Control of Ion Binding by Cooperative Ion-Pair Recognition Using a Flexible Heterotopic Receptor

Tatsuya Nabeshima,* Takeshi Hanami, Shigehisa Akine, and Toshiyuki Saiki
Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305-8571

(Received March 21, 2001; CL-010248)

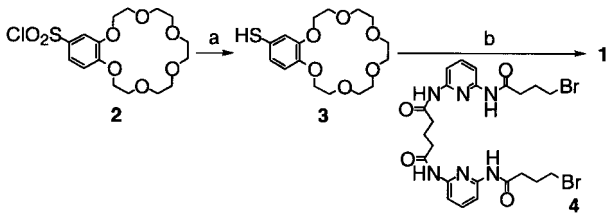
Complex of the host, which bears four amide groups and two crown ethers, and Cs^+, recognizes chloride and bromide anions much more strongly than the free host, because the host captures one Cs^+ ion with the two crown rings in a face-to-face fashion to cyclize the host, and the preorganization of the amide protons forms the good binding site for the anions.

Cooperative binding is important and useful for strong and precise recognition of complicated guest molecules. In addition, hosts with several cooperative sites allosterically regulate binding abilities of the hosts using an effector.[1] Allosteric systems have attracted much attention, because the mechanism is highly effective to control molecular functions of biological and artificial systems.[2] Recently ditopic receptors have been employed to differentiate ion pairs as a guest and to enhance the complexabilities to ion pairs.[3] In particular, cesium salts are very interesting target ion pairs because a Cs^+ ion is an important cation for nuclear waste.[4] Thus, we wish to report here **1**, which exhibits a remarkably large and positive allosteric effect on complexation with a halide ion using a Cs^+ ion as an effector.

Host **1** possesses two 18-crown-6 rings and two 2,6-bis(acylamido)pyridine moieties as cation[5] and anion[6] binding sites, respectively. Cs^+ is known to make a 1:2 sandwich complex with benzo-18-crown-6.[7] CPK model examination suggests that complexation of **1** with a Cs^+ ion in this fashion results in conformational change of the host to give a cyclic anion binding site surrounded by the amide groups (Figure 1).

Host **1** was synthesized according to a similar route for that of a 15-crown-5 analogue (Scheme 1).[8] The structure of **1** was confirmed by NMR, MS, and elemental analysis.[9]

At first we chose tetrakis[3,5-bis(trifluoromethyl)phenyl] borate anion ($TFPB^-$) as an uncomplexable anion with the amide moieties (vide infra). Complexation of **1** and CsTFPB was examined by ^1H NMR. The addition of CsTFPB into a solution of **1** ($CDCl_3$:CD_3CN = 4:1) caused significant changes of signals assigned to the crown ether methylene and aromatic protons.



Scheme 1. Reagents and conditions: (a) $LiAlH_4$, THF, rt, 10 h, reflux, 1 h (34%); (b) NaH, EtOH, rt, 23 h (42%).

Until one equivalent of CsTFPB was added, an upfield shift of the signal for H_a was observed. Beyond one equivalent, the change is inverse. Excess (2 equiv) of Cs^+ causes a downfield shift, even compared to the free host **1**. This result suggests that a Cs^+ ion initially complexes with the two crown rings in a face-to-face fashion and then form a 1:2 complex where each crown ether moiety binds to a Cs^+ ion. Non-linear regression analysis of the titration curve gives K_1 for **1**:Cs^+ = 1:1 and K_2 for 1:2. Each chemical shift of the aromatic proton H_a derived from the species **1**, **1**·Cs^+, **1**·2Cs^+ was written as δ_0, δ_1, δ_2, and assumed the simultaneous equations written below. The value of K_1 is large but estimated to be $> 1.0 \times 10^5$ M^{-1}. The value of K_2 is calculated to be 1.0×10^4 M^{-1}. Hence, only the **1**·Cs^+ complex exists in a 1:1 solution of **1** and CsTFPB.

$$\mathbf{1} + 2Cs^+ \overset{K_1}{\rightleftharpoons} \mathbf{1}\cdot Cs^+ + Cs^+ \overset{K_2}{\rightleftharpoons} \mathbf{1}\cdot 2Cs^+$$

$$\delta = \delta_0 \frac{[\mathbf{1}]}{[\mathbf{1}]_0} + \delta_1 \frac{[\mathbf{1}\cdot Cs^+]}{[\mathbf{1}]_0} + \delta_2 \frac{[\mathbf{1}\cdot 2Cs^+]}{[\mathbf{1}]_0}$$

$$K_1 = \frac{[\mathbf{1}\cdot Cs^+]}{[\mathbf{1}][Cs^+]} \qquad K_2 = \frac{[\mathbf{1}\cdot 2Cs^+]}{[\mathbf{1}\cdot Cs^+][Cs^+]}$$

$$[\mathbf{1}] = [\mathbf{1}]_0 - [\mathbf{1}\cdot Cs^+] - [\mathbf{1}\cdot 2Cs^+]$$

$$[Cs^+] = [Cs^+]_0 - [\mathbf{1}\cdot Cs^+] - 2[\mathbf{1}\cdot 2Cs^+]$$

ESI-MS spectroscopy also confirms the formation of these complexes. Signals assigned to **1**·Cs^+ were observed from the

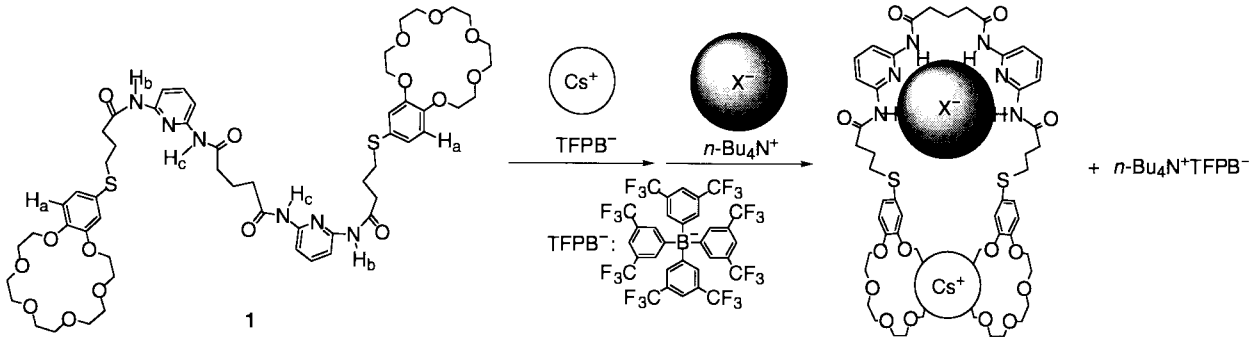


Figure 1. Formation of a second host (**1**·Cs^+ complex) from a first host (**1**).

MS spectrum of a 1:1 mixture of **1** and CsBr. **1**·2Cs$^+$ appeared as the concentration of CsBr increases.

Interactions between **1**·Cs$^+$ and Cl$^-$ or Br$^-$ anions were also examined by ^{1}H NMR spectroscopy.[10] We chose tetrabutylammonium chloride and bromide as halogen anion sources because tetrabutylammonium cation is uncomplexable with 18-crown-6 ethers. Thus the binding constants obtained from these experiments reflect the affinity of the new cavity of **1**·Cs$^+$ to halogen anions. Upon adding the *n*-Bu$_4$N$^+$ salts into a solution of **1**·Cs$^+$, downfield shifts of the two kinds of amide protons in **1** were observed (Figure 2). These changes are ascribed to the formation of hydrogen bonds between four amide moieties of **1**·Cs$^+$ and the halogen anion as shown in Figure 1. Chloride anion induces a larger downfield shift of amide protons than bromide. For example, addition of 4 equiv of *n*-Bu$_4$NCl and 4 eq. of *n*-Bu$_4$NBr to the **1**·Cs$^+$ complex caused 1.4 ppm and 0.8 ppm downfield shift of the amide protons, respectively. Association constants of **1**·Cs$^+$ with chloride and bromide were calculated from the chemical shifts of H$_b$ or H$_c$, assuming a 1:1 complexation of **1**·Cs$^+$ with anions (Table 1).

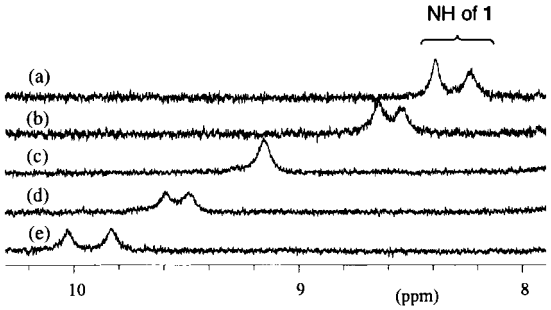


Figure 2. ^{1}H NMR spectral changes of **1** by the addition of Bu$_4$NCl in the presene of 1 equiv of Cs$^+$. [**1**] = 1.0×10^{-3} M in $CDCl_3$:CD_3CN = 4:1 (300 MHz). (a) **1**:Cs$^+$ = 1:1. (b) **1**: Cs$^+$:*n*-Bu$_4$NCl = 1:1:0.2. (c) **1**:Cs$^+$:*n*-Bu$_4$NCl = 1:1:0.6. (d) **1**: Cs$^+$:*n*-Bu$_4$NCl = 1:1:1. (e) **1**:Cs$^+$:*n*-Bu$_4$NCl = 1:1:4.

Table 1. Association constants of **1**[a] determined by ^{1}H NMR (300 MHz) titration in $CDCl_3$:CD_3CN = 4:1

Anion	K_a/M^{-1}	
	without Cs$^+$	with Cs$^+$
Cl$^-$	210 ± 30	9000 ± 700
Br$^-$	290 ± 60	3400 ± 200

[a][**1**] = 1.0×10^{-3} M.

In the absence of Cs$^+$, association constants of **1** and the anions were calculated from titration curves obtained under similar conditions. The values obtained were much lower than those of **1**·Cs$^+$. As shown in Table 1, addition of 1 equiv of Cs$^+$ provided a 45-fold enhancement of binding of **1** to Cl$^-$, and 10-fold to Br$^-$ due to hydrogen bonding in the preorganized cavity. The enhancement caused by Cl$^-$ is considerably larger than a very recent example of ion pair recognition.[11] These results clearly show that the Cs$^+$ ion acts as an effector of the host–guest complexation of **1** with a halogen anion. This system, therefore, is considered to be a heterotropic allosteric system. Addition of *n*-Bu$_4$NTFPB gave no meaningful change of the chemical shift of **1**, indicative of very weak or no interaction. This fact again supports preorganization of the amide moieties to provide the cyclic framework as a binding site.

^{1}H NMR spectral changes of the **1**·2Cs$^+$ complex by addition of *n*-Bu$_4$NCl or *n*-Bu$_4$NBr were monitored to estimate intrinsic interactions between **1** and the anions without an alkali metal ion to cause formation of an anion receptor. When 1 equiv of halide anion was added, a white precipitate appeared and changes of the signals for the NH and aromatic protons were observed. Addition of a large excess (10 equiv) of the salts to the solution of **1**·2Cs$^+$ gave nearly the same ^{1}H NMR spectrum as that obtained from a mixture of **1**·Cs$^+$ and 10 equiv of *n*-Bu$_4$NCl or *n*-Bu$_4$NBr. These results indicate that the **1**·2Cs$^+$ complex is converted to **1**·Cs$^+$, probably accompanied by the precipitation of the Cs$^+$ halide salt. **1**·Cs$^+$ thus produced catches a halide anion in the cavity.

In conclusion, we designed and synthesized host **1** in which the two crown rings and four amide moieties are assembled via guest binding to form two heterotopic binding sites. It was found that one Cs$^+$ cation and one halide anion are simultaneously recognized by host **1** and that halide anion binding of **1** is totally controlled by Cs$^+$. This fact clearly shows that Cs$^+$ acts as a positive allosteric effector for the binding of halide anions in this system. This simultaneous recognition of anion and cation by **1** would provide a useful strategy not only for regulating ion pair recognition but also for precise and selective recognition of molecules and complexes with a large dipole moment, such as zwitterions and CT complexes. Now we are investigating the precise recognition of various inorganic and organic salts and zwitterions by host **1**.

References and Notes

1 M. F. Perutz, "Mechanisms of Coorperativity and Allosteric Regulation in Proteins," Cambridge University Press, Cambridge (1989).
2 a) J. Rebek, Jr., *Acc. Chem. Res.*, **17**, 258 (1984). b) I. Tabushi, *Pure Appl. Chem.*, **60**, 581 (1988). c) T. Nabeshima, *Coord. Chem. Rev.*, **148**, 151 (1996).
3 a) M. J. Deetz, M. Shang, and B. D. Smith, *J. Am. Chem. Soc.*, **122**, 6201 (2000) and references therein. b) P. D. Beer and S. W. Dent, *Chem. Commun.*, **1998**, 825. c) J. Scheerder, J. P. M. van Duynhoven, J. F. J. Engbersen, and D. N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, **35**. 1090 (1996).
4 a) K. Kavallieratos, R. A. Sachleben, G. J. Van Berkel, and B. A. Moyer, *Chem. Commun.*, **2000**, 187. b) "Science and Technology for Disposal of Radioactive Tank Wastes," ed. by W. W. Schultz and N. J. Lombardo, Plenum, New York (1998).
5 R. M. Izatt, K. Pawlak, and J. S. Bradshaw, *Chem. Rev.*, **91**, 1721 (1991).
6 F. P. Schmidtchen and M. Berger, *Chem. Rev.*, **97**, 1609 (1997).
7 a) E. J. Harris, B. Zaba, M. R. Truter, D. G. Parsons, and J. N. Wingfield, *Arch. Biochem. Biophys.*, **182**, 311 (1977). b) C. C. Chen and T. W. Smith, *J. Polym. Sci., Polym. Symp.*, **74**, 171 (1986). c) R. M. Izatt, G. A. Clark, J. D. Lamb, J. E. King, and J. J. Christensen, *Thermochim. Acta*, **97**, 115 (1986).
8 T. Nabeshima and T. Hanami, *Heterocycles*, **50**, 1091 (1999).
9 **1**: mp 55.7–57.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (2H, br s), 7.87–7.83 (4H, br m), 7.76 (2H, br s), 7.66 (2H, dd, *J* = 8, 8 Hz), 6.99–6.94 (4H, m), 6.77 (2H, d, *J* = 8 Hz), 4.14–4.10 (8H, m), 3.90–3.85 (8H, m), 3.76–3.66 (24H, m), 2.92 (4H, t, *J* = 7 Hz), 2.57–2.48 (8H, m), 2.17–2.10 (2H, m), 2.02–1.96 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.9, 149.5, 149.4, 149.1, 148.3, 140.6, 126.9, 124.7, 117.2, 114.2, 109.4, 109.3, 70.8, 70.7, 70.6, 69.5, 69.0, 68.9, 36.1, 35.6, 34.8, 25.0, 21.1. MS (ESI) observed *m/z* 1139 ([M+H]$^+$). Anal. Calcd for $C_{55}H_{74}N_6O_{16}S_2 \cdot H_2O$: C, 57.08; H, 6.62; N, 7.26. Found: C, 56.88; H, 6.82; N, 6.99%.
10 In cases of F$^-$ and I$^-$, the association constants could not be determined due to considerable broadening of the NH signals and very slow equilibrium, respectively.
11 R. Shukla, T. Kida, and B. D. Smith, *Org. Lett.*, **2**, 3099 (2000).