constants are less than 15 % except those of K_a < 10 M^{-1}, in which cases, errors increase up to 30 %.
[b]The chemical shift changes during the titration were too small to determine the association constant.

Cyclic tetraindoles

A cyclic tetraindole **6** was prepared by connecting two molecules of the biindole scaffold through an ethynyl linker [4]. There is a small cavity with four indole NHs, thus capable of binding anions by hydrogen bonds. The cavity is almost square with distances of 2.6 Å (side) and 3.7 Å (diagonal) between indole NHs, which allows for the coordination of just one atom. The X-ray crystal structure of the complex **6**·*n*-$Bu_4N^+Cl^-$ shows that the chloride ion is in the center of the cavity by forming four hydrogen bonds with indole NHs. The chloride ion is not completely inserted into the cavity due to the limited space (Fig. 1).

Due to slow exchange on the NMR timescale, two sets of the ^1H signals of **6** can be seen when 0.5 equiv of tetrabutylammonium chloride is added in CD_3CN at room temperature, but only the sig-

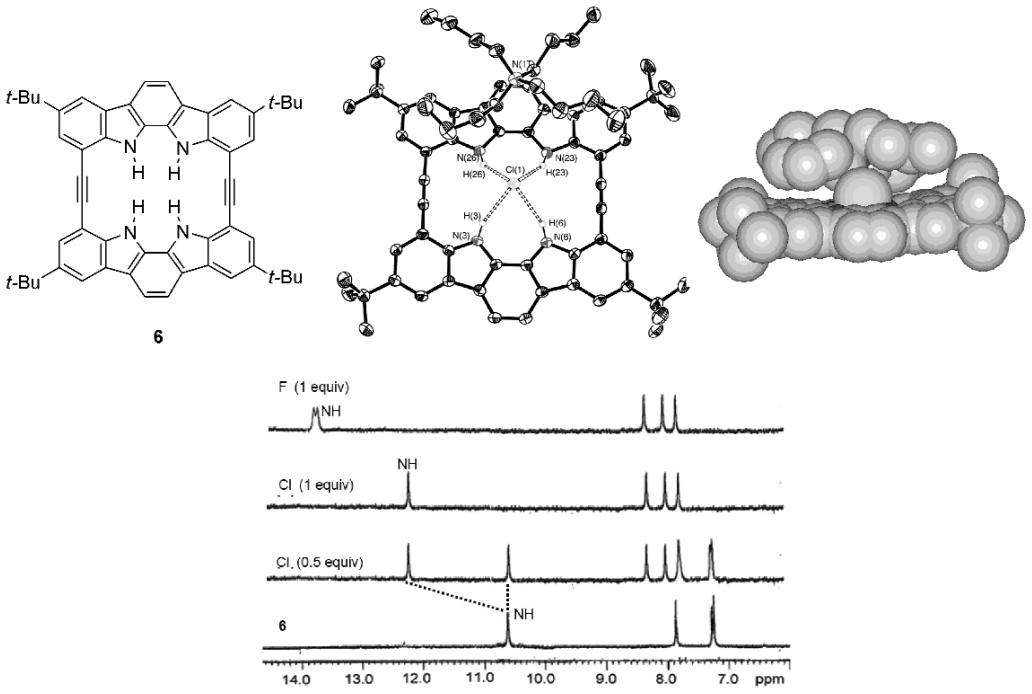


Fig. 1 ORTEP view (middle) and CPK view (right) of X-ray crystal structures of the complex between **6** and *n*-$Bu_4N^+Cl^-$, and partial ^1H NMR spectra (500 MHz, CD_3CN, 25 °C) of **6** and its complexes with tetrabutylammonium chloride and fluoride.

nals corresponding to the complex exist upon addition of more chloride (Fig. 1). The NH signal when bound with chloride is largely downfield-shifted by $\Delta\delta$ = 1.7 ppm as a result of hydrogen bonds. It should be mentioned that the NH signal of the fluoride complex is shown at 13.9 ppm as a doublet (J = 43 Hz) due to spin–spin coupling between NH and fluoride.

We prepared another cyclic tetraindole **7** with a larger rectangular cavity, by modifying the linker from the ethynyl into the butadiynyl (Fig. 2). The distances between indole NHs are 2.6 Å (side), 5.1 Å (side), and 5.8 Å (diagonal). Since the cavity sizes are quite different, **6** and **7** possibly display different binding modes with polyatomic anions such as azide. That is, the smaller macrocycle **6** may bind anions by the coordination of just one atom due to the limited space of the cavity, but more than one atom can simultaneously coordinate to the cavity of the larger macrocycle **7**. This possibility was nicely

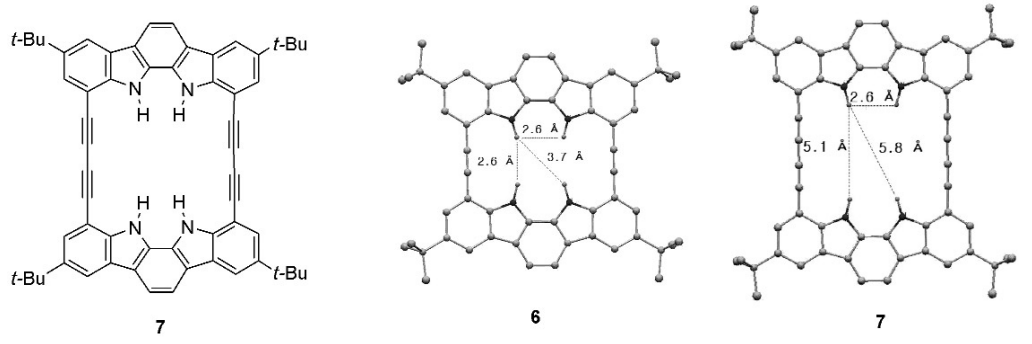


Fig. 2 Molecular structure of **7** and energy-minimized structures (MacroModel 7.1, MMFF force field) of **6** and **7**.

illustrated by single crystal X-ray diffraction of two complexes of tetrabutylammonium azide with **6** and **7** (Fig. 3) [22].

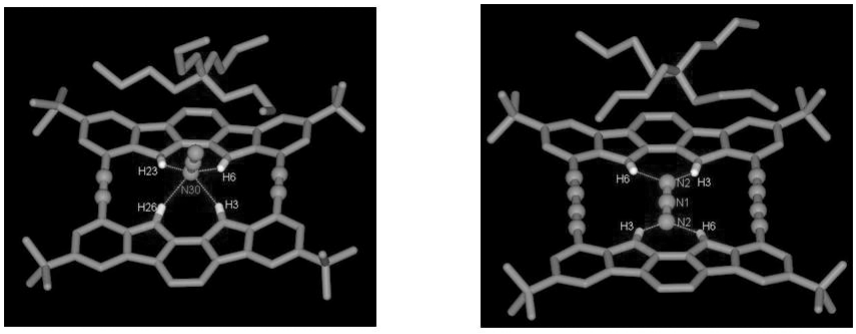
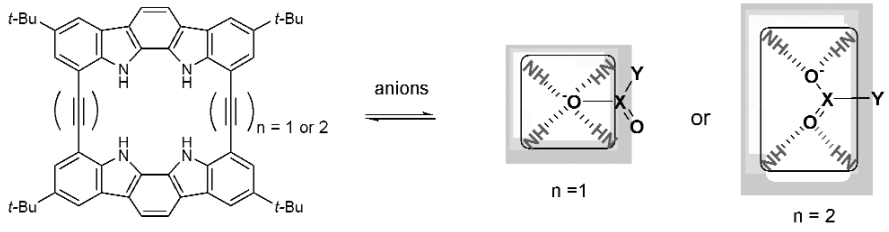


Fig. 3 X-ray crystal structures of two complexes, **6**·*n*-$Bu_4^+N_3^-$ (left) and **7**·*n*-$Bu_4^+N_3^-$ (right).

In complex **6**·*n*-$Bu_4^+N_3^-$, one nitrogen atom of azide is directed to the cavity of **6**, making four hydrogen bonds with the average distance of 2.92 Å between the indole nitrogen and the azide nitrogen. The distances between three nitrogen atoms of the bound azide are unequal; the hydrogen-bonded side (1.191 Å) is slightly longer than the other side (1.171 Å), which can be rationalized by the resonance structures of azide. In addition, the countercation tetrabutylammonium is located on the aromatic plane and close to the other end nitrogen, stabilized by cation-π and electrostatic interactions. This countercation may hinder the formation of possible 2:1 (**6**/azide) complex in the solid state as well as in solution. In complex **7**·*n*-$Bu_4^+N_3^-$, both end nitrogen atoms of the azide are simultaneously bound to the cavity of **7** in a bridged manner, each forming two hydrogen bonds with indole NHs (N···N distance 2.84 Å). In complex **7**·*n*-$Bu_4^+N_3^-$ with the crystallographic inversion center, the distance between three nitrogen atoms of the bound azide is now identical (1.188 Å).



Two complexes have the same number of hydrogen bonds and the same type of NH–N hydrogen bonds. Which complex is more stable in solution? The answer for this intriguing question has been obtained from the UV/vis titration experiments in 10 % (v/v) methanol–acetone at 23 ± 1 °C. The association constants (K_a ± 20 %) of **6** and **7** with *n*-$Bu_4^+N_3^-$ were measured to be 2300 M^{-1} and 81 000 M^{-1}, respectively, suggesting that complex **7**·*n*-$Bu_4^+N_3^-$ is more stable than complex **6**·*n*-$Bu_4^+N_3^-$ by the free energy difference ($\Delta\Delta G$) of –2.1 kcal mol^{-1}. Furthermore, we compared the association constants between two macrocycles **6** and **7** with various oxoanions and the results are summarized in Table 3. In all cases, **7** binds oxoanions more strongly than **6**.

Table 3 Association constants (K_a ± 20 %, M^{-1}) of **6** and **7** with tetrabutylammonium anions in 10 % (v/v) methanol–acetone at 23 ± 1 °C [22].

Association constants (K_a, M^{-1})			
Anion	**6**	**7**	Ratio (**7**/**6**)
N_3^-	2300	81 000	35
$CH_3CO_2^-$	21 000	170 000	8.1
$H_2PO_4^-$	4300	220 000	51
NO_3^-	94	15 000	160
HSO_4^-	81	13 000	160
Cl^-	1800	430	0.24
Br^-	72	320	4.2
I^-	<10	2400	>240

In a series of halides, the association constants of **6** increase in the order of $Cl^- > Br^- > I^-$. In contrast, **7** binds most strongly iodide, which is the largest, most diffuse anion and therefore forms the weakest hydrogen bond among halides. These results reflect the size complementarity between the cavity and halide, which is an important element to increase the binding affinity and selectivity.

Oligoindole foldamers

Foldamers are defined as synthetic molecules capable of folding into an ordered array such as secondary structures of proteins (helix, sheet, etc.) by the combination of various noncovalent interactions [23,24]. The synthesis and characterization of new foldamers gives an insight into understanding fundamental principles of folding, which determines the function of biomacromolecules such as proteins and nucleic acids. In addition, foldamers exist in two distinct states, extended or compact conformations, depending on the environment. If two states display different electrical or optical properties, the foldamers can be utilized as functional materials responsive to external stimulation.

We prepared a series of oligoindoles **8–10** containing four, six, and eight indoles by sequentially connecting indole and biindole derivatives via Sonogashira reactions [3]. According to computer modeling, the oligoindoles exist as an extended zigzag conformation in which the inside biindole adopts a transoid conformation to minimize dipole repulsion between two indole NHs. When chloride is added, however, the biindole moiety switches the conformation from transoid into cisoid so that all of the existing NHs are able to form hydrogen bonds with chloride. As a consequence, the oligoindoles fold into helical structures. Tetramer **8** makes one complete turn, and longer oligoindoles **9** and **10** make helical structures of 1.5 and 2 turns, respectively.

The ^{1}H NMR spectroscopy provides clear evidences for helical folding of the oligoindoles when complexed with chloride in solution. For example, hexamer **9** shows a characteristic ^{1}H NMR spectral behavior; one-half of the aromatic signals in the biindole are upfield-shifted by 0.4–0.5 ppm and the other half remain almost unchanged upon addition of chloride (Fig. 4). This is nicely matched with the folded structure of **9**, in which only one-half of the biindole moieties become stacked with terminal indoles. The 2D rotating-frame nuclear Overhauser enhancement spectroscopy (ROSEY) experiment also supports the helical folding, showing the nuclear Overhauser effect (NOE) cross-peaks between the stacked aromatic signals.

The binding affinities of the oligoindoles with tetrabutylammonium chloride increase as the chain length grows. The association constants (K_a) in CH_3CN at 22 ± 1 °C were found to be 1.3×10^5 M^{-1} for tetramer **8**, 1.2×10^6 M^{-1} for hexamer **9**, and $>10^7$ M^{-1} for octamer **10**. In a more competitive medium, 10 % (v/v) water-CH_3CN, **10** ($K_a = 2.3 \times 10^4$ M^{-1}) binds chloride more strongly than **9** (K_a =

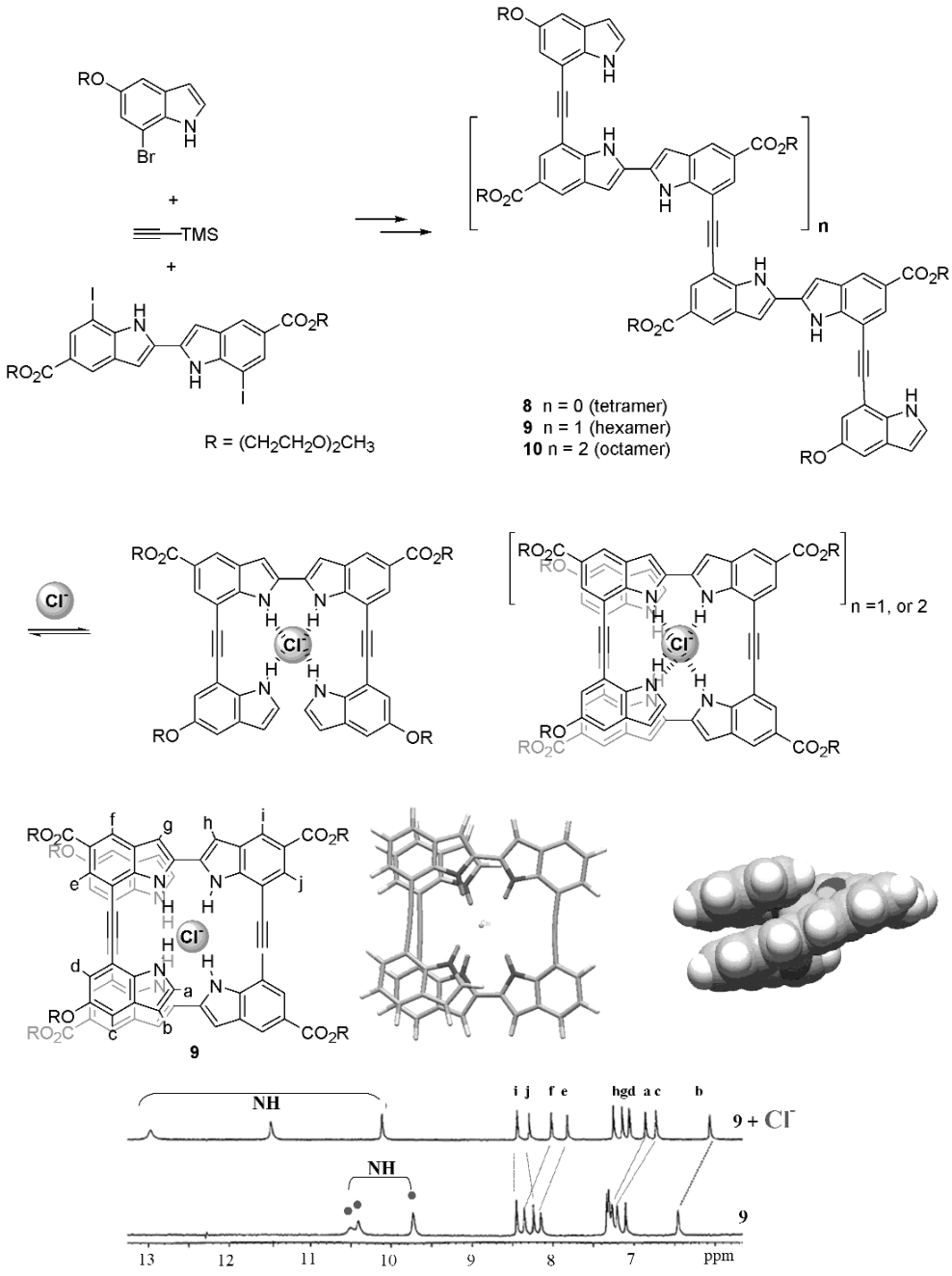


Fig. 4 Molecular structure of hexamer **9**, its energy-minimized structures (MacroModel 7.1, MMFF force field, tube model and CPK model), and partial ^{1}H NMR (500 MHz, CD_3CN) spectra of **9** in the absence and in presence of chloride (1 equiv).

2.1×10^2 M^{-1}). The continuous variation method (Job's plot) showed that the oligoindoles form 1:1 complexes with chloride. These binding properties provide an additional evidence for helical folding of the oligoindoles upon binding chloride by multiple hydrogen bonds.

The foldamer can form either a right-handed helix (*P*-helix) or a left-handed helix (*M*-helix). The oligoindoles described above should give 1:1 mixtures of two helical isomers. To induce the preferential formation of one particular isomer, we are currently investigating two different approaches, (i) incorporation of a chiral segment to the oligoindole or (ii) binding a chiral guest. On the other hand, we are also pursuing creating functional oligoindole foldamers. The foldamers may display characteristic fluorescence properties because they have two unique conformations, folding and unfolding. When folded, the aromatic planes are stacked next to each other. Consequently, the red shift of the emission wavelength is anticipated due to the formation of intramolecular eximer and exiplex between the stacked aromatic planes. If this is the case, the foldamer has a great potential as an anion sensor or a functional material responsive to external chemical species.

CONCLUSION

We have demonstrated that indole bearing a good hydrogen bond donor can serve as a versatile building block for the synthesis of anion receptors. A biindole derivative **1** with two indole NHs was efficiently synthesized from *p*-substituted aniline and used as the actual scaffold for our indole-based receptors. Two cleft-like receptors **2** and **3** were prepared by incorporating more hydrogen bond donors or acceptors to the biindole scaffold. It has been clearly illustrated that the presence of additional binding groups increases not only the binding affinities but also the selectivity toward a specific ion. Two macrocycles **6** and **7** with a rigid, planar cavity surrounded by four conversing indole NHs were also prepared by coupling two molecules of the biindole scaffold. Two macrocycles display distinct hydrogen-bonding modes with polyatomic anions (e.g. azide), depending on the size of their cavities, according to X-ray crystal structures and binding studies. Finally, a series of oligoindole foldamers **8–10** were prepared which fold into helical structures upon binding with chloride.

As the receptor, the foldamer is a particularly attractive molecule in that the folding generates an internal cavity capable of binding a guest, as in proteins and enzymes. Our ongoing and future work is directed to the creation of various functional foldamers including helically biased foldamers, molecular sensors, external stimuli-responsive materials, water-soluble anion receptors, etc.

ACKNOWLEDGMENTS

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