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Indolocarbazole-based anion receptors and molecular switches*

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Abstract: A number of indolocarbazole-based anion receptors were prepared and their anion-binding behaviors were characterized in solution and in the solid state. First, chain-length-dependent binding affinities of chloride ion were revealed using a series of indolocarbazoles that consisted of one to four indolocarbazole units. The binding affinities were steadily enhanced from monomer to dimer, then to trimer by Gibb's free energy ($-\Delta\Delta G$) = 2.4 ± 0.1 kcal/mol, and then nearly saturated. Second, a water-soluble trimer folded to generate an internal helical cavity with six convergent NHs, wherein small halides bound in water in the order of Cl^- (65 M^{-1}) > F^- (46 M^{-1}), and Br^- (19 M^{-1}). Third, X-ray crystal structures clearly proved helical folding of a trimer in the presence of sulfate ion, in which left- and right-handed helices stacked alternatively. It was also shown that the selectivity of anion binding could be varied by the modification of the spacer groups connecting indolocarbazole units. Finally, we prepared chiral indolocabazole dimers that adopted helical structures by intramolecular hydrogen bonds and displayed complete inversion of the helical sense upon anion binding. The dimers gave characteristic optical readouts in a reversible manner according to chemical stimuli, thus functioning as chirooptical molecular switches.

Keywords: anion receptors; foldamers; helical structures; hydrogen bonding; indolocarbazole; molecular recognition; molecular switches; oligomers; supramolecular chemistry.

INTRODUCTION

Anions and anionic species are ubiquitous and play key roles in biological systems. A number of proteins have been known to bind and transport anions across cell membranes, which is closely associated with many important biological processes; e.g., regulation of cellular pressure, production of biological signals, and activation of signal transduction pathways. A large number of synthetic anion receptors have been prepared based on hydrogen-bonding interactions [1–3]. As hydrogen-bond donors, diverse functional groups have been used, including amido, ureido, and pyrrolic NHs, polarized CHs, and hydroxyl groups. In recent years, the indole NH proton has been also utilized as a hydrogen-bond donor in the construction of anion receptors [4]. For example, we prepared a series of oligoindoles **1** that contained four, six, and eight indole units for hydrogen bonding with anions [5]. These oligoindoles existed in extended zigzag conformations but adopted helically folded structures in the presence of chloride ion. Gale et al. prepared a variety of anion receptors by the combination of indole units with amido and ureido groups to bind anions strongly and selectively [6,7].

Indolocarbazoles are a class of pentacyclic compounds with two NHs capable of simultaneously participating in hydrogen bonding with anions. In 2005, Beer et al. reported for the first time that

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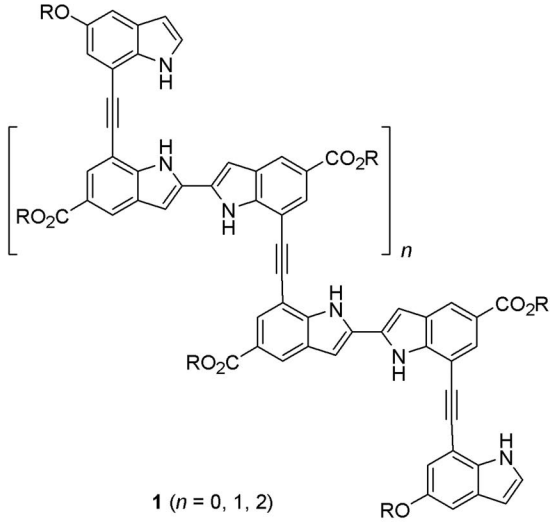
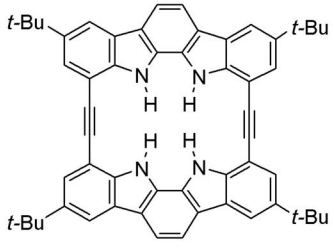
indolocarbazoles could strongly bind carboxylates, phosphates, and halides by hydrogen-bonding interactions [8,9]. We also proved that the indolocarbazole scaffold could be served as a useful building block for the construction of anion receptors. For example, macrocycle **2** contains a small cavity with four convergent NHs, thus binding halides such as fluoride and chloride with extremely high affinities and selectivity [10]. Some of these works were already described in the previous article [11]. Herein, we will describe acyclic indolocarbazoles that can function as anion receptors and molecular switches, as presented in the symposium.



1 (*n* = 0, 1, 2)



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RESULTS AND DISCUSSION

Chain-length-dependent affinities between indolocarbazoles and chloride ion

The design of molecular building blocks is most critical and challenging for the development of anion receptors based on foldamers [12–15]. It should have proper functional groups or appendages for hydrogen bonding, elongation, solubility, etc. Using an indolocarbazole derivative **3** as a molecular building block, we prepared a series of indolocarbazoles **4–7** by Sonogashira coupling reactions [16,17]. A spherical chloride ion was chosen to reveal relative binding affinities of the indolocarbazoles **4–7**. In less polar solvents, their binding affinities were too large to be determined accurately by normal titration methods, and even in dimethyl sulfoxide (DMSO), the association constants (K_a) of trimer **6** and tetramer **7** were greater than 10^6 M^{-1}. Therefore, the binding affinities were evaluated in 4:1 (v/v) DMSO/MeOH at 24 ± 1 °C, under which conditions the association constants could be determined and compared using ^{1}H NMR and fluorescence spectroscopy. ^{1}H NMR titration experiments gave the association constants of 11 M^{-1} for **4** and 560 M^{-1} for **5**. However, ^{1}H NMR spectra of **6** and **7** were completely broaden out at room temperature owing to slow exchange between self-aggregates in the ^{1}H NMR (400 MHz) time scale. When tetrabutylammonium chloride was added, sharp and well-resolved ^{1}H NMR signals appeared immediately. The intensities continued to increase and saturated upon addition of 1 equiv of chloride ion in acetone-d_6, indicating that longer oligomers **6** and **7** formed 1:1 complexes with chloride ion. The fluorescence titrations afforded the association constants of 37 000 M^{-1} for **6** and 140 000 M^{-1} for **7**. To sum up, the association constants were enhanced by 51-fold from **4** to **5** and 66-fold from **5** to **6**, but only 4-fold from **6** to **7**, corresponding to the increments of Gibb's free energy ($-\Delta\Delta G$) = 2.4 ± 0.1 kcal/mol from **4** to **5**, then to **6**, but only 0.8 kcal/mol from **6** to **7**.

According to computer models (Fig. 1), longer indolocarbazoles **6** and **7** folded into helical structures when complexed with chloride ion, thus all the existing NHs capable of participating simultaneously in hydrogen bonding with chloride ion. In the case of trimer **6**, the NH···Cl^- distances (2.5 ± 0.2 Å) are in the range of forming normal hydrogen bonds. On the other hand, the inside six NHs of tetramer **7** are close to the bound anion with NH···Cl^- distances of 2.5 ± 0.2 Å, but two terminal NHs, one at each end, are distant away (3.1 Å) from the anion, thus exerting weak hydrogen-bonding interactions. This possibly explains why the binding affinities of chloride ion are steadily enhanced from monomer **4** to trimer **6**, and then nearly saturated. This study suggests that the binding affinity and selectivity to a specific anion may be modulated by adjusting the chain length of foldamer-based anion receptors.

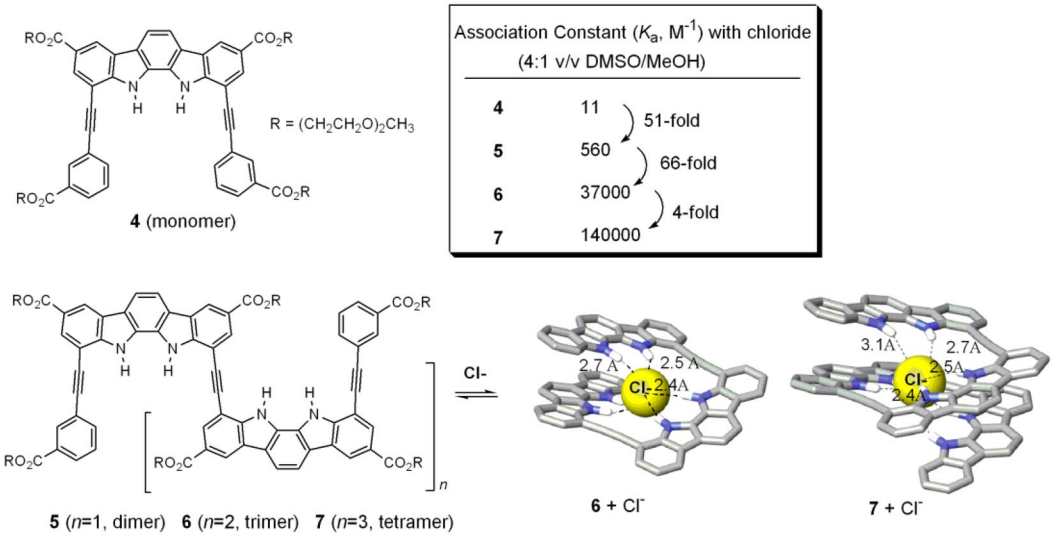

Fig. 1 Molecular structures of indolocarbazoles **4–7**, association constants between the indolocarbazoles and tetrabutylammonium chloride in 4:1 (v/v) DMSO/MeOH at 24 ± 1 °C, and energy-minimized structures of **6** (trimer) and **7** (tetramer) upon complexation with chloride (MacroModel 9.1, MMFFs force field, gas phase). The ester side chains were replaced by hydrogen atoms on the energy minimization, and terminal ethynylbenzoates and the CH hydrogen atoms are omitted for clarity.

A water-soluble indolocarbazole trimer

Proteins are known to bind anions in water by polar interactions such as hydrogen bonds and electrostatic forces. On the contrary, most synthetic anion receptors strongly bind anions in organic media but negligibly in water. Water forms strong hydrogen bonds with polar functional groups, and therefore the binding sites of synthetic receptors are strongly solvated by water molecules, which greatly reduces the binding affinities in water. On the other hand, proteins fold into ordered structures primarily by hydrophobic interactions, thus resulting in the anion-binding sites positioned inside the molecules and hidden from outside bulk water. As a consequence, the binding sites are much weakly solvated by water molecules. This is possibly responsible for the strong affinities between proteins and anions by hydrogen bonds in water, as seen in sulfate- and phosphate-binding proteins [18,19].

How can one design a synthetic mimic able to bind anions in water? Aromatic helical foldamers might be plausible candidates if soluble in water. In particular, indolocarabzole oligomers have large aromatic surfaces which offer sufficient hydrophobic and π-stacking interactions to fold into helical structures. Helical folding may create an internal cavity with multiple convergent NHs capable of

hydrogen bonding with anions of complementary size, shape, and geometry. In this context, trimer **6** with ester groups was hydrolyzed under basic aqueous conditions to afford a water-soluble derivative **8** with carboxylates [16a]. ^{1}H NMR spectra clearly suggested **8** fold in a helical conformation in water. ^{1}H NMR signals of terminal benzoates were upfield shifted by $\Delta\delta$ = 0.4~1 ppm, compared with those in monomer analogue **9** (Fig. 2). Upon being folded, the benzoate rings of **8** become stacked above or below the indolocarbazole plane, thus the signals upfield shifted, but such stacking is impossible in **9**.

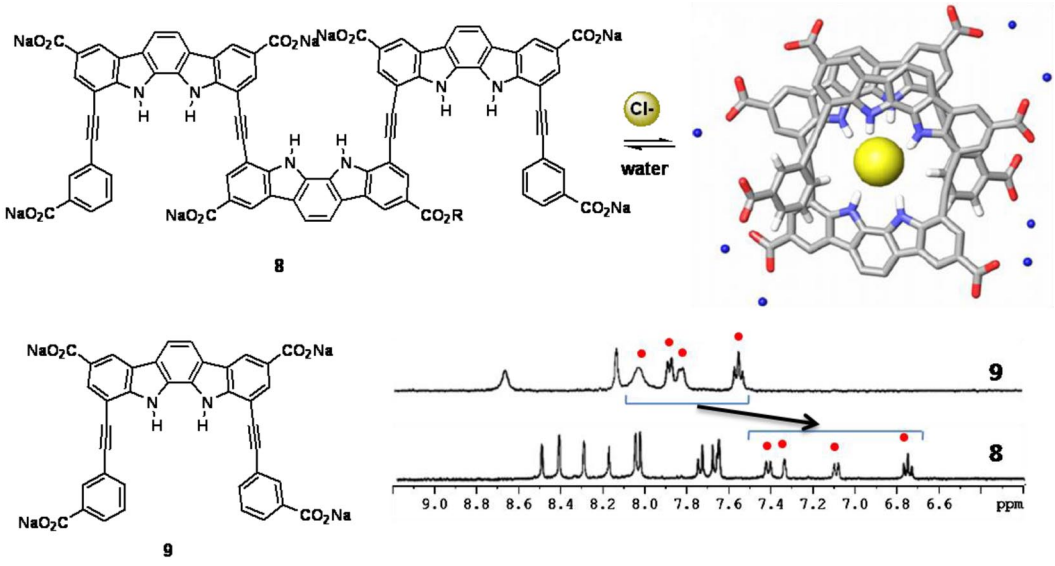

Fig. 2 Molecular structures of **8** and **9**, an energy-minimized structure (MacroModel 9.1, MMFFs force field, in water) of complex between **8** and chloride (right, above), and ^{1}H NMR spectra (400 MHz, D_2O, 25 °C) of **8** and **9** (right, below) where the CH signals of terminal benzoates are marked as red dots.

The binding affinities of **8** with sodium halides were revealed in D_2O in ^{1}H NMR spectroscopy, showing noticeable changes in the chemical shifts of aromatic CH signals upon addition of small halides (F^-, Cl^-, and Br^-) but negligible change by large anions (ClO_4^- and I^-). The association constants (K_a) were estimated to be in the order of Cl^- (65 M^{-1}) > F^- (46 M^{-1}), and Br^- (19 M^{-1}) >> $I^- \approx ClO_4^-$ (<1 M^{-1}). In general, fluoride ion has been known to form stronger hydrogen bonds than chloride ion in organic solvents, but in this system the latter was found to bind more strongly than the former, possibly due to much stronger hydration of small and hard fluoride. Although binding affinities are moderate here, the result nicely demonstrates that a helically foldable receptor with neutral functional groups can bind small hydrophilic anions by hydrogen-bonding interactions in water.

Indolocarbazole receptors with OH functional groups

For hydrogen bonding with anions, proteins utilize not only the NH protons in the backbone peptide bonds and in the side chains of amino acids but also the OH protons in the side chains of Ser, Tyr, and Thr, as seen in phosphate-binding proteins [19] and a ClC chloride channel [20]. Only a few examples of synthetic receptors have been known wherein hydroxyl groups were incorporated for hydrogen bonding with anions [21]. We prepared a cleft-type anion receptor **10**, which possesses two NHs and two OHs as hydrogen-bond donors for anion binding [22]. The binding constant of **10** with tetrabutylammonium chloride was determined to be 34 700 M^{-1} in 1 % H_2O/CH_3CN. In the crystal structure of the complex, chloride ion was in the middle of the cavity by four hydrogen bonds and tetrabutylammonium cation was located on the indolocarbazole plane possibly due to cation-π interactions (Fig. 3). It is worth mentioning that the hydrogen-bonding mode of the chloride complex is similar to that observed in a ClC chloride channel, two with NHs and two with OHs (Ser and Tyr).

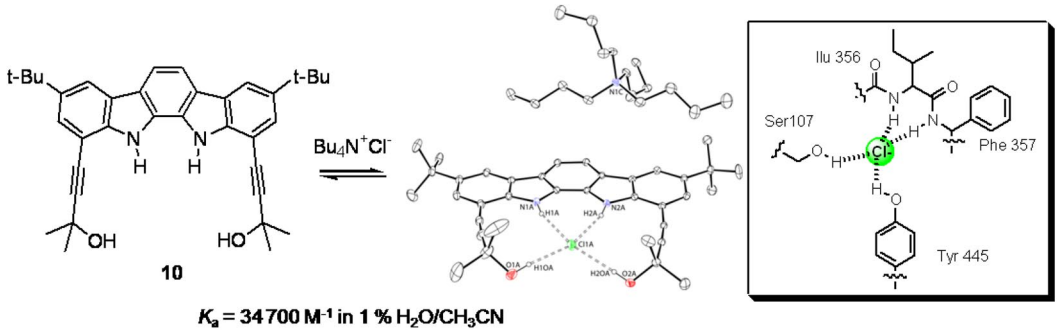

Fig. 3 Compound **10** and its complex with tetrabutylammonium chloride. In the crystal structure (middle), tetrabutylammonium ion sits on the indolocarbazole plane and chloride ion is held by our hydrogen bonds with two NHs and two OHs as observed in the ClC chloride channel (in box).

Next, trimer **11** with *t*-butyl side chains and two hydroxyl groups at the ends was prepared to get crystal structures that might provide us with a direct evidence for helical folding [23]. To our delight, its sulfate complex afforded single crystals suitable for X-ray diffraction analysis. The sulfate ion was entrapped in the middle of the helical cavity by forming eight hydrogen bonds, six with NHs, and two with OHs. Each oxygen atom of the sulfate ion formed two hydrogen bonds by folding of **11** into a helical structure. The complex was found to be a racemate crystal with two enantiomeric helices (*M* and *P*) stacked alternatively in the solid state. Tetrabutylammonium cations were intercalated in between the indolocarbazole planes of two helical isomers, thus rendering 3D aggregates of a helical structure (Fig. 4).

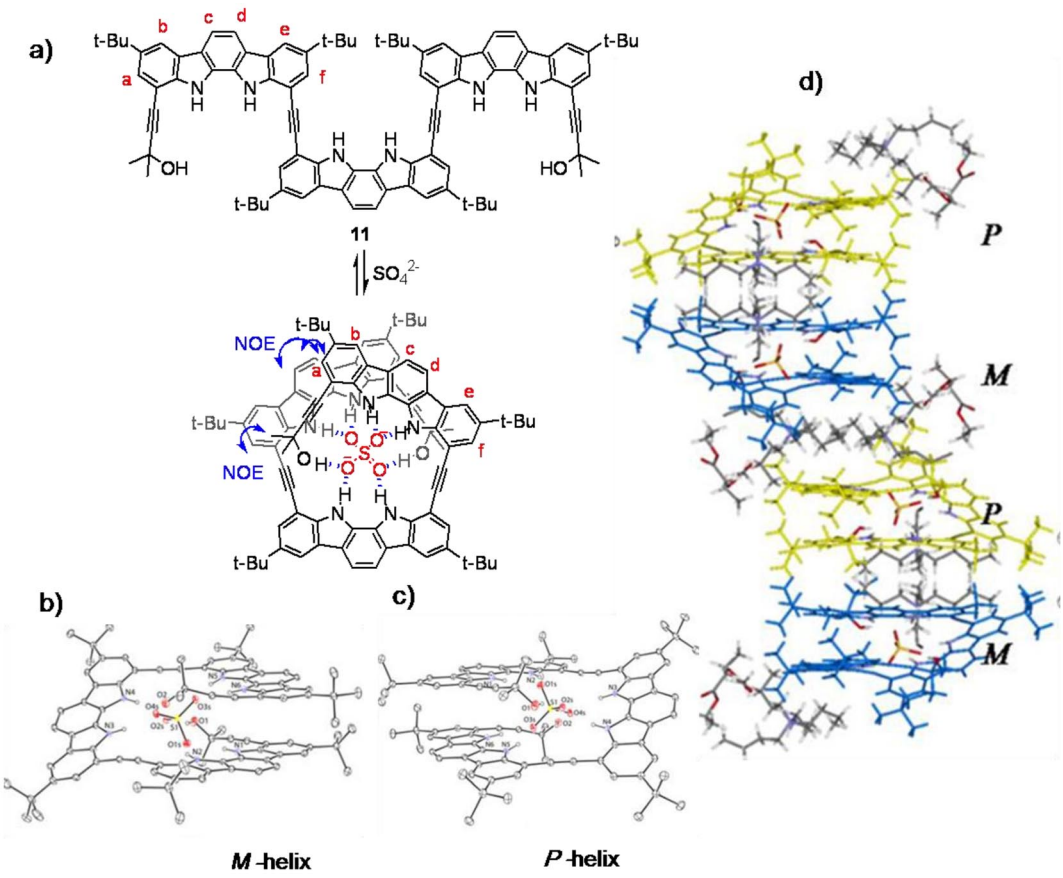

Fig. 4 (a) Molecular structures of **11** and its sulfate complex, (b) and (c) left- and right-handed helices of the crystal structures of complex **11**·SO_4^{2-}, and (d) the packing structure of complex **11**·$(Bu_4N)_2SO_4$ displaying *M*- and *P*-helices stacked alternatively.

^{1}H NMR and fluorescence studies were agreed well to the crystal structure. When complexed with sulfate, large downfield shifts ($\Delta\delta$ = 2.0~3.4 ppm) of NH and OH signals were observed, together with characteristic upfield shifts ($\Delta\delta$ = 0.2~1.1 ppm) of aromatic CH signals (H_a, H_b, H_c, and H_d) which stacked in the crystal structure. Helical folding was also confirmed by ^{1}H-^{1}H nuclear Overhauser enhancement spectroscopy (NOESY) experiment, showing clearly characteristic NOE cross-peaks between H_a and distant hydrogens H_c and H_d as well as CH_3 and H_f. In the fluorescence spectrum, **11** exhibited hypochromic (I/I_0 = 0.38) and bathochromic shifts ($\Delta\lambda$ = 40 nm) of the emission band centered around 413 nm when complexed with sulfate ion. This observation can be explained by the intramolecular excimer-like stacked array of the indolocarbazole units in a helically folded conformation. The association constant between **11** and bis(tetrabutylammonium) sulfate was found to be 640 000 M^{-1} in 10 % MeOH/CH_3CN at 24 ± 1 °C. As summarized in Table 1, sulfate ion was determined to bind much higher than any other anion examined (dihydrogen phosphate, acetate, cyanide, azide, chloride, bromide, and iodide) by more than two orders of the magnitudes.

Table 1 Association constants of **11** and **12** with anions in 10 % (v/v) MeOH/CH_3CN at 24 ± 1 °C.

Anion	Association constant (K_a, M^{-1})		Ratio (**12/11**)
	11	**12**	
$H_2PO_4^-$	3 600	261 000	73
SO_4^{2-}	640 000	63 000	0.1
$CH_3CO_2^-$	5 700	57 500	10
Cl^-	8 800	17 800	2
N_3^-	790	9 700	12
Br^-	2 800	3 500	1.3

Foldamer-based receptors differ from conventional receptors in that the binding cavity is not preorganized by covalent bonds but generated in situ as a result of folding. The binding cavity depends on the chain length of foldamers, kind of spacers in between the repeating units, and others. With this in mind, we prepared an indolocarbazole trimer **12** linked by butadiynyl groups [24]. As anticipated, trimer **12** was found to bind more strongly large polyatomic anions ($H_2PO_4^-$, $CH_3CO_2^-$, and N_3^-) except sulfate ion by more than one order of the magnitude relative to trimer **11** having short ethynyl spacers (Table 1). In particular, **12** bound dihydrogen phosphate most strongly and selectively. As shown in Fig. 5, energy-minimized structures showed that dihydrogen phosphate was held by six NH···O (anion), two OH···O (anion), and one O···HO (anion) in the internal cavity of the helically folded structure. Accordingly, three NH signals in the ^1H NMR spectroscopy were largely downfield shifted by $\Delta\delta$ = 1.8~4.3 ppm upon binding of sulfate ion in 1 % H_2O/CD_3CN. In addition, the OH signal was moved from 3.69 to 6.13 ppm under the same conditions. The CH signals of the indolocarbazoles at both ends were upfield shifted by $\Delta\delta$ = 0.3~0.9 ppm, indicating that two terminal indolocarbazole planes became stacked against each other.

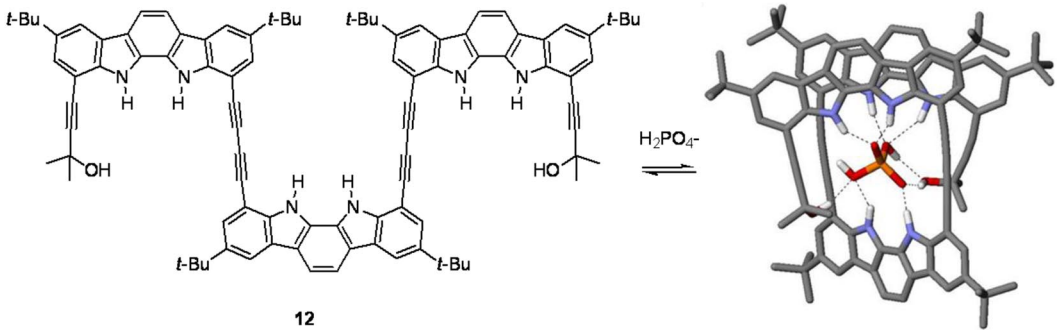

Fig. 5 Molecular structure **12** and an energy-minimized structure (MacroModel 9.1, MMFFs force field, gas phase) of complex between **12** and dihydrogen phosphate.

Indolocarbazole dimers as molecular switches

Molecular switches can be defined as molecules that have two or more inter-convertible, (semi)stable states responsive to external stimulation such as light, temperature, pH, and solvents. Each of the conformational or constitutional isomers should display unique physical, spectroscopic, or optical properties. Several molecular scaffolds including dithienylethenes, sterically overcrowded olefins, and interlocked molecules have been employed to date for the construction of molecular switches [25].

Synthetic molecules capable of folding into helical conformations could be good candidates for molecular switches because they may adopt two distinct conformations according to folding and unfolding. In particular, helical foldable molecules offer an additional switching mode associated with the helical sense, left- or right-handed helices, which enables them to utilize as a new class of chirooptical molecular switches.

Herein, we prepared a chiral indolocarbazole dimer **14** where two indolocarbazole units are connected by a butadiynyl linker to achieve intramolecular hydrogen bonds between amide oxygen and indolocarbazole on the other side [26]. These intramolecular hydrogen bonds enable this dimer to adopt a helically folded conformation even in the absence of anion binding, as proven by ^{1}H NMR spectroscopy. One of the indolocarbazole NHs signals were downfield shifted by $\Delta\delta$ = 1.1 ppm relative to a reference molecule **13**, and the CH signals of terminal chiral units were upfield shifted by $\Delta\delta$ = 0.4~1.1 ppm. The optical properties of **14** also supported the helical folding induced by intramolecular hydrogen bonds. **14** showed a very strong circular dichroism (CD) signal with a negative Cotton effect ($\Delta\varepsilon$ = –104 M^{-1} cm^{-1}) in CH_2Cl_2 (Fig. 6). The intensity ($\Delta\varepsilon$) of the CD signal decreased in more polar solvents such as acetonitrile, acetone, and DMSO. It should be noted that the reference molecule **13** was completely CD-silent. In addition, the optical rotation of **14** was also found to be highly sensitive to the polarity of solvents. The specific rotation ($[\alpha]_D$) was –31° in DMSO but greatly increased up to –913° in CH_2Cl_2. This large variation of the specific rotation should be ascribed to unique conformational features that **14** adopts for a helically folded conformation in nonpolar solvents, but exists in an extended structure in polar solvents.

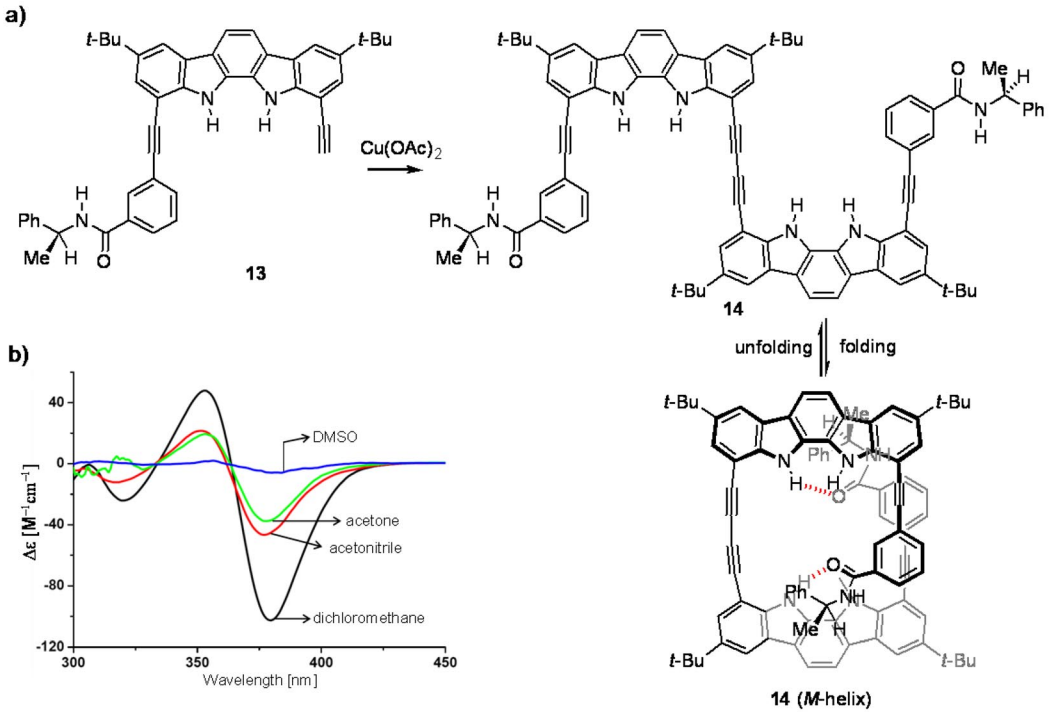

Fig. 6 (a) Molecular structures **13** and **14**, and (b) CD spectra of **14** in four different organic solvents.

More interestingly, dimer **14** exhibited complete switching of the helical sense upon anion binding. As described earlier, **14** gave a strong CD signal with a negative Cotton effect around 380 nm, corresponding to the absorption of the indolocarbazole chromophore. Addition of

bis(tetrabutylammonium) sulfate led to complete inversion of the CD spectrum in CH_2Cl_2 (Fig. 7), suggesting that the helical sense reversed. The magnitude of the Δε value was identical to that of free **14** but an opposite Cotton effect (Δε = +104 M^{-1} cm^{-1}). The reversibility of the CD spectral change was examined using trimer **11**, which bound sulfate ion more strongly (~34-fold) than **14** under the same conditions. The original CD spectrum of free **11** was restored when **14** (~1 equiv) was added to a CH_2Cl_2 solution of the sulfate complex. Then, addition of more sulfate ion led to the reappearance of the CD spectrum corresponding to the sulfate complex. According to the exciton chirality method developed by Nakanishi et al. [27], dimer **14**, showing a negative Cotton effect at the longer wavelength, folds to a *M*-helix while its sulfate complex with a positive Cotton effect forms a *P*-helix.

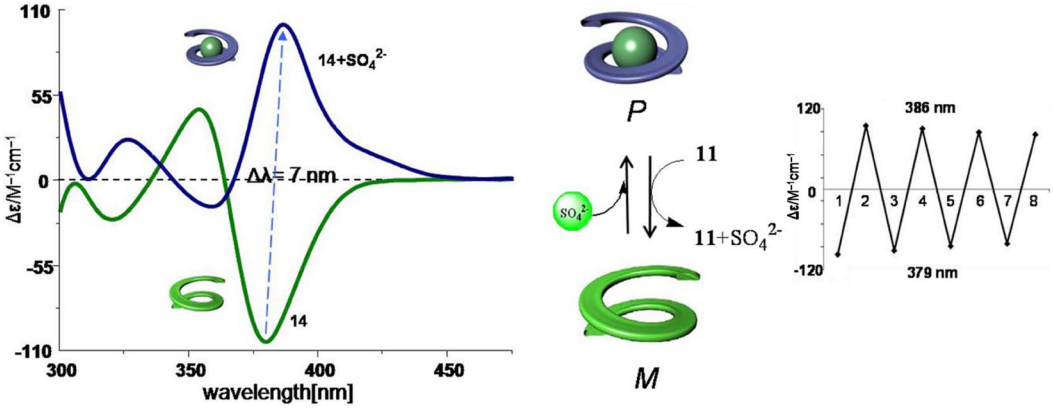

Fig. 7 CD spectra of **14** in the absence of and in the presence of bis(tetrabutylammonium) sulfate. Addition of sulfate ion led to the complete switching of the helical sense from *M* (free) to *P* (complex), and the original spectrum was be restored by addition of a sulfate-sequestering reagent **11**. The cycle could be repeated several times.

In order to investigate how terminal chiral units vary the degree of the helical bias, dimer **15** with the (*S*)-1-naphthylethylamido moiety was prepared. The CD spectra of **15** and its sulfate complexes were exactly overlapped with those of **14**, in particular in the absorption region of the indolocarbazole chromophore. This result suggested that both dimers **14** and **15** fold to left-handed (*M*) helices and their complexes to right-handed (*P*) helices at least predominantly not able to distinguish small differences in the ratio of two helical isomers. The absolute stereochemistry of the sulfate complex of **15** was confirmed by X-ray crystal structures (Fig. 8). Two different types of single crystals were isolated, and both were *P*-helices as anticipated by the CD signals. In one crystal structure (Fig. 8b), one of two amides is involved in hydrogen bonding with sulfate ion and the other is rotated away from the cavity, not involving hydrogen bonding with sulfate. Instead, the CH proton at the para position is involved in the hydrogen bond with sulfate. In the other crystal (Fig. 8c), both amide NHs are directed in the cavity and involved in hydrogen bonding with sulfate ion. In two crystal structures, the distances of N(indole)···O(sulfate) hydrogen bonds are in the range of 2.58~2.71 Å while those of N(amide)···O(sulfate) bonds are 2.83~2.96 Å, implying that the latter forms relatively weak hydrogen bonds. This is possibly responsible for the formation of two different crystals with the comparable stability of the CH···O and NH(amide)···O hydrogen bonds.

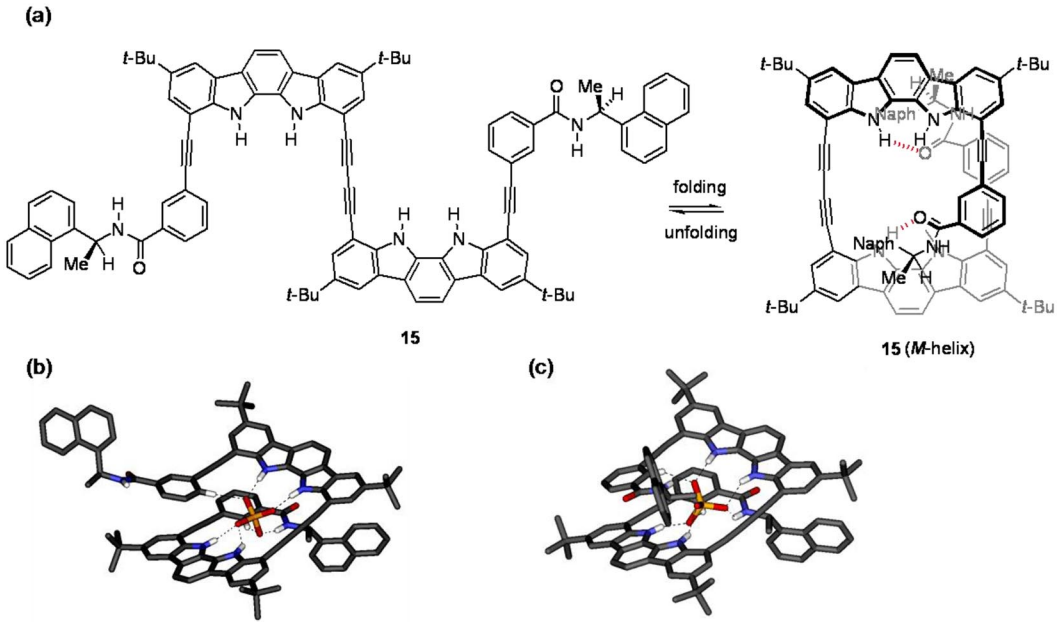

Fig. 8 (a) Molecular structures of **15**, and (b) and (c) two independent single-crystal structures of complex between **15** and bis(tetrabutylammonium) sulfate. In each structure, the sulfate ion is entrapped in the middle of the cavity by multiple hydrogen bonds. Countercations and hydrogen atoms except hydrogen-bonded ones are omitted for clarity.

CONCLUSION

We have demonstrated that indolocarbazole scaffolds can serve as a versatile building block for the construction of anion receptors and molecular switches. Considering that anions have diverse sizes, shapes, and geometries, foldable oligomers are particularly attractive as anion receptors in that the binding affinity and selectivity of an anion could be controlled by the chain length, direction, and angle for the chain elongation, and spacer groups, as demonstrated with a series of indolocarbazoles **4**, **5**, **6**, **7**, **11**, and **12**. Moreover, some oligomers fold to helical structures in water by hydrophobic interactions and other nonpolar interactions. This folding process may generate an internal cavity isolated from the bulk water at least partially, allowing for anion binding in water, as demonstrated with a water-soluble trimer **8**. Finally, helically foldable molecules could be utilized as chirooptical molecular switches if the helical sense of left- and right-handed helices can be controlled by external stimulus. This possibility was examined with chiral indolocarbazole dimers **14** and **15**, which displayed reversible switching of the helical sense, thus producing characteristic optical signals according to chemical stimulation.

ACKNOWLEDGMENTS

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