A Thiourea-Functionalized Benzo-15-crown-5 for Cooperative Binding of Sodium Ions and Anions

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A new bifunctional receptor **1** for cooperative complexation of cations and anions is synthesized on the basis of benzo-15-crown-5, functionalized with a thiourea moiety as anion binding sites. When Na^+ is bound to the crown moiety of **1**, the association constants of I^-, Br^- and NO_3^- in CD_3CN are significantly increased, as compared with free **1**. Thermodynamic studies indicate that these large increases in complex stabilities can be ascribed primarily to the enthalpic effect.

Due to many possible potentials as a new class of reagents for membrane transports, ion-selective electrodes as well as reaction catalysts, the design and synthesis of bifunctional receptors for simultaneous binding of cations and anions is of ongoing interest in supramolecular chemistry.[1-8] In bifunctional receptors, the binding sites for anions and cations are covalently linked so as to exhibit allosteric or cooperative complexation where the binding affinity for anions (cations) is modified as a result of the cation (anion) complexation.[8] To date, however, only a few receptors of this class have been reported.[1-8] In addition, little attention has been paid to the effect of cation binding on complexation behavior with anions from the thermodynamic point of view. Examination of thermodynamic parameters for complexation would provide important insight into a rational design strategy of new receptors for cooperative binding of cations and anions.

In this study, a very simple benzo-15-crown-5 derivative **1**, which contains a thiourea group as potential hydrogen bond donors to recognize anions,[9-12] has been prepared, and the anion complexation in the absence and presence of Na^+ has been examined in CD_3CN by ^1H NMR spectroscopy. As a result, **1** is found to work as a novel bifunctional receptor for simultaneous complexation of Na^+ and anions, where the ability of **1** to bind anions is significantly enhanced when Na^+ is bound to the crown moiety. Furthermore, the origin of cooperative binding of Na^+ and anions by the bifunctional receptor **1** is discussed on the basis of the thermodynamic parameters.

Compound **1** was synthesized in one step by reaction of 4'-aminobenzo-15-crown-5 with methyl isothiocyanate in ethanol, and purified three times by recrystallization from ethanol. The new receptor **1** was characterized by ^1H, ^{13}C NMR, and elemental analyses as well as mass spectrometry.[13]

Association constants of **1** with guest anions were determined by ^1H NMR titration experiments in CD_3CN. The addition of anions as $N(C_4H_9)_4^+$ salt resulted in significant downfield shifts for both thiourea protons of **1**, suggesting that hydrogen-bond

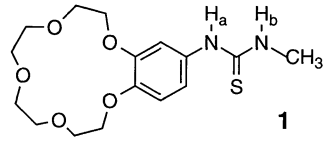

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Table 1. Association constants (K_{11}/M^{-1}, in CD_3CN at 295 K) of receptor **1** and Ph-TU[a] with anions[b] in the absence and presence (2 eq.) of $NaBPh_4$.

	1		Ph-TU	
	no Na^+	+ Na^+	no Na^+	+ Na^+
$H_2PO_4^-$	7.7×10^2	____[c]	1.2×10^3	____[c]
NO_3^-	6.0	6.6×10	2.0×10	$\leq 2.0 \times 10$
Cl^-	1.3×10^2	____[c]	4.7×10^2	____[c]
Br^-	2.5×10	2.6×10^2	7.5×10	4.5×10
I^-	4.3	2.0×10	6.6	6.4

[a]Ph-TU: phenylthiourea. [b]Counter-ion: $N(C_4H_9)_4^+$. [c]Association constants could not be determined because of precipitation.

mediated complexation of **1** with anions takes place in the thiourea moiety of the receptor. In all cases the resulting titration curves for both thiourea protons can be analyzed by a non-linear regression curve with a 1:1 complexation model.[14] ^1H NMR titration experiments were carried out repeatedly in the presence of 2 eq. of $NaBPh_4$ (4.0 mM, 1 M = 1 mol dm^{-3}), under which over 95% of **1** is complexed with Na^+ (K_{11}: 8.2×10^3 M^{-1}).[15] For comparison, the same experiments were performed with *N*-phenylthiourea (Ph-TU), which has no Na^+ binding sites. Association constants thus obtained are summarized in Table 1.

Table 1 shows that the association constants follow the trend $H_2PO_4^- > Cl^- > Br^- > NO_3^- > I^-$ for **1** as well as Ph-TU. The observed binding selectivity, as expected for neutral mono (thio)urea-based receptors, can be roughly explained by the anion basicity order,[11,12] and does not change significantly even in the presence of Na^+.

On the other hand, it is noteworthy that **1** complexed with Na^+ shows a substantial increase in the anion binding ability as compared to free **1**. The association constants of I^-, Br^- and NO_3^- complexes are indeed increased approximately by a factor of 5, 10 and 11, respectively. By contrast, Ph-TU, which lacks crown ether moiety for Na^+ binding, shows a small decrease rather than an increase in the association constants for anions in the presence of Na^+. These results suggest that **1** can act as a bifunctional receptor, and complexation of Na^+ at the crown moiety plays a crucial role for the increase in the anion binding ability of **1**.

To understand how the anion binding is affected by Na^+ complexation, thermodynamic parameters for complexation of anions with **1** were determined through the van't Hoff analysis of the association constants obtained by the variable-temperature ^1H NMR titration method.[16] A comparison of the data for Br^- in the

absence and presence of Na^+ (free **1**, ΔH = +0.93 kcal/mol, ΔS = +9.5 cal/mol K; **1**-Na^+, ΔH = -1.1 kcal/mol, ΔS = +7.4 cal/mol K) indicates that the enhanced stability for **1**-Na^+ can be ascribed primarily to the increased enthalpic gain, while the entropic gain is kept relatively unchanged. Similarly, the difference in complexation of NO_3^- with **1** is due mainly to the enthalpic contribution (free **1**, ΔH = +1.74 kcal/mol, ΔS = +9.5 cal/mol K; **1**-Na^+, ΔH = -0.54 kcal/mol, ΔS = +6.5 cal/mol K). The favorable enthalpic gain observed for **1**-Na^+ may be understood by considering an electron withdrawing effect of the crown moiety complexed with Na^+. This is supported by ^1H NMR spectra of **1**, in which downfield shifts for both thiourea protons were observed upon complexation of Na^+ at the crown moiety.[15] The chemical shifts of the NH adjacent to the phenyl group, H_a, and the NH adjacent to the methyl group, H_b, in the Na^+ complex were larger by 0.07 and 0.05 ppm, respectively, than in the free receptor. This difference in chemical shift, such as found in comparison of phenylurea and phenylthiourea derivatives in $CDCl_3$,[10] is indicative of stronger acidity of the thiourea hydrogens of **1**-Na^+ than those of free **1**.[17] It is therefore likely that complexation of Na^+ at the crown moiety enhances the hydrogen bond donation ability of the thiourea NH protons, which leads to a favorable enthalpic gain in the anion binding. A similar effect has recently also been observed for simultaneous complexation of cations and carboxylate anions by a calix[4]arene-based receptor.[7] An intramolecular electrostatic interaction between Na^+ ion and anion, being bound to the crown and thiourea moieties, respectively, may be another reason for the favorable enthalpic gain in the anion binding.

In summary, we have demonstrated that **1** can act as a novel bifunctional receptor for simultaneous recognition of cations and anions, where complexation of Na^+ at the crown moiety cooperates in the anion binding at the thiourea moiety. Thermodynamically, the difference in binding ability of **1** in the absence and presence of Na^+ can be attributed primarily to the enthalpic effect. The greater enthalpic gain of **1**-Na^+ over free **1** is probably rationalized by the enhanced hydrogen bond donation ability of the thiourea NH protons and by the favorable electrostatic attraction caused by the closely located Na^+.

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13 Identifying data for **1**: ^1H NMR (500 MHz, CD_3Cl): δ 7.44 (s, 1H, ar NH), 6.87 (d, J = 8.4 Hz, 1H, ar), 6.76 (dd, J = 8.4 Hz, 2.4 Hz, 1H, ar), 6.71 (d, J = 2.4 Hz, 1H, ar), 5.87 (s, br., 1H, $NHCH_3$), 4.14 (m, 2H), 4.10 (m, 2H), 3.91(m, 4H), 3.77-3.73 (m, 8H), 3.12 (d, J = 4.6 Hz, 3H, $NHCH_3$). ^{13}C NMR (125 MHz, CD_3Cl): δ 182.2, 150.1, 148.8, 128.8, 119.2, 114.4, 112.2, 71.0, 70.4, 70.3, 69.4, 69.3, 69.2, 68.9, 32.1. EI mass spectrum, m/z 356.1 (M^+, Calcd 356.1). Anal. Calcd for $C_{16}H_{24}N_2O_5S$ (356.44): C, 53.92; H, 6.79; N, 7.86; S, 8.99%. Found: C, 54.03; H, 7.05; N, 7.92; S, 8.82%.

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15 Complexation of **1** with Na^+ in CD_3CN was confirmed by ^1H NMR spectroscopy. A titration of a CD_3CN solution of **1** with Na^+ (as BPh_4^- salt) resulted in downfield shifts for all the crown ether methylene protons. Non-linear regression showed that all these shifts can be explained as due to a formation of 1:1 complex.

16 ^1H NMR titration experiments were performed over a temperature range of 273-323 K. Plots of ln K_{11} vs $1/T$ gave straight lines ($R > 0.95$) from which ΔH and ΔS values of complexation were derived.

17 We have found an empirical linear relationship between the pK_a's and ^1H chemical shifts of the NH protons in a series of simple (thio)ureas. ^1H chemical shift (ppm, in DMSO-d_6 at 295 K): $(H_2N)_2CO$: 5.64; $(H_2N)_2CS$: 7.02; $(PhNH)_2CO$: 8.63; $(PhNH)_2CS$: 9.78. pK_a (in DMSO at 298 K):[18] $(H_2N)_2CO$: 26.9; $(H_2N)_2CS$: 21.0; $(PhNH)_2CO$: 19.5; $(PhNH)_2CS$: 13.5.

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