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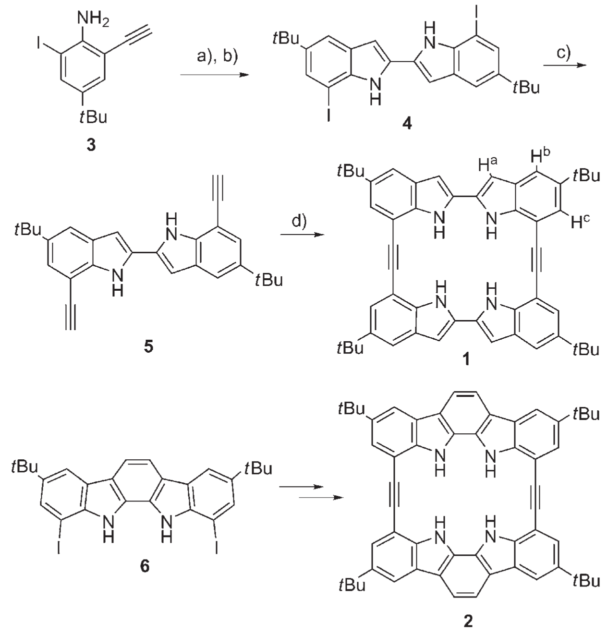
Indole-Based Macrocycles as a Class of Receptors for Anions**

*Kyoung-Jin Chang, Dohyun Moon, Myoung Soo Lah, and Kyu-Sung Jeong**

The development of synthetic receptors and chemosensors for anions[1] has attracted much attention in recent years as the fundamental role of anions in biological and chemical processes has become increasingly understood. Biomacromolecules such as sulfate-binding proteins and a CIC chloride channel make use of hydrogen bonds as a major driving force to bind or transport anions through cell membranes.[2] Similarly, hydrogen-bonding interactions are widely implemented for the construction of artificial receptors, and amido and ureido groups have frequently been incorporated for this purpose.[1,3,4] Furthermore, the pyrrolic NH group has also been used as a hydrogen-bond donor to an anion, as demonstrated in calixpyrroles,[5] expanded porphyrinoids,[6] and amidopyrroles.[7]

Herein, we describe the synthesis and binding properties of indole-based macrocycles **1** and **2**, which can function as a new class of synthetic receptors for anions.[8] The macrocycles contain a well-defined internal cavity surrounded by four indole NH hydrogen atoms, thus are capable of binding anions strongly through hydrogen-bonding interactions. More interestingly, **1** and **2** showed separate sets of ^{1}H NMR signals for the free macrocycles and their complexes at room temperature in all cases and thus can serve as chemosensors for anions based on ^{1}H NMR chemical shifts.

The synthesis of **1** and **2** is outlined in Scheme 1. The key molecular building block 7,7′-diiodo-2,2′-biindole (**4**) was prepared by oxidative dimerization ($Cu(OAc)_2$, 95 %)[9] followed by double indolization (CuI, 81 %)[10] of 4-*tert*-butyl-2-ethynyl-6-iodoanilne (**3**).[11] In turn, **4** was converted into a diethynyl derivative **5**. After numerous unsuccessful attempts,[12] the coupling reaction of **4** and **5** under the copper-free conditions described by Soheili et al. gave **1** in a reasonable yield (64 %).[13] Similarly, the ethynylene-bridged macrocycle **2** was synthesized from compound **6**,[11] and the yield for the final coupling step was 73 %. The structures of **1** and **2** were elucidated by elemental analyses, ^{1}H NMR spectroscopy (including ^{1}H-^{1}H NOESY experiments), and FAB mass spectrometry.



Scheme 1. Reaction conditions: a) $Cu(OAc)_2 \cdot H_2O$, pyridine, RT, 95 %; b) CuI, DMF, 100–110 °C, 81 %; c) $[Pd(dba)_2]$, CuI, PPh_3, TMS-acetylene, Et_3N/THF, 54–55 °C, 80 %, then K_2CO_3, MeOH, RT, 90 %; d) $[(allylPdCl)_2]$, $P(tBu)_3$, DABCO, CH_3CN/toluene, RT, 64 %. dba = *trans,trans*-dibenzylidineacetone, TMS = trimethylsilyl, DABCO = 1,4-diazabicyclo[2.2.2]octane.

Computer modeling studies show that **1** and **2** are highly rigid, flat structures[14] as a result of full conjugation of all the indole rings without any flexible bonds (see the Supporting Information). The cavity sizes of **1** and **2** are nearly identical; the diagonal distances between the NH hydrogen atoms in the internal cavities are 3.7 Å for **1** and 3.6 Å for **2**. The widths and heights of the cavities of **1** and **2** are 2.5 and 2.7 Å, and 2.8 and 2.3 Å, respectively. These structural features were confirmed by single-crystal X-ray diffraction analysis[15] of the complex formed between **2** and $Bu_4N^+Cl^-$ (Figure 1). The chloride ion is located in the middle of four indole NH groups and stabilized by four hydrogen bonds with $N\cdots Cl^-$ distances of 3.14($\pm$0.01) Å. The chloride ion is only partially inserted into the cavity of **2**, which implies that the internal size is slightly too small for the chloride ion. It is also worth mentioning that the tetrabutylammonium countercation sits in the plane of the aryl rings, possibly as a consequence of cation–π interactions.The binding properties of **1** and **2** in solution were studied first by ^{1}H NMR spectroscopy. The symmetrical nature of **1** and **2** results in the ^{1}H NMR spectra being very simple; for example, **1** exhibits only five singlets at $\delta = 10.9$ (NH), 7.15 (H$_c$), 7.01 (H$_b$), 6.56 (H$_a$), and 1.24 ppm (*t*Bu) in CD_3CN. Addition of an anion (0.5 equiv) resulted in a new set of ^{1}H NMR signals corresponding to its complex

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[*] K.-J. Chang, Prof. Dr. K.-S. Jeong
Center for Bioactive Molecular Hybrids and Department of Chemistry
Yonsei University
Seoul 120-749 (Korea)
Fax: (+82) 2-364-7050
E-mail: ksjeong@yonsei.ac.kr

D. Moon, Prof. Dr. M. S. Lah
Department of Chemistry and Applied Chemistry
College of Science and Technology
Hanyang University
1271 Sa-1-dong, Ansan, Kyunggi-do 426-791 (Korea)

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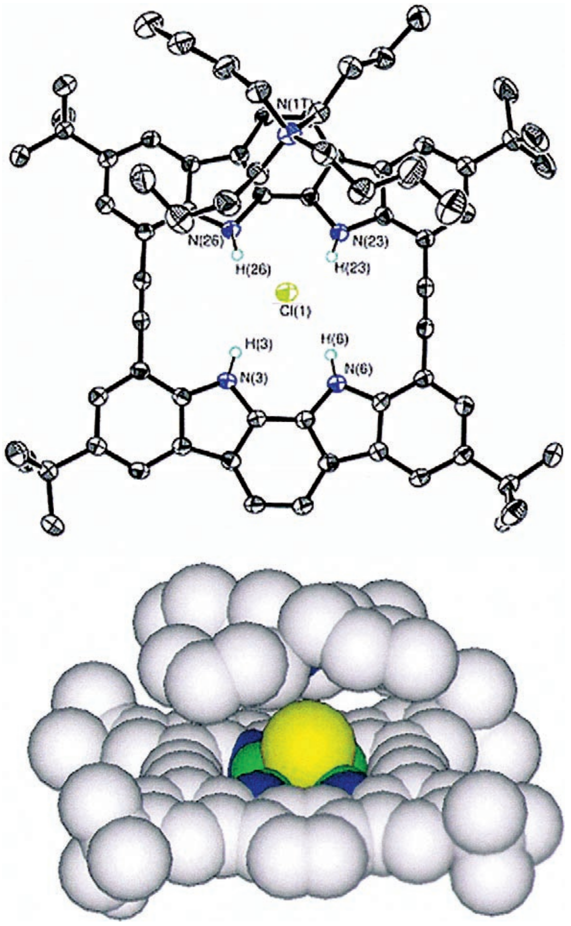

Figure 1. Crystal structures of the complex formed between **2** and $Bu_4N^+Cl^-$: Ortep plot (top) and CPK representation (bottom). Displacement ellipsolids represent 50% probability. Hydrogen-bonding distances and angles between the indole nitrogen atoms and chloride ion are 3.13–3.15 Å and 149–153°, respectively.

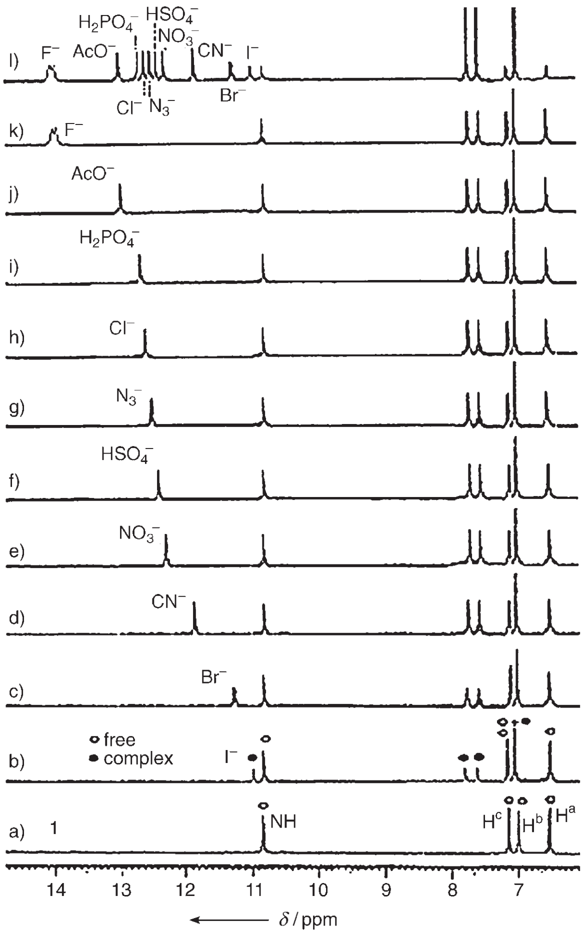

Figure 2. Partial ^1H NMR spectra (500 MHz, CD_3CN, 298 K) of a) **1** (1.0×10^{-4} M); b–k) **1** containing approximately 0.5 equivalents of I^-, Br^-, CN^-, NO_3^-, HSO_4^-, N_3^-, Cl^-, $H_2PO_4^-$, AcO^-, and F^-, respectively, and l) **1** (2.0×10^{-4} M) containing approximately 0.1 equivalents of each of 10 different anions. The anions were used as their tetrabutylammonium salts.

that appear at the expense of those of the free macrocycles **1** and **2**, as a consequence of slow exchange on the NMR time scale at ambient temperature (Figure 2). In particular, the NH signals of the complexes were significantly shifted downfield as a result of the formation of hydrogen bonds between the macrocycle and the anions. It should be mentioned that separate sets of ^1H NMR signals were observed even with the weakly binding anions Br^- and I^- at room temperature. This type of slow exchange is quite unusual for macrocycles, regardless of the binding strength.[16] All the anions studied gave different chemical shifts for the NH protons of the complexes, and ranged from $\delta = 10.7$ (I^-) to 13.9 ppm (F^-; Table 1).

The NH signals of the complexes appear as a sharp singlet in all cases except for **1**·F^-, which split into a doublet as a consequence of coupling between the NH protons and the bound fluoride nucleus. These NH signals have allowed us to identify and analyze an anion at a micromolar concentration (for example, 5.0×10^{-6} M for Cl^-) by ^1H NMR (500 MHz) spectroscopy. Furthermore, the NH signals of all 10 complexes were nicely resolved at room temperature when 10 different anions were added at the same time to a solution of **1** (2.0×10^{-4} M) in CD_3CN. The macrocycle **2** also showed identical spectroscopic behaviors when complexed with anions, but the NH chemical shifts of the complexes were slightly different from those derived from **1** (see the Supporting Information). As a result, the presence of an anion can be detected qualitatively and even quantitatively from the NH chemical shifts and ^1H NMR integrals. Therefore, **1** and **2** can be considered as chemical shift based chemosensors capable of sensing and analyzing anions in solution.

The association constants between the macrocycles and anions were determined by UV/Vis titration experiments in CH_3CN at 295 ± 1 K. Incremental addition of an anion to a solution of the macrocycle in CH_3CN (2.0×10^{-5} M) led to gradual changes in the UV absorption spectra, with isosbestic points at several different wavelengths. The association constants (K_a) were determined by nonlinear fitting analyses of the titration curves (Table 1).[17] Job's plots[17b] showed that **1** and **2** formed 1:1 complexes with all of the anions except Br^- and I^-. These larger halides form 2:1 macrocycle/anion complexes, possibly sandwich-type complexes as observed in

Table 1: Association constants (K_a, M^{-1}) and NH chemical shifts of complexes (CD_3CN) formed between **1** and **2** and anions.

Anion	NH chemical shift[a] (δ, ppm)		Association constant (K_a, M^{-1})[b]	
	1	**2**	**1**	**2**
F^-[c]	13.9	13.9	2.0×10^8	5.6×10^8
AcO^-	13.0	12.8	5.9×10^6	6.5×10^6
$H_2PO_4^-$	12.7	12.5	2.1×10^6	3.2×10^6
Cl^-	12.6	12.3	1.5×10^6	2.1×10^6
N_3^-	12.5	12.1	8.8×10^5	9.1×10^5
HSO_4^-	12.4	12.0	6.5×10^5	6.8×10^5
NO_3^-	12.3	11.8	3.9×10^5	3.9×10^5
CN^-	11.9	11.5	6.5×10^4	7.5×10^4
Br^-	11.3	10.9	$K_1=1.9\times10^3$ $K_2=10$	$K_1=1.9\times10^3$ $K_2=14$
I^-	11.0	10.7	$K_1=3.1\times10^2$ $K_2=6$	$K_1=3.0\times10^2$ $K_2=5$

[a] The NH chemical shifts of the free macrocycles **1** and **2** are $\delta=10.9$ and 10.6 ppm, respectively. [b] Titrations were all duplicated in CH_3CN at 295 ± 1 K and the errors in the K_a values were within $\pm6\%$. The CH_3CN containing less than 0.05% water was used directly as purchased. [c] The association constants between macrocycles and fluoride ions were determined by competition experiments with chloride by using ^1H NMR spectroscopy.

the binding mode of alkali metals with crown ethers having small cavities.[18] As anticipated from the cavity size, macrocycles **1** and **2** generally show similar binding affinities toward anions. The association constants for a series of halides decrease dramatically in the order $F^- > Cl^- \gg Br^- > I^-$. This large difference is probably attributed to the charge density of the anion surfaces and to the size complementarities of the anions and the internal cavity. Finally, it should be noted that there is a good linear relationship between the binding affinities and the NH chemical shifts of the complexes (see the Supporting Information).

In conclusion, macrocycles **1** and **2** strongly bind various anions through hydrogen-bonding interactions and function as chemosensors capable of distinguishing between anions on the basis of the ^1H NMR chemical shifts of the complex. We are currently developing more practical and selective chemosensors for anionic species by incorporating a chromophore or a fluorophore and by tuning the cavity size.

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[15] Single crystals of $\mathbf{2}\cdot Bu_4N^+Cl^-$ were obtained by slow vapor diffusion of diethyl ether into a solution of **2** and $Bu_4N^+Cl^-$ (1:1) in CH_3CN/CH_2Cl_2. The data collection was performed at −100°C with $Mo_{K\alpha}$ radiation ($\lambda=0.71073$ Å) on a Bruker SMART CCD equipped with a graphite crystal, incident-beam

monochromator. Cell constants and orientation matrices for data collection were obtained from least-squares refinement with a set of 45 narrow-frame (0.3° in ω) scans. The SMART and SAINT software packages were used for data collection and integration, respectively. Collected data were corrected for absorbance by using SADABS based upon Laue symmetry using equivalent reflections. The structure was solved by direct methods and refined by full-matrix least-squares calculations with the SHELXTL-PLUS software package (version 5.1). All non-hydrogen atoms were refined anisotropically; hydrogen atoms except those on the nitrogen atoms were assigned isotropic displacement coefficients U(H) = 1.2U (C) or 1.5U (C_{methyl}), and their coordinates were allowed to ride on their respective atoms. Four hydrogen atoms on the nitrogen atoms could be found in the difference Fourier map and refined with isotropic displacement coefficients. Crystal data for **2**·Cl^- at 173 K: $C_{72}H_{88}N_5Cl$, $0.38\times0.33\times0.30$ mm^3, orange crystal, monoclinic, space group $P2_1/c$, $a = 15.664(2)$ Å, $b = 19.343(2)$ Å, $c = 20.201(2)$ Å, $\beta = 92.752(2)°$, $V = 6114(1)$ Å^3, $Z = 4$; $M_r = 1058.92$, $\rho_{calcd} = 1.150\ g\,cm^{-3}$, $\mu(Mo_{K\alpha}) = 0.109\ mm^{-1}$, final R1 = 0.0554 for 14549 reflection of $I > 2\sigma(I)$, $R1 = 0.1111$, $wR2 = 0.1633$ for all 37737 reflections. CCDC-288190 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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