JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Chloride Selective Macrocyclic Bisurea Derivatives with 2,2′-Binaphthalene Moieties as Spacers

Akira Satake,[†] Yuki Ishizawa,[†] Hiroshi Katagiri,[‡] and Shin-ichi Kondo*[,†,§]

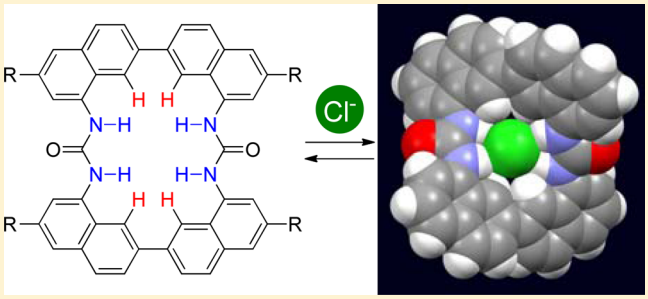
[†]Department of Material and Biological Chemistry, Faculty of Science, Yamagata University, Yamagata-shi, Yamagata 990-8560, Japan

[‡]Graduate School of Science and Engineering, Yamagata University, 4-3-16 Jonan, Yonezawa, Yamagata 992-8510, Japan

[§]Institute for Regional Innovation, Yamagata University, Kanakame, Kaminoyama, Yamagata 999-3101, Japan

Supporting Information

ABSTRACT: A cyclic bisurea derivative **2a** has been successfully prepared from the corresponding diamine and diisocyanate in the presence of tetrabutylammonium chloride as a template. A more soluble cyclic bisurea **2b** has also been prepared by introduction of sterically bulky *tert*-butyl groups. X-ray crystal analyses of $[\mathbf{2a}\cdot Cl]^-$ and $[\mathbf{2b}\cdot Cl]^-$ revealed that overall structure was saddle like and the chloride anion was located in the center of the cavity. The bound chloride anion was hydrogen bonded by four N−H of urea groups and weakly hydrogen bonded by four 1-C−H of naphthyl groups, respectively. After removal of the bound chloride anions of $[\mathbf{2b}\cdot Cl]^-$ with silver nitrate, two different X-ray crystals of free **2b** were obtained; one was intermolecular hydrogen bonded shrunken structure and the other was extended structure. Receptor **2b** showed large binding ability for Cl^-, however, the selectivity for Cl^- against basic anions, such as AcO^- and F^-, has been insufficient. In aqueous MeCN, the association constant of **2b** for Cl^- was reduced but still large, and the selectivity for hydrophobic Cl^- was greatly improved. In this solvent, **2b** also selectively recognized alkaline metal chloride salts. Therefore, cyclic bisurea **2b** is highly selective and effective Cl^- selective receptor.



INTRODUCTION

Anionic species, such as chloride, sulfate, phosphate, and carboxylate, were ubiquitous in organisms and environment, and these anions are not only fundamental components of biological substances, such as DNA, but also play significant roles in metabolism processes, membrane transport, and regulation of osmotic pressure. Therefore, association and detection of these anions by artificial receptors are primarily important in medicinal and environmental science.[1−4] In particular, chloride anion is the most abundant anion in cytoplasm, and plays a critical role in biological processes. Abnormal regulation of the concentration of chloride ion in blood causes diseases, such as cystic fibrosis.[5] However, recognition of chloride anions by an artificial anion receptor is still challenging due to its weak hydrogen bond acceptability arising from the low basicity. Although various anion receptors have recently been reported, chloride selective receptors, in particular, neutral ones, have been less explored.[6−9]

Urea and thiourea N−H groups have been frequently used as hydrogen bonding sites for recognition of anions by these cooperative and directional binding motifs.[10,11] Recently, we have unexpectedly found that a 2,2′-binaphthalene derivative **1a** (Scheme 1) bearing two urea groups at 8- and 8′-positions exhibited remarkable binding ability for less basic chloride anion in MeCN presumably owing to the suitable binding geometry for effective hydrogen bonds of four urea N−H groups with chloride.[12] For instance, the binding constants (K_{11}) of **1a** for Cl^- and AcO^- were found to be 5.4×10^5 and 6.3×10^5 $mol^{-1}dm^3$, respectively. In addition, we have also reported that related bisurea **1b**, which is more soluble in various organic solvents, was sufficient for analytical use for a chloride selective electrode.[13] However, unfortunately the binding ability of **1** for chloride was not sufficient, in particular, in competitive medium, such as aqueous acetonitrile. In general, the binding ability of macrocyclic receptors is larger than the corresponding acyclic ones, because of reduced entropic loss during the complexation (macrocyclic effect).[14] Indeed, several macrocyclic anion receptors have been explored.[15−26] Therefore, we have designed a novel cyclic bisurea derivatives **2a** and a more soluble analogue **2b** for effective and selective binding for chloride anion. Receptor **2b** showed excellent binding ability for chloride including alkaline metal salts in pure and aqueous acetonitrile.

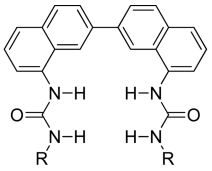
RESULTS AND DISCUSSION

Design of a Cyclic Bisurea Receptor. We recently reported that two urea groups of **1** formed cooperative hydrogen bonds with various anions, in particular chloride anion.[12] The macrocyclic receptor **2a** has two urea moieties as

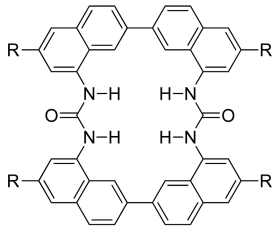
Received: August 10, 2016
Published: October 5, 2016

DOI: 10.1021/acs.joc.6b01959
J. Org. Chem. 2016, 81, 9848−9857

Scheme 1. Acyclic and Cyclic Bisurea Derivatives



1a: R = Bu
1b: R = *t*-Bu



2a: R = H
2b: R = *t*-Bu

hydrogen bond donors connecting with two 2,2′-binaphthyl skeletons to form a binding cavity in the center of the macrocyclic structure and the binding site is suitable for complexation with spherical anions like chloride. The optimized structure of $[\mathbf{2a}\cdot Cl]^-$ complex by DFT calculation at the B3LYP/6-31+G(d,p) level of theory using the Gaussian 09 software[27] as shown in Figure 1 predicted that chloride ion should be captured by **2a**, and the naphthyl moieties of 2,2′-binaphthyl skeleton was slightly twisted. Four N−H groups of two urea moieties directed inward of the cavity of **2a** forming hydrogen bonds with Cl^-. The distances N···Cl were optimized to be 3.3127 and 3.3130 Å within the hydrogen bond range. In addition, four C−H hydrogen atoms located in the inner cavity also weakly hydrogen bond with Cl^- (C···Cl = 3.7525 and 3.7519 Å). These results strongly suggest that receptor **2a** should be an effective anion receptor for Cl^-.

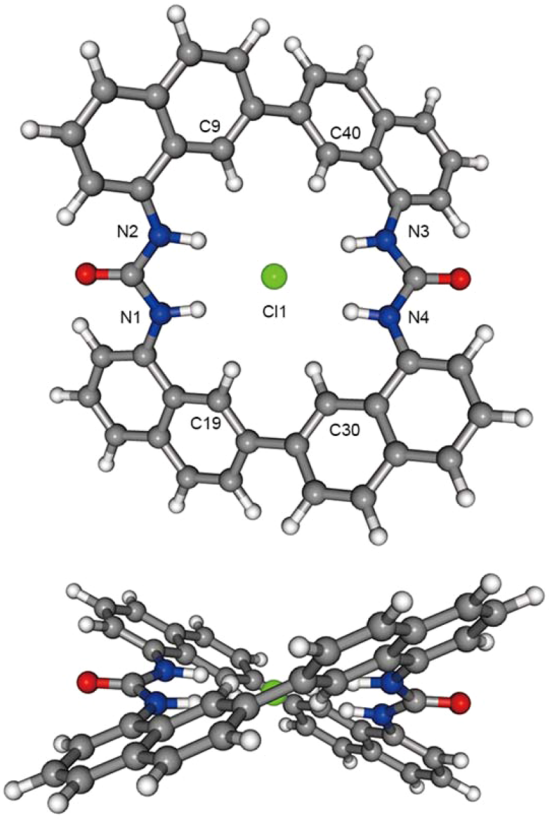


Figure 1. Optimized structure of $[\mathbf{2a}\cdot Cl]^-$ complex by DFT calculation (B3LYP/6-31+G(d,p) level of theory).

Synthesis of Receptor 2a. Urea functionality can be easily prepared from the corresponding amine and isocyanate. Then we planned cyclization of the corresponding diamine and the diisocyanate based on 2,2′-binaphthyl moieties as a spacer group to form the macrocyclic bisurea **2a**. An important intermediate, 8,8′-diamino-2,2′-binaphthalene (**3**) was prepared by the previously reported procedure and was converted into the corresponding diisocyanate (**4**) by treatment with triphosgene in THF.[13] Cyclization from these two components to form a macrocyclic compound is generally competitive to polymerization by unfavorable intermolecular reaction. Initially, high dilution method in THF was employed for preparation of **2a** from **3** and **4** to overcome this difficulty. The product exhibited high melting point >280 °C, and low solubility in many organic solvents. Figure 2a shows the ^{1}H NMR spectrum

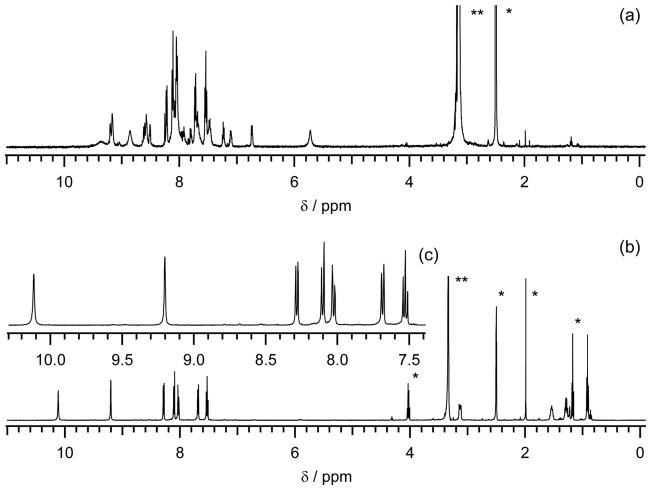
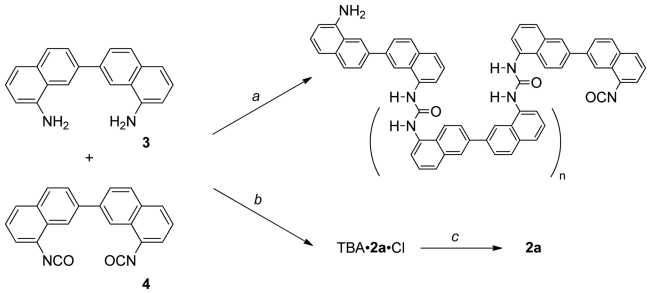


Figure 2. ^{1}H NMR spectra of the cyclization products from **3** and **4** by dilution method (a) and template method (b). Inset (c): enlarged aromatic region of (b). Asterisks indicates residual solvents and water.

of the product prepared by the dilution method in DMSO-d_6. Many peaks with various intensities were observed in the aromatic region and the amine N−H signal was observed at ca. 5.7 ppm suggesting formation of poly- or oligourea derivatives in this condition. Reactions at different temperature and in other solvents such as $CHCl_3$ gave not desired compound and the similar ^{1}H NMR spectra could be obtained. The most stable conformer of urea functionality is *cis-trans* conformation. After reaction of one of the amine of **3** and one of the isocyanate of **4** to form urea, remaining amine and isocyanate groups are far away in this conformation, therefore intermolecular reaction is favored. Template synthesis is another potent method for the synthesis of macrocyclic compounds such as crown ethers.[28] Anion-template syntheses have also been developed in the last two decades.[29−34] Then, we attempted synthesis of **2a** in the presence of tetrabutylammonium chloride as a template as shown in Scheme 2. Figure 2b shows ^{1}H NMR spectrum of the product from **3** and **4** in the presence of TBACl. As expected, sharp symmetrical peaks could be observed, and all the signals

DOI: 10.1021/acs.joc.6b01959
J. Org. Chem. 2016, 81, 9848−9857

Scheme 2. Synthesis of Receptor 2a[a]



[a]Reagents and conditions: (a) Highly diluted condition in $CHCl_3$ or THF; (b) TBACl, $CHCl_3$, r.t., 58%; (c) $AgNO_3$, DMSO, 60 °C, 83%.

could be assigned to TBA$^+$·[**2a**·Cl]$^-$. The structure of TBA$^+$·[**2a**·Cl]$^-$ was confirmed by ^{1}H, ^{13}C, COSY, HMQC, and HMBC NMR techniques, and HRMS. These results strongly indicate that the chloride anion was bound by the monourea derivative by the reaction of **3** and **4**, in which the urea group may adopt *trans-trans* conformation resulting in favorable intramolecular reaction of remaining amine and isocyanate groups to form **2a**.

It should be noted that the produced TBA$^+$·[**2a**·Cl]$^-$ can be easily purified by silica gel chromatography without a release of bounded chloride anion even with AcOEt–MeOH (10:1 *v*/*v*) as an eluent, indicating that receptor **2a** is expected to be strong association with chloride.

X-ray Crystallographic Analysis of 2a·Cl$^-$. The structure of TBA$^+$·[**2a**·Cl]$^-$ was proven unambiguously by single X-ray crystallography as shown in Figure 3 and crystallographic

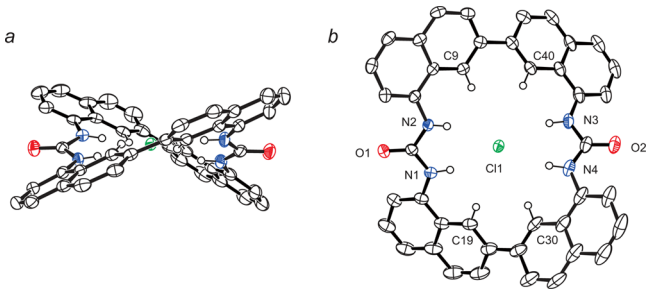


Figure 3. ORTEP drawings of the molecular structure of [**2a**·Cl]$^-$. Displacement ellipsoids are scaled to the 50% probability level. Tetrabutylammonium cation and solvent ($CHCl_3$) were omitted for clarify.

parameters are summarized in Table 1. Single crystals of TBA$^+$·[**2a**·Cl]$^-$ were grown from vapor diffusion of hexane into a solution of TBA$^+$·[**2a**·Cl]$^-$ in $CHCl_3$. The overall crystal structure of [**2a**·Cl]$^-$ was quite similar to the optimized structure predicted by DFT calculation as shown in Figure 1. Two urea units adopt *trans–trans* conformation. Two naphthyl groups of 2,2′-binaphthyl units were twisted and angles of mean planes of these naphthyl groups are 27.4 and 35.1° (the twisted angles from DFT calculation as shown in Figure 1 were 35.3°). All four N–H groups directed inward of the cavity to form a 1:1 complex. The guest chloride anion was occupied in the center of receptor **2a** and hydrogen bonded from four N–H groups and [**2a**·Cl]$^-$ showing pseudo-D_2 symmetry. The distances N···Cl range 3.226(2)–3.275(3) Å indicating strong hydrogen bonds. Two 2,2′-binaphthyl moieties adopt *cisoid* conformation and 1-C–H of naphthyl groups made small

Table 1. Association Constants of 1a and 2b with Tetrabutylammonium Salts of Anions

	K_{11}/mol^{-1}dm^3[a]		
	1a[b]	2b	
anion	MeCN	MeCN	5% H_2O/MeCN
AcO^-	6.3×10^5	$1.59 \pm 0.37 \times 10^7$	$5.43 \pm 0.27 \times 10^3$
$H_2PO_4^-$	3.1×10^4	$4.39 \pm 1.67 \times 10^6$	
HSO_4^-	1.4×10^3	ND[d]	ND[d]
NO_3^-	4.7×10^2	$5.46 \pm 0.75 \times 10^3$	ND[c]
ClO_4^-	ND[c]	ND[c]	ND[c]
F^-	2.9×10^6	$5.78 \pm 0.71 \times 10^6$	$2.34 \pm 0.60 \times 10^4$
Cl^-	5.4×10^5	$1.19 \pm 0.18 \times 10^7$	$9.95 \pm 0.25 \times 10^5$
Br^-	1.2×10^4	$9.55 \pm 0.83 \times 10^5$	$3.61 \pm 0.15 \times 10^4$
I^-	4.9×10^2	$7.70 \pm 0.24 \times 10^3$	ND[c]

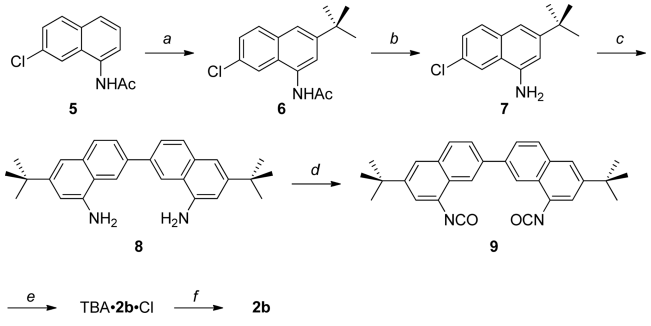
[a]The association constants were determined by UV–vis spectroscopy. [**2b**] = 2.0×10^{-5} mol dm^{-3} in MeCN. [b]Ref 12. [c]Not determined due to small spectral changes. [d]The titration was not fit to the 1:1 binding model.

contribution by weak hydrogen bonds to the guest chloride anion (C···Cl = 3.696(3)–3.758(3) Å). A tetrabutylammonium cation was located upper of the macrocycle to balance the charge.

Removal of Chloride from 2a·Cl$^-$. The removal of chloride anion from prepared TBA$^+$·[**2a**·Cl]$^-$ was successfully achieved by excess silver nitrate in DMSO as shown in Scheme 2. The product was identified by ^{1}H NMR in DMSO-d_6 at 80 °C due to the low solubility as shown in Figure S9 (Supporting Information). All signals assigned to TBA$^+$ disappeared and N–H and 1–CH signals were largely upfield shift corresponding to the removal of chloride anion from [**2a**·Cl]$^-$ to form free **2a**. However, the solubility of free **2a** in common organic solvents is very low even in DMSO at r.t. In addition, the purification of **2a** was not sufficient for further studies including titration experiments.

Synthesis of 2b. To improve the solubility, introduction of bulky alkyl groups as peripherals is effective.[35−38] Therefore, we attempted the introduction of bulky *tert*-butyl groups into the naphthyl skeleton of **2a** as shown in Scheme 3. Friedel–Crafts alkylation of 7-chloro-2-acetamidonaphthalene (**5**) with *tert*-butyl chloride in the presence of aluminum chloride successfully gave the corresponding alkylated product **6** in excellent yield. It should be noted that *tert*-butyl group was

Scheme 3. Synthesis of 2b.[a]



[a]Reagents and conditions: (a) *tert*-Butyl chloride, $AlCl_3$, 96%; (b) conc HCl, MeOH, reflux, 97%; (c) $NiCl_2$, Zn, PPh_3, 2,2′-bipyrindine, *N*,*N*-dimethylacetamide, 60 °C, 48%; (d) *i*-Pr_2NEt, triphosgene, THF, 0 °C, 83%; (e) **5**, TBACl, THF, 58%; (f) $AgNO_3$, DMSO, 60 °C, 69%.

DOI: 10.1021/acs.joc.6b01959
J. Org. Chem. 2016, 81, 9848–9857

introduced at 3-position of naphthalene determined by COSY, HMQC, and HMBC techniques, which may due to the steric hindrance at 4-position with *peri*-hydrogen. Analogous Friedel–Crafts alkylation of naphthalene with *tert*-butyl chloride in the presence of aluminum chloride gave 2-*tert*-butylnaphthalene.[39] The product was hydrolyzed with conc HCl to give amine **7**, and **7** was successively homocoupled by nickel catalysis to yield the diamine **8**. The diamine **8** was reacted with triphosgene to give the corresponding diisocyanate **9**. These diamine and diisocyanate were cyclized in the presence TBACl as a template as described above giving the desired macrocyclic compound TBA$^+$·[**2b**·Cl]$^-$ in good yield. ^{1}H and ^{13}C NMR spectra of TBA$^+$·[**2b**·Cl]$^-$ were fully assigned by COSY, HMQC, and HMBC NMR techniques, and identified by HRMS. In addition, cyclization from **8** and **9** in the presence of TBABr also gave TBA$^+$·[**2b**·Br]$^-$ in 47% yield after recrystallization from hexane/chloroform suggesting that Br$^-$ can also be used as effective template for **2b**.

Removal of Chloride from 2b·Cl$^-$. Chloride anion was also successfully removed from TBA$^+$·[**2b**·Cl]$^-$ by silver nitrate in DMSO. The product was soluble in various organic solvents and can be purified by column chromatography on silica gel and the structure was confirmed by NMR techniques and HRMS. ^{1}H NMR spectra of TBA$^+$·[**2b**·Cl]$^-$ and free **2b** in DMSO-d_6 are shown in Figure 4. The spectra showed

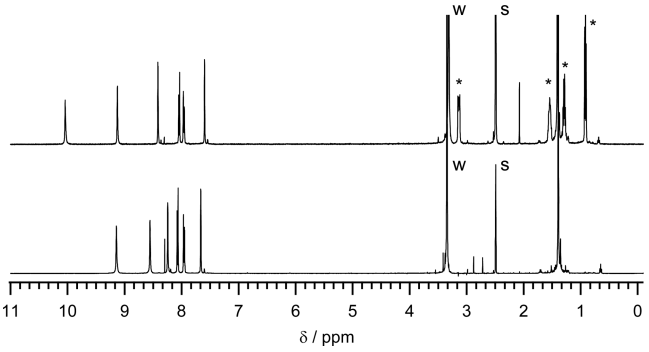


Figure 4. ^{1}H NMR spectra (500 MHz) of TBA$^+$·[**2b**·Cl]$^-$ (upper) and **2b** (lower) in DMSO-d_6. Asterisks, w, and s indicate peaks corresponding to tetrabutylammonium cation, water, and residual solvents, respectively.

symmetrical structure. Four signals of TBA$^+$ were disappeared after removal of chloride. N–H of urea and 1–CH of naphthyl group of TBA$^+$·[**2b**·Cl]$^-$ were observed at 10.04 and 9.13 ppm and significantly upfield shift at 9.14 and 8.55 ppm after removal of chloride, respectively. These results clearly indicate that tetrabutylammonium chloride was completely removed.

X-ray Crystallographic Analysis of 2b·Cl$^-$ and 2b. Single crystals of TBA$^+$·[**2b**·Cl]$^-$ were obtained by vapor diffusion of hexane into chloroform solutions and the crystal structure is shown in Figure 5. The overall structure of TBA$^+$·[**2b**·Cl]$^-$ was almost same to the structure of TBA$^+$·[**2a**·Cl]$^-$ (Figure 3). Two naphthyl groups of 2,2′-binaphthyl spacers were also twisted and angles of mean planes of naphthyl groups are 30.4 and 31.9°, respectively. Chloride anion was hydrogen bonded with four urea N–H (N···Cl = 3.236(3)–3.297(3) Å) and weakly hydrogen bonded with four 1-CH of naphthyl groups (C···Cl = 3.713(3)–3.733(3) Å).

Single crystals suitable for X-ray analysis of free **2b** can also be obtained by vapor diffusion of hexane into the solution in chloroform. Three chloroform molecules were incorporated from the solvent. As shown in Figures 6a and b, two naphthyl groups adopt transoid conformation and urea groups adopt *cis-trans* configurations resulting in shrunken structure. One of the N–H group that directed to outer forming hydrogen bond with carbonyl oxygen of the urea group in the neighboring molecules in the solid state.

Other crystals were obtained by slow recrystallization from DMSO and water. Interestingly, the structure of free **2b** from DMSO-H_2O (Figures 6c and d) was similar to the structure of [**2b**·Cl]$^-$, i. e., distorted D_2 symmetry without any anionic guest. Two naphthyl groups adopt cisoid conformation and twist angles of mean planes of naphthyl groups are 32.6–42.8°. Two urea groups adopt *trans-trans* configurations, therefore, all N–H groups are directed toward its cavity suggesting well preorganized structure for the anion binding. Three **2b** molecules formed cage like structure in the solid state.

NMR Titration of 2b with Cl$^-$. The ^{1}H NMR titration of **2b** with Cl$^-$ (as tetrabutylammonium salt) was performed in DMSO-d_6 as depicted in Figure 7. In the absence of Cl$^-$, NH of urea and 1-CH of naphthyl peaks appeared at 9.14 and 8.55 ppm, respectively. Upon the addition of 0.25 equiv of Cl$^-$, these peaks were broadened and reduced, and simultaneously new signals appeared at 10.04 and 9.13 ppm, respectively. Elevating temperature of **2b** in the presence of 0.5 equiv of Cl$^-$ in DMSO-d_6 by VT NMR (Figure 8) showed coalescence of these two sets of signals and obvious broad peaks can be found in equilibrium positions (NH = 9.554 and 1-CH = 8.534 ppm) clearly indicating slower equilibrium between free **2b** and [**2b**·Cl]$^-$ complex than NMR time scale at room temperature.

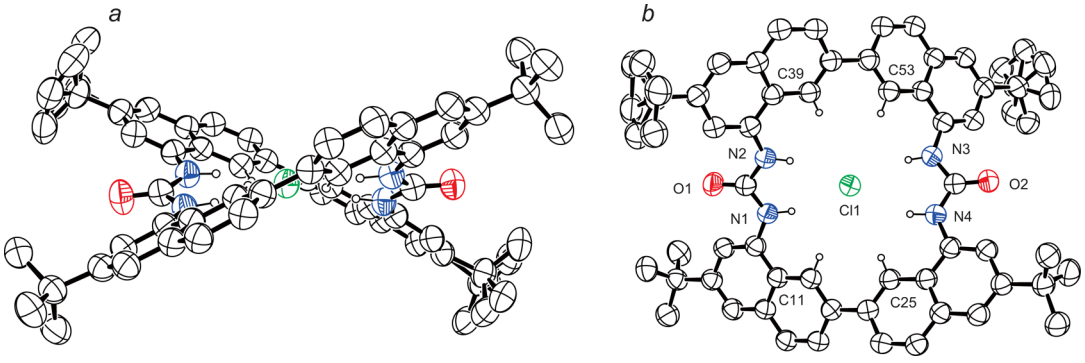


Figure 5. ORTEP views of the molecular structure of [**2b**·Cl]$^-$. Displacement ellipsoids are scaled to the 30% probability level. Tetrabutylammonium cation and solvent (DMSO) were omitted for clarify.

DOI: 10.1021/acs.joc.6b01959
J. Org. Chem. 2016, 81, 9848–9857

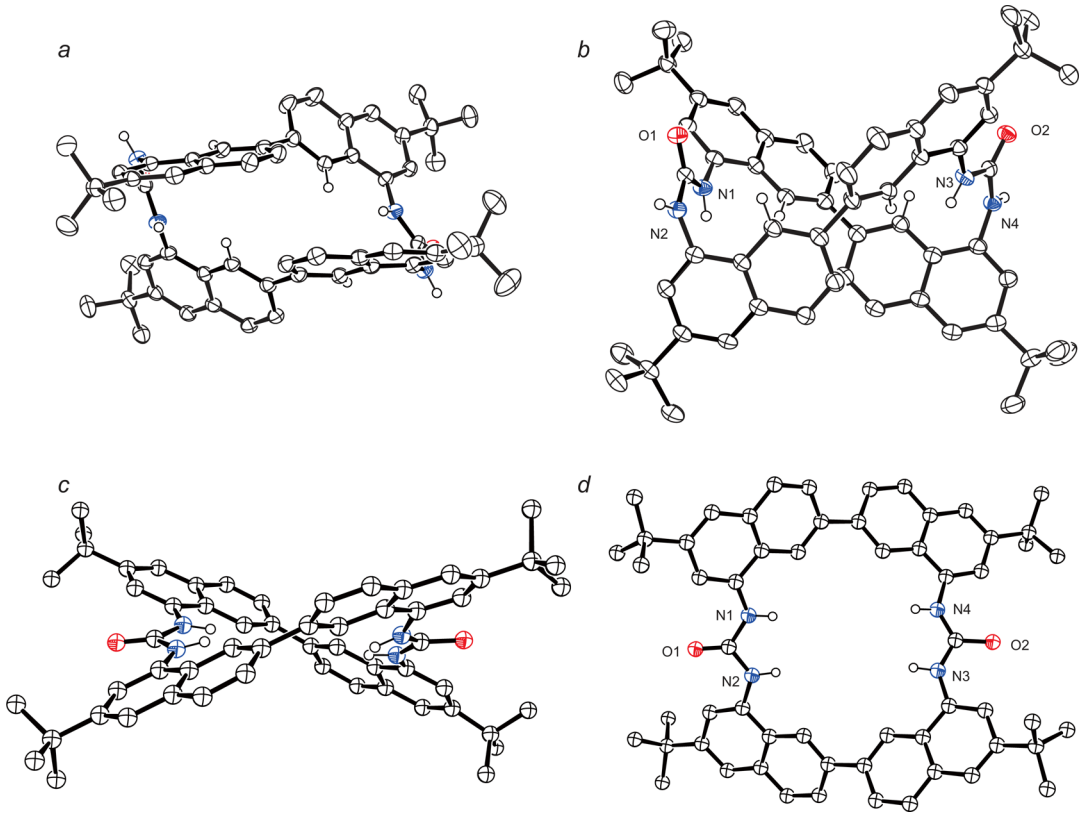


Figure 6. ORTEP views of the molecular structure of free **2b** by vapor diffusion of hexane into a solution of **2b** (a and b) and by slow recrystallization from DMSO and water (c and d). Displacement ellipsoids are scaled to the 50% probability level. Solvent molecules ($CHCl_3$, DMSO, and H_2O) were omitted for clarify.

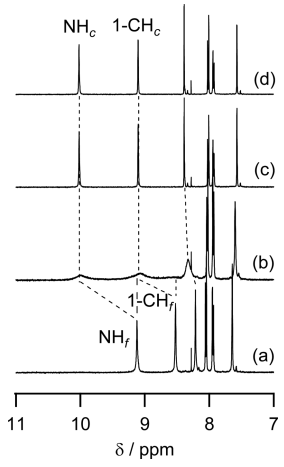


Figure 7. Partial ^{1}H NMR spectra of the **2b** in the absence (a) and in the presence of 0.5 (b), 1.0 (c), and 2.0 (d) equiv of tetrabutylammonium chloride in DMSO-d_6 at 298 K. NH$_c$ and 1-CH$_c$ represent complexed ([**2b**·Cl]$^-$) signals and NH$_f$ and 1-CH$_f$ represent the signals of free **2b**.

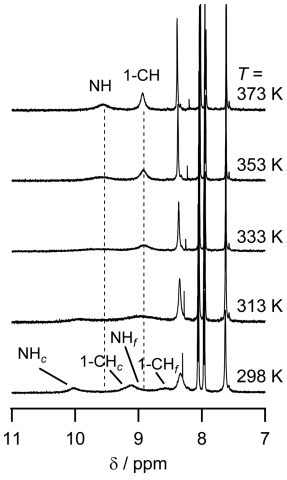


Figure 8. VT-NMR of **2b** in the presence of 0.5 equiv of tetrabutylammonium chloride in DMSO-d_6. NH$_c$ and 1-CH$_c$ represent complexed ([**2b**·Cl]$^-$) signals and NH$_f$ and 1-CH$_f$ represent the signals of free **2b**.

Increasing amount of Cl^-, original NH and 1−CH peaks were diminished concomitant with increase of the peaks corresponding to [**2b**·Cl]$^-$ complex and the peaks were sharpened and the original peaks perfectly disappeared upon the addition of 1.0 equiv of Cl^-. These results showed that Cl^- anion was hydrogen bonded with inner N−H and 1-C−H in solution as shown in the solid state.

UV−vis and Fluorescence Titrations of 2b with Cl^-. Anion binding properties of soluble **2b** were evaluated by means of UV−vis and fluorescence titrations in 0.67% DMSO/MeCN with anions (F^-, Cl^-, Br^-, I^-, AcO^-, HSO_4^-, $H_2PO_4^-$, NO_3^-, and ClO_4^-) as their tetrabutylammonium salts. In the absence of anions, receptor **2b** showed absorption maximum at 319 nm and addition of Cl^- induced bathochromic shift of absorption maximum to 323 nm through isosbestic points at 315.5 and 291.5 nm suggesting host:guest = 1:1 complexation as shown in Figure 9. The smaller spectral changes comparing with those of receptor **1** suggests that the conformational

DOI: 10.1021/acs.joc.6b01959
J. Org. Chem. 2016, 81, 9848−9857

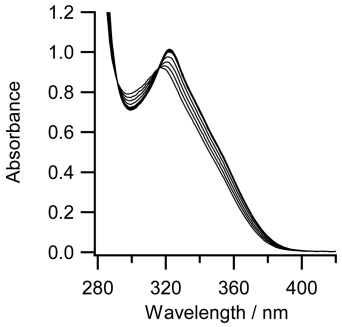


Figure 9. UV−vis spectral changes of **2b** upon the addition of tetrabutylammonium chloride in 0.67% DMSO−MeCN at 298 K. [**2b**] = 2.0×10^{-5} mol dm^{-3}.

change during complexation is small for **2b**, therefore the conformation of free **2b** in solution is mainly similar to the extended X-ray structure depicted in Figure 6c not 6a (the folded conformer of **2b**). Addition of other anions such as F^-, Br^-, AcO^-, and $H_2PO_4^-$ induced similar spectral changes, however, small spectral change was observed upon the addition of I^- (Figures 10 and S14). Virtually no spectral changes were

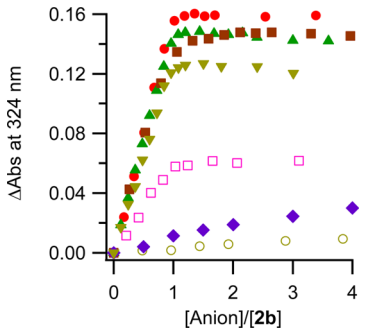


Figure 10. Absorbance changes of **2b** at 324 nm upon the addition of tetrabutylammonium salts of (red filled circle) AcO^-, (pink empty square) $H_2PO_4^-$, (brown empty circle) NO_3^-, (yellow filled triangle) F^-, (green filled triangle) Cl^-, (orange filled square) Br^-, and (purple filled diamond) I^- in 0.67% DMSO−MeCN at 298 K. [**2b**] = 2.0×10^{-5} mol dm^{-3}.

observed upon the addition of weakly basic anions such as NO_3^- and ClO_4^- indicating weak complexation by **2b** with these anions. Job plot analyses of **2b** with Cl^- and AcO^- were performed and the results are shown in Figure 11. The maxima at a mole fraction of 0.5 also clearly suggesting that host:guest = 1:1 complexation and the results agree with X-ray structure of [**2b**·Cl]$^-$.

Receptor **2b** showed broad and structureless fluorescence in MeCN at 430 nm excited at 316 nm, which is one of the isosbestic points during UV−vis titration with Cl^-. Addition of Br^- and AcO^- induced large quench of the fluorescence and $H_2PO_4^-$ induced less significant quench of **2b** as shown in Figure S16 (Supporting Information). Interestingly, virtually no fluorescence change of **2b** was observed upon the addition of Cl^-. The fluorescence spectral changes were less reproducible possibly due to instability of **2b** against photo irradiation in our experimental condition.

Association Constants of 2b for Anions in Acetonitrile. The association constants of receptor **2b** with anions were elucidated from the UV−vis spectral titrations by multiwavelength nonlinear curve fitting analysis to a theoretical

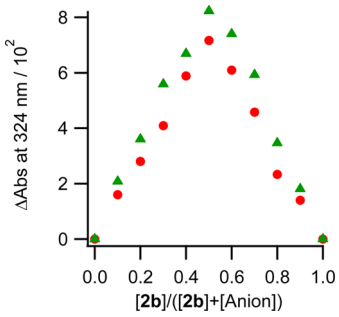


Figure 11. Job's plots of **2b** with tetrabutylammonium salts of (red filled cirlce) AcO^- and (green filled triangle) Cl^- by UV−vis spectroscopy in 0.67% DMSO−MeCN at 298 K. [**2b**]+[Anion] = 2.0×10^{-5} mol dm^{-3}.

1:1 complexation model and the results are summarized in Table 1. The titration profile of **2b** for HSO_4^- was not fitted to a theoretical 1:1 binding isotherm and the spectral change with ClO_4^- was too small to determine the binding constant. The association constants of **2b** for other anions were one or 2 orders of magnitude larger than those of acyclic receptor **1a**. Interestingly, the association constant of **2b** for F^- was about twice of that of **1a** due to small ionic radius of F^-. These results clearly indicate macrocyclic structure of **2b** is effective for complexation with any anions as expected. The selectivity trend of the association by **2b** was $AcO^- \approx Cl^- > F^- > H_2PO_4^- > Br^- > I^- > NO_3^-$. As observed for many hydrogen bond donor-based anion receptor, the association constants of **2b** for basic anions (good hydrogen bond acceptors), such as AcO^-, $H_2PO_4^-$, and F^-, are larger than less basic anions. It should be noted that the association constant for Cl^-, which is typical less basic anion, was $1.19 \pm 0.18 \times 10^7$ mol^{-1}dm^3 and the value was comparable to that for basic AcO^- ($1.59 \pm 0.37 \times 10^7$ mol^{-1}dm^3) and greater than that for highly basic F^-. These results strongly suggested that the binding cavity of **2b** is well preorganized for the association with Cl^-, however, ionic radius of F^- is too small for the effective binding by four urea N−H groups.

Association Constants of 2b for Anions in Aqueous Acetonitrile. The strong binding ability of **2b** for anions in MeCN prompted us to attempt anion binding study in aqueous MeCN solution. The anion recognition study in aqueous solvents has been a challenging task since water itself is a highly competitive polar solvent for hydrogen bonding in the complexation.[40−42] Figure 12 shows effect of water contents on the association constants of **2b** for AcO^-, NO_3^-, F^-, Cl^-, Br^-, and I^-. Increasing water contents, the association constants of **2b** were dramatically reduced. Importantly, the slopes for hydrophilic anions, such AcO^- and F^-, were larger than those for hydrophobic anions, such as Cl^-, Br^-, and I^-. The hydrophilic anions are effectively hydrated by water molecules preventing complexation with **2b** by hydrogen bonds. The association constants of **2b** in 5% H_2O/MeCN (v/v) for anions are also summarized in Table 1. Although the association constant for AcO^-, F^-, and Cl^- in MeCN were comparable as described above, the association constants for Cl^- in 5% H_2O/MeCN (v/v) was at least 1 order of magnitude larger than those for AcO^- and F^-. Therefore, neutral receptor **2b** can be used as a chloride selective receptor in aqueous MeCN, even though receptor **2b** is neutral.

Finally, recognition of alkaline salts with **2b** in 5% H_2O/MeCN (v/v) was studied toward practical use for environ-

DOI: 10.1021/acs.joc.6b01959
J. Org. Chem. 2016, 81, 9848−9857

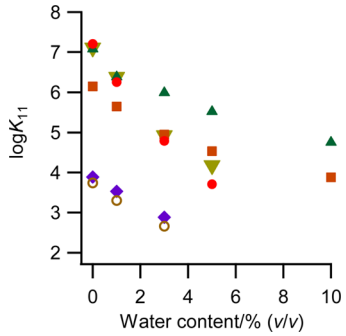


Figure 12. Effect of water content (*v*/*v*) on the association constants of **2b** with tetrabutylammonium salts of (red filled circle) AcO^-, (brown empty cirlce) NO_3^-, (yellow filled triangle) F^-, (green filled triangle) Cl^-, (orange filled square) Br^-, and (purple filled diamond) I^- in MeCN at 298 K. [**2b**] = 2.0×10^{-5} mol dm^{-3}.

mental and medicinal applications. UV−vis spectral changes of **2b** upon the addition of sodium and potassium salts (AcO^-, F^-, Cl^-, Br^-, and I^-) showed similar changes to those of tetrabutylammonium salts and the association constants calculated from the titrations are summarized in Table 2. The association constants of **2b** for alkaline salts were slightly smaller or similar order for all anions with those for tetrabutylammonium salts. It is notable that the association constants for sodium chloride (K_{11} = 3.31 ± 0.01 × 10^5 $mol^{-1}dm^3$) and potassium chloride (K_{11} = 2.91 ± 0.05 × 10^5 $mol^{-1}dm^3$) were the largest among the salts tested in this condition. In addition, titrations of **2b** with rubidium and cesium chlorides (K_{11} = 2.84 ± 0.04 × 10^5 and 3.21 ± 0.02 × 10^5 $mol^{-1}dm^3$, respectively) were also performed and the association constants for all alkaline chlorides were indeed same order. These results clearly show that receptor **2b** is effective and selective receptor for Cl^- in aqueous solutions.

CONCLUSION

We have successfully prepared cyclic bisurea **2a** from the corresponding diamine and diisocyanate in the presence of tetrabutylammonium chloride as a template. Sterically bulky *tert*-butyl groups have been introduced by Friedel−Crafts alkylation and more soluble **2b** have also been prepared in the same manner for **2a**. X-ray crystal analyses of **2a**·TBACl and **2b**·TBACl revealed that chloride anion was located in the center of the cavity of **2a** and **2b**, and was hydrogen bonded by four N−H of urea groups and weakly hydrogen bonded by four 1-C−H of naphthyl groups, respectively.

The binding ability of **2b** was evaluated by ^{1}H NMR and UV−vis spectroscopic titrations in MeCN. Receptor **2b** showed large binding ability for Cl^-, however, the selectivity for Cl^- against basic anions, such as AcO^- and F^-, have not been sufficient. Importantly, receptor **2b** can be used as anion receptor in aqueous MeCN even in the presence of 5% water. In this solvent, the binding ability for Cl^- was reduced, however, the selectivity for Cl^- was greatly improved. In conclusion, cyclic bisurea **2b** is highly selective and effective Cl^- selective receptor. Catalytic properties in organic synthesis and Cl^- transport across native and artificial membranes by receptor **2b** and derivatives have been in progress in our laboratory.

EXPERIMENTAL SECTION

General. All reagents used were of analytical grade. Tetrahydrofuran was dried over Na/benzophenone. *N*,*N*-Dimethylacetamide (DMAc) and diisopropylethylamine were dried over calcium hydride. Chloroform was washed with water followed by drying over calcium hydride. UV−vis spectra were recorded on a spectrometer with a thermal regulator (±0.5 °C). NMR spectra were measured on a 500 MHz spectrometer. Fluorescence spectra were recorded on a fluorescence spectrometer at r.t. HRMS (FAB and ESI) were recorded on tandem and TOF mass spectrometers, respectively. FT-IR spectra were recorded on a spectrometer at r.t. Melting points are uncorrected. The DFT calculation [**2a**·Cl]$^-$ was performed with Gaussian 09 program.[27]

1-Acetamido-4-tert-butyl-7-chloronaphthalene (**6**). Into a mixture of 1-acetamido-7-chloronaphthalene (220 mg, 1.0 mmol) and *tert*-butyl chloride (5.5 mL, 50 mmol), aluminum chloride (200 mg, 1.5 mmol) was added at 0 °C. After the mixture was stirred for 30 min, 2 mol/L of hydrochloric acid was added. The mixture was extracted with chloroform (10 mL × 2) and the combined organic layer was dried over anhydrous sodium sulfate. After evaporation under reduced pressure, the residue was recrystallized from chloroform:hexane = 1:2 to give the product as colorless needles. Yield 267 mg, 96%. mp 194.2−196.0 °C. ^{1}H NMR (500 MHz, DMSO-*d*6) δ 9.89 (1H, s), 8.05 (1H, s), 7.95 (1H, d, *J* = 8.5 Hz), 7.88 (1H, s), 7.71 (1H, s), 7.49 (1H, dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz), 2.18 (3H, s), 1.34 (9H, s). ^{13}C NMR (126 MHz, DMSO-*d*6) δ 169.0, 148.5, 132.9, 132.0, 130.5, 130.0, 126.6, 126.3, 121.4, 121.3, 120.1, 34.7, 30.8, 23.5. HRMS (ESI, positive mode): Calcd for $C_{16}H_{18}ClNNaO$ $[M+Na]^+$, 298.0975. Found 298.0981.

8,8′-Diamino-6,6′-di-tert-butyl-2,2′-binaphthalene (**8**). A mixture of 1-acetamido-4-*tert*-butyl-7-chloronaphthalene (200 mg, 0.725 mmol) and conc HCl (0.58 mL) in methanol (5 mL) was refluxed under argon atmosphere for 3 h. After basicified with aqueous sodium hydroxide, the mixture was extracted with diethyl ether (40 mL × 2), and the combined organic layer was washed with brine and dried over anhydrous sodium sulfate. After evaporation under reduced pressure, the residue was passed through short column (silica gel, chloroform: ether −5:1) to give 1-amino-4-*tert*-butyl-7-chloronaphthalene (**7**) as orange solids (yield 161 mg, 97%). The amine **7** was easily decomposed, therefore, the next reaction was carried out immediately after purification. Into a mixture of zinc powder (217 mg, 3.32 mmol), triphenylphosphine (155 mg, 0.59 mmol), 2,2′-binaphthalene (17 mg, 0.11 mmol), and anhydrous nickel(II) chloride (14.3 mg, 0.11 mmol), dry DMAc (1.2 mL) was added and the mixture was stirred under argon atmosphere at 60 °C for 20 min. A solution of 1-amino-4-*tert*-butyl-7-chloronaphthalene (517 mg, 2.21 mmol) was added into the

Table 2. Association Constants of 2b for M^+X^- in aqueous MeCN

	K_{11}/$mol^{-1}dm^3$[a]			
	Na^+	K^+	Rb^+	Cs^+
AcO^-	6.83 ± 0.15 × 10^3	5.02 ± 0.09 × 10^3		
F^-	9.47 ± 0.18 × 10^3	5.37 ± 0.01 × 10^3		
Cl^-	3.31 ± 0.01 × 10^5	2.91 ± 0.05 × 10^5	2.84 ± 0.04 × 10^5	3.21 ± 0.02 × 10^5
Br^-	4.12 ± 0.05 × 10^4	3.90 ± 0.12 × 10^4		
I^-	6.16 ± 0.42 × 10^2	6.16 ± 0.03 × 10^2		

[a]The association constants were measured in 5% H_2O/MeCN (*v*/*v*) at 298 K. [**2b**] = 2.0×10^{-5} mol dm^{-3}

DOI: 10.1021/acs.joc.6b01959
J. Org. Chem. 2016, 81, 9848−9857

Table 3. Crystallographic Data and Structure Refinement for 2a and 2b

	2a·TBACl	free **2b** from $CHCl_3$	free **2b** from DMSO	**2b**·TBACl
formula	$C_{60}H_{66}Cl_7N_5O_2$	$C_{61}H_{63}Cl_9N_4O_2$	$C_{176}H_{186}N_{12}O_7S$	$C_{75}H_{102}ClN_5O_{2.5}S_{0.5}$
formula weight	1137.33	1203.20	2613.42	1165.10
crystal system	monoclinic	monoclinic	monoclinic	monoclinic
space group	$P2_1/c$	$P2_1/c$	$C2/c$	$C2/c$
a/Å	8.5439(13)	17.154(2)	31.448(8)	34.4480(6)
b/Å	25.359(4)	19.517(3)	17.914(4)	16.3547(3)
c/Å	27.711(4)	26.195(3)	72.329(18)	24.2238(4)
α/°	90	90	90	90
β/°	103.197(5)	127.031(6)	93.536(4)	95.6897(7)
γ/°	90	90	90	90
V/Å^3	5845.4(15)	7001.1(16)	40670(17)	13580.1(4)
ρ_{calcd}/g cm^{-3}	1.292	1.142	0.854	1.140
Z	4	4	8	8
radiation	Mo Kα	Mo Kα	Mo Kα	Cu Kα
μ/mm^{-1}	0.386	0.399	0.062	1.011
T/K	113	113	113	203
reflections corrected	70694	113255	110054	118268
independent reflections	13358	16012	32635	12075
GOF	1.115	1.047	1.041	1.006
R_1 ($I > 2\sigma(I)$)	0.0754	0.0767	0.0847	0.0714
wR_2 ($I > 2\sigma(I)$)	0.1758	0.2266	0.2609	0.1830
CCDC number	1498501	1498503	1498499	1498502

mixture via syringe. The mixture was stirred at 60 °C overnight. The mixture was filtered with Celite pad and washed with ethyl acetate (200 mL). The organic layer was washed with distilled water and brine, then dried over anhydrous sodium sulfate. The mixture was evaporated under reduced pressure, and the residue was washed with chloroform:hexane = 1:2, repeatedly to give the product **8** as pale yellow powder. Yield 208 mg, 48%. mp > 280 °C. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.44 (2H, s), 7.96 (2H, dd, J_1 = 7.0 Hz, J_2 = 1.5 Hz), 7.80 (2H, d, J = 8.5 Hz), 7.06 (2H, d, J = 1.5 Hz), 6.82 (2H, J = 2.0 Hz), 5.74 (4H, s), 1.34 (18H, s). ^{13}C NMR (126 MHz, DMSO-*d6*) δ 149.0, 144.6, 134.7, 133.2, 128.5, 124.4, 121.6, 119.1, 110.8, 106.6, 34.4, 31.1. HRMS (ESI, positive mode): Calcd for $C_{28}H_{32}N_2$ M$^+$, 396.2566. Found 396.2597.

*8,8′-Diisocyanate-6,6′-di-tert-butyl-2,2′-binaphthalene (**9**).* Into a solution of 8,8′-diamino-6,6′-di-*tert*-butyl-2,2′-binaphthalene (0.119 g, 0.30 mmol) and diisopropylamine (0.261 mL, 1.5 mmol) in THF (8.6 mL), triphosgene (0.178 g, 0.60 mmol) in THF (3 mL) was added dropwise via syringe at 0 °C. The mixture was stirred at r.t. overnight and evaporated under reduced pressure. The residue was chromatographed on silica gel (chloroform:hexane = 1:1 as an eluent) to give the product **9** as colorless powder. Yield 0.112 g, 83%. mp 198.0−202.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (2H, s), 7.93 (4H, m), 7.68 (2H, d, J = 1.0 Hz), 7.42 (2H, d, J = 2.0 Hz), 1.43 (18H, s). ^{13}C NMR (126 MHz, CDCl3) δ 149.2, 138.4, 133.4, 129.8, 129.0, 127.1, 126.5, 125.3, 121.7, 121.1, 120.6, 35.0, 31.1. HRMS (ESI, positive mode): Calcd for $C_{30}H_{29}N_2O_2$ [M+H]$^+$, 449.2229. Found 449.2250.

*Synthesis of TBA$^+$ [**2a**·Cl]$^-$.* Into a solution of tetrabutylammonium chloride (164 mg, 0.59 mmol) and 8,8′-diamino-2,2′-binaphthalene (82 mg, 0.29 mmol) in dry chloroform (40 mL), 8,8′-diisocyanato-2,2′-binaphthalene (98 mg, 0.29 mmol) in chloroform (40 mL) was added dropwise via syringe at r.t. under argon atmosphere. The solution was stirred overnight. After the mixture was evaporated under reduced pressure, the residue was chromatographed on silica gel with AcOEt:MeOH = 10: 1 (v/v) to give the product as pale yellow solid. 152 mg, 58% yield. mp > 280 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.10 (s, 4H), 9.19 (s, 4H), 8.28 (d, 4H, J = 8.1 Hz), 8.09 (d, 4H, J = 8.6 Hz), 8.01 (dd, 4H, J_1 = 8.6, J_2 = 1.7 Hz), 7.68 (d, 4H, J = 8.1 Hz), 7.52 (t, 4H, J = 8.1 Hz), 3.11−3.08 (m, 8H, NCH_2), 1.50 (m, 8H, CH_2), 1.25 (sex, 8H, J = 7.5 Hz, CH_2), 0.88 (t, 12H, J = 7.5 Hz, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 152.9, 137.8, 134.7, 133.0, 129.3, 126.1, 125.5, 125.4, 122.1, 120.2, 116.8, 57.4, 23.0, 19.2, 13.4. HRMS (ESI, negative mode): Calcd for $C_{42}H_{28}ClN_4O_2$ [M+Cl]$^-$: m/z 655.1901; found: 655.1897.

*Preparation of Cyclic Bisurea **2a**.* The mixture of **2a**·TBACl (30 mg, 0.033 mmol) and silver nitrate (28.4 mg, 0.167 mmol) in DMSO (5 mL) was stirred under argon atmosphere at 60 °C overnight. The mixture was filtered and distilled water was added into the filtrate. The produced pale yellow solids were filtered off and washed with 5% aqueous ammonia and distilled water to give the product as pale yellow solids. Yield 17.2 mg, 83%. mp > 280 °C. ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C) δ 9.41 (s, 4H), 8.87 (s, 4H), 8.21 (d, 4H, J = 7.5 Hz), 8.11 (d, 4H, J = 8.6 Hz), 8.03 (d, 4H, J = 8.6 Hz), 7.71 (d, 4H, J = 8.1 Hz), 7.52 (dd, 4H, J_1 = 8.1, J_2 = 7.5 Hz). ^{13}C NMR cannot be measured due to the low solubility of **2a** in DMSO-d_6.

*Synthesis of TBA$^+$ [**2b**·Cl]$^-$.* Into a solution of 8,8′-diamino-6,6′-di-*tert*-butyl-2,2′-binaphthalene (175.3 mg, 0.442 mmol) and tetrabutylammonium chloride (264 mg, 0.95 mmol) in chloroform (60 mL), a chloroform solution of 8,8′-diisocyanato-6,6′-di-*tert*-butyl-2,2′-binaphthalene (216 mg, 0.442 mmol) was added via syringe. The mixture was stirred at r.t. overnight, then evaporated under reduced pressure. The residue was recrystallzied from DMSO to give the product as pale yellow solid. Yield 441 mg, 89%. mp > 280 °C. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.03 (bs, 4H), 9.10 (bs, 4H), 8.40 (s, 4H), 8.05 (d, 4H, J = 8.5 Hz), 7.96 (d, 4H, J = 8.5 Hz), 7.61 (s, 4H), 3.12 (m, 8H, J = 8.5 Hz), 1,53 (m, 8H), 1.41 (s, 36H), 1.27 (sex, 8H, J = 7.5 Hz), 0.91 (t, 12H, J = 7.5 Hz). ^{13}C NMR (126 MHz, DMSO-*d6*) δ 153.0, 148.2, 137.0, 134.2, 132.6, 128.9, 124.7, 124.1, 119.4, 117.1, 115.8, 57.6, 34.4, 30.7, 22.8, 18.8, 12.9. HRMS (ESI, negative mode): Calcd for $C_{58}H_{60}ClN_4O_2$ [M+Cl]$^-$: m/z 879.4405; found: 879.4422.

*Preparation of Cyclic Bisurea **2b**.* The mixture of **2b**·TBACl (120 mg, 0.107 mmol) and silver nitrate (90 mg, 0.534 mmol) in DMSO (5 mL) was stirred under argon atmosphere at 60 °C overnight. The mixture was filtered and distilled water was added into the filtrate. The produced solid was filtered off and washed with 5% aqueous ammonia and distilled water. The solid was dissolved in chloroform and dried over anhydrous sodium sulfate. After evaporation under reduced pressure, the residue was chromatographed on silica gel (5% diethyl ether/chloroform as an eluent) to give the product as colorless solid. Yield 62 mg, 69%. mp > 280 °C. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.14 (s, 4H), 8.56 (s, 4H), 8.25 (s, 4H), 8.07 (d, 4H, J = 8.6 Hz), 7.96 (d, 4H, J = 8.6 Hz), 7.67 (s, 4H), 1.39 (s, 36H). ^{13}C NMR (126 MHz, DMSO-*d6*) δ 153.7, 148.5, 137.3, 134.2, 132.9, 129.5, 125.5, 125.1,

DOI: 10.1021/acs.joc.6b01959
J. Org. Chem. 2016, 81, 9848−9857

119.1, 118.3, 117.5, 34.8, 31.0. HRMS (ESI, positive mode): Calcd for $C_{58}H_{60}N_4NaO_2$ $[M+Na]^+$, 867.4614. Found 867.4621.

Single Crystal X-ray Diffraction. Crystallographic data for **2a**·TBACl, free **2b** from $CHCl_3$/hexane, free **2b** from DMSO, and **2b**·TBACl are summarized in Table 3.

Crystals of **2a**·TBACl were obtained by vapor diffusion of hexane into a solution in $CHCl_3$. Data collection was carried out at 113 K on a diffractometer with CCD detector and graphite-monochromated Mo Kα radiation (λ = 0.70860 Å) . The structure was solved by direct method (SHELXS-97) and refined by full-matrix least-squares methods on F^2 using SHELXL-97.[43] Non-hydrogen atoms were refined anisotropically. Diffused solvent molecules were treated with the SWAT option.

Crystals of free **2b** were obtained by vapor diffusion of hexane into a solution in $CHCl_3$. Data collection was carried out at 113 K on a diffractometer with CCD detector and graphite-monochromated Mo Kα radiation (λ = 0.70860 Å) . The structure was solved by direct method (SHELXS-97) and refined by full-matrix least-squares methods on F^2 using SHELXL-97.[43] Non-hydrogen atoms were refined anisotropically. The visual judgment of the difference electron density map indicates that five molecules of chloroform ($CHCl_3$) are located within the voids. Therefore, the compounds probably best showed as described as $C_{58}H_{60}N_4O_2{\cdot}5(CHCl_3)$. However, the displacement parameters of two of chloroform molecules show that it is clearly disordered. To improve the fit of the model to the data, the contributions of the disordered chloroform molecules were removed from the diffraction data with a SQUEEZE procedure in PLATON.[44] This treatment allows a large solvent accessible void(s) in the structure.

Other crystals of free **2b** were also obtained by slow recrystallization from DMSO. Data collection was carried out at 113 K on a diffractometer with CCD detector and graphite-monochromated Mo Kα radiation (λ = 0.70860 Å) . The structure was solved by direct method (SHELXT[45]) and refined by full-matrix least-squares methods on F^2 using SHELXL2014.[46] Non-hydrogen atoms were refined anisotropically. The long unit-cell length in the *c* dimension and large crystal mosaicity reduced diffraction signal-to-noise and increased spot overlap. Moreover, there was a large amount of disorder of *tert*-butyl groups, urea groups, and some water molecules. Consequently, a number of reflections were missing especially in the range of 0.91−0.77 Å resolution. Additionally, to improve the fit of the model to the data, the contributions of the disordered water molecules were removed from the diffraction data with a SQUEEZE method.[44]

Crystals of **2b**·TBACl were obtained by vapor diffusion of hexane into a solution in $CHCl_3$. Data collection was carried out at 203 K on a diffractometer with rapid imaging plate area detector and graphite-monochromated Cu Kα radiation (λ = 1.54187 Å). The structure was solved by direct method (SHELXS-97) and refined by full-matrix least-squares methods on F^2 using SHELXL-97.[43] Non-hydrogen atoms were refined anisotropically. All N−H hydrogens of urea groups were fully optimized and other hydrogens were geometrically generated and optimized by riding model.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01959.

Spectral data for receptors as well as UV−vis and fluorescence spectral titrations (PDF)

X-ray crystallographic data for **2a**·TBACl, free **2b**, and **2b**·TBACl (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*kondo@sci.kj.yamagata-u.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Prof. Nobuhiro Takeda, Gunma University, for measurement of the preliminary X-ray crystal structural analysis. The authors thank Prof. Tatsuya Nabeshima and Prof. Masaki Yamamura, University of Tsukuba, for the HRMS measurements. This work was supported in part by a JSPS KAKENHI Grant Number 24550144, The Salt Science Research Foundation, Nos. 1006 and 1104, and a research grant from The Mazda Foundation.

■ REFERENCES

(1) Bianchi, A.; Bowman-James, K.; Garcia-España, E. *Supramolecular Chemistry of Anions*; Wiley-VCH: New York, 1997.

(2) Sessler, J. L.; Gale, P. A.; Cho, W.-S. *Anion Receptor Chemistry*; Royal Society of Chemistry: Cambridge, 2006.

(3) Evans, N. H.; Beer, P. D. *Angew. Chem., Int. Ed.* **2014**, *53*, 11716.

(4) Gale, P. A.; Caltagirone, C. *Chem. Soc. Rev.* **2015**, *44*, 4212.

(5) Foskett, J. K. *Annu. Rev. Physiol.* **1998**, *60*, 689.

(6) Schazmann, B.; Alhashimy, N.; Diamond, D. *J. Am. Chem. Soc.* **2006**, *128*, 8607.

(7) Hancock, L. M.; Beer, P. D. *Chem. - Eur. J.* **2009**, *15*, 42.

(8) Collins, C. G.; Peck, E. M.; Kramer, P. J.; Smith, B. D. *Chem. Sci.* **2013**, *4*, 2557.

(9) Elmes, R. B. P.; Turner, P.; Jolliffe, K. A. *Org. Lett.* **2013**, *15*, 5638.

(10) Mikláš, R.; Kasák, P.; Devínsky, F.; Putala, M. *Chem. Pap.* **2009**, *63*, 709.

(11) Bregović, V. B.; Basarić, N.; Mlinarić-Majerski, K. *Coord. Chem. Rev.* **2015**, *295*, 80.

(12) Kondo, S.; Nagamine, M.; Karasawa, S.; Ishihara, M.; Unno, M.; Yano, Y. *Tetrahedron* **2011**, *67*, 943.

(13) Kondo, S.; Sonoda, H.; Katsu, T.; Unno, M. *Sens. Actuators, B* **2011**, *160*, 684.

(14) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039.

(15) Ahmed, N.; Geronimo, I.; Hwang, I.-C.; Singh, N. J.; Kim, K. S. *Chem. - Eur. J.* **2011**, *17*, 8542.

(16) Suresh, V.; Ahmed, N.; Youn, I. S.; Kim, K. S. *Chem. - Asian J.* **2012**, *7*, 658.

(17) White, N. G.; Carvalho, S.; Félix, V.; Beer, P. D. *Org. Biomol. Chem.* **2012**, *10*, 6951.

(18) Martí-Centelles, V.; Burguete, M. I.; Galindo, F.; Izquierdo, M. A.; Kumar, D. K.; White, A. J. P.; Luis, S. V.; Vilar, R. *J. Org. Chem.* **2012**, *77*, 490.

(19) Saha, S.; Akhuli, B.; Chakraborty, S.; Ghosh, R. *J. Org. Chem.* **2013**, *78*, 8759.

(20) Schaly, A.; Belda, R.; García-España, E.; Kubik, S. *Org. Lett.* **2013**, *15*, 6238.

(21) Hirsch, B. E.; Lee, S.; Qiao, B.; Chen, C.-H.; McDonald, K. P.; Tait, S. L.; Flood, A. H. *Chem. Commun.* **2014**, *50*, 9827.

(22) Ema, T.; Okuda, K.; Watanabe, S.; Yamasaki, T.; Minami, T.; Esipenko, N. A.; Anzenbacher, P. *Org. Lett.* **2014**, *16*, 1302.

(23) Yousuf, M.; Ahmed, N.; Shirinfar, B.; Miriyala, V. M.; Youn, I. S.; Kim, K. S. *Org. Lett.* **2014**, *16*, 2150.

(24) Sommer, F.; Kubik, S. *Org. Biomol. Chem.* **2014**, *12*, 8851.

(25) Ramabhadran, R. O.; Liu, Y.; Hua, Y.; Ciardi, M.; Flood, A. H.; Raghavachari, K. *J. Am. Chem. Soc.* **2014**, *136*, 5078.

(26) Jin, S.; Kato, S.-i.; Nakamura, Y. *Chem. Lett.* **2016**, *45*, 869.

(27) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; J. A. Montgomery, J.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.;

DOI: 10.1021/acs.joc.6b01959
J. Org. Chem. 2016, 81, 9848−9857

Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*; Gaussian, Inc.: Wallingford CT, 2010.
(28) Gerbeleu, N. V.; Arion, V. B.; Burgess, J. *Template Synthesis of Macrocyclic Compounds*; Wiley-VCH: Wienheim, 1999.
(29) Lankshear, M. D.; Beer, P. D. *Coord. Chem. Rev.* **2006**, *250*, 3142.
(30) Gimeno, N.; Vilar, R. *Coord. Chem. Rev.* **2006**, *250*, 3161.
(31) Meshcheryakov, D.; Böhmer, V.; Bolte, M.; Hubscher-Bruder, V.; Arnaud-Neu, F.; Herschbach, H.; Van Dorsselaer, A.; Thondorf, I.; Mögelin, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 1648.
(32) Caballero, A.; Zapata, F.; White, N. G.; Costa, P. J.; Félix, V.; Beer, P. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 1876.
(33) Dabrowa, K.; Niedbala, P.; Majdecki, M.; Duszewski, P.; Jurczak, J. *Org. Lett.* **2015**, *17*, 4774.
(34) Martí-Centelles, V.; Burguete, M. I.; Luis, S. V. *J. Org. Chem.* **2016**, *81*, 2143.
(35) Masson, G.; Lough, A. J.; Manners, I. *Macromolecules* **2008**, *41*, 539.
(36) Constable, E. C.; Hostettler, N.; Housecroft, C. E.; Kopecky, P.; Neuburger, M.; Zampese, J. A. *Dalton Trans.* **2012**, *41*, 2890.
(37) Kumar, B.; Strasser, C. E.; King, B. T. *J. Org. Chem.* **2012**, *77*, 311.
(38) Mallory, F. B.; Mallory, C. W.; Regan, C. K.; Aspden, R. J.; Ricks, A. B.; Racowski, J. M.; Nash, A. I.; Gibbons, A. V.; Carroll, P. J.; Bohen, J. M. *J. Org. Chem.* **2013**, *78*, 2040.
(39) Fieser, L. F.; Price, C. C. *J. Am. Chem. Soc.* **1936**, *58*, 1838.
(40) Kubik, S.; Reyheller, C.; Stuwe, S. *J. Inclusion Phenom. Mol. Recognit. Chem.* **2005**, *52*, 137.
(41) Kubik, S. *Chem. Soc. Rev.* **2010**, *39*, 3648.
(42) Langton, M. J.; Serpell, C. J.; Beer, P. D. *Angew. Chem., Int. Ed.* **2016**, *55*, 1974.
(43) SHELXL-97: Sheldrick, G. M. Program for the Refinement of Crystal Structures. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64*, 112.
(44) Spek, A. L. *Acta Crystallogr., Sect. D: Biol. Crystallogr.* **2009**, *65*, 148.
(45) SHELXT: Sheldrick, G. M. Program for the Solution of Crystal Structures. *Acta Crystallogr., Sect. A: Found. Adv.* **2015**, *71*, 3.
(46) SHELXL2014: Sheldrick, G. M. Program for the Refinement of Crystal Structures. *Acta Crystallogr., Sect. C: Struct. Chem.* **2015**, *71*, 3.

DOI: 10.1021/acs.joc.6b01959
J. Org. Chem. 2016, 81, 9848−9857