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A regioselectively bis(thiourea)-substituted dibenzo-diaza-30-crown-10: a new strategy for the development of multi-site receptors

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Abstract

Due to our interest in the functionalization of dibenzo-30-crown-10 moiety, a regioselectively dinitro-derived congener **1** was conveniently synthesized. The availability of the compound as a building block to develop new molecular systems allowed us to prepare a multi-site receptor **3**, desirable for cooperative complexation of cationic and anionic species in an induced fit fashion. Indeed, K^+ accommodated in the crowned cavity did not only tune the conformation to bind anions but also associated in the anion binding efficiently.

Keywords: crown ethers; macrocycles; molecular recognition; thioureas.

Numerous effects have been devoted to the development of synthetic receptors possessing crown ether units[1] since the discovery of crown ether complexes by Pedersen. Moreover, recently, use of dibenzo-24-crown-8 has attracted much attention for the generation of novel psudorotaxanes.[2] However, surprisingly, the study of dibenzo-30-crown-10-derived systems is limited in spite of the fact that unique complex structures with potassium ion (K^+)[3] and electron-deficient pyridinium derivatives[4] were obtained; this may be due to the difficulty in modification of the skeleton. Indeed, the rare examples of disubstituted dibenzo-30-crown-10s[5] required multiple stepwise synthesis involving troublesome protection–deprotection.[6] Meanwhile, in our ongoing program to develop function-tunable molecular systems (e.g. allosteric effect),[7] we have been intrigued by the utilization of the highly flexible dibenzo-30-crown-10 macrocycle, the large conformation change of which upon complexation leads us to design the relevant systems. However, according to the desired property, suitable functional groups should be pre-organized in the system. Based

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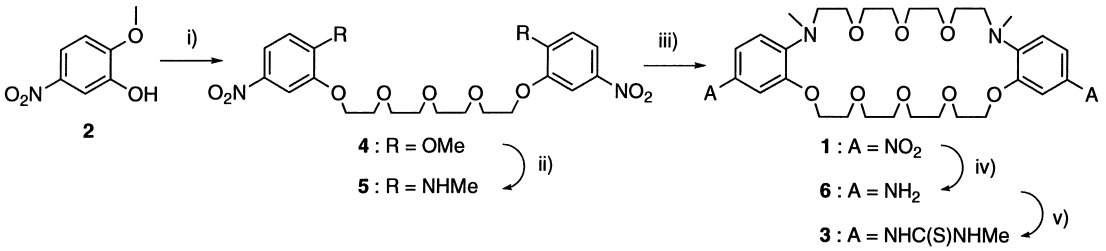
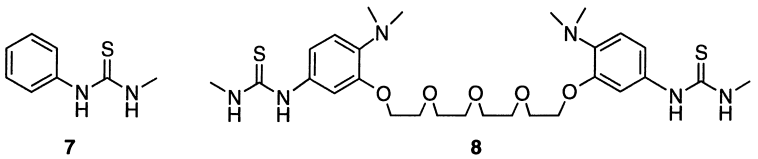
on a retro-synthesis, we succeeded in synthesizing regioselectively dinitro-substituted diaza congener **1** from commercially available material **2** in only three steps, which would be a key building block to develop new receptors because the conversion of the nitro substituent to several functional groups is quite easy. With this strategy in mind, incorporating thiourea units as an efficient anion-binding site[8] onto the building block can create a multi-site receptor for a unique cooperative recognition of cationic and anionic species.[9] As detailed below, this does in fact occur upon the title receptor **3**.

The synthetic procedure is shown in Scheme 1. The commercial compound **2** was reacted with 3,6,9-trioxaundecane-1,11-diyl bistosylate in the presence of K_2CO_3 to produce podand **4**, followed by nucleophilic reaction with $MeNH_2$ to afford **5** in quantitative yield.[10] Again, the Williamson synthesis with 3,6,9-trioxaundecane-1,11-diyl bistosylate was performed to give the synthon **1**[11] in 22% yield after column chromatography. This, via reduction (to produce **6**) and the reaction with MeNCS, converted into the desired **3**[12] conveniently.



Scheme 1. Reagents and conditions: (i) 3,6,9-trioxaundecane-1,11-diyl bistosylate, K_2CO_3, dry acetone, reflux, quant.; (ii) methanolic solution of $MeNH_2$ (40% v/v), in sealed tube, 100°C, quant.; (iii) 3,6,9-trioxaundecane-1,11-diyl bistosylate, NaH, dry DMF, 80°C, 22%; (iv) 10% Pd/C, H_2 (2 atom), EtOH, rt; (v) MeNCS, CH_2Cl_2, 40°C; 40% (from **1** to **3**)



^{1}H NMR dilution experiments in CD_3CN on **3** and *N*-phenylthiourea **7** were carried out so that almost no concentration-dependent shifts of thiourea hydrogens took place, suggesting that the effect arising from interaction between the thiourea units was quite small. As a consequence, system **3** was deduced to have a flexible structure in the polar solvent. Quantitative assessment of the cooperative ion-pair binding properties was made by ^{1}H NMR titration using CD_3CN solution. We initially tested the complexation behavior with potassium tetrakis(*p*-chlorophenyl)borate (KTCPB) as a putative cation. The K^+-induced spectral shifts were observed with overall chemical shifts of the crowned moiety; in particular, the proximal proton resonances in terms of nitrogens shifted upfield by 0.34 ppm for N-CH_3 and 0.26 ppm for N-CH_2CH$_2$-, respectively, indicating that K^+ was accommodated in the concave cavity of the crowned site. Also noted is that K^+ led the resonances of thiourea NHs to downfield by ca. 0.1 ppm, bringing about an enhancement of the acidity. Use of a Job plot analysis[13] suggested a 1:1 stoichiometry of the complex. The association constant was calculated as 5,600 M^{-1} by use of a nonlinear curve-fitting procedure and adding of 3 equiv. of K^+ to **3** (2 mM) allowed for ca. 95% of K^+-**3** complex. Based on this finding, we

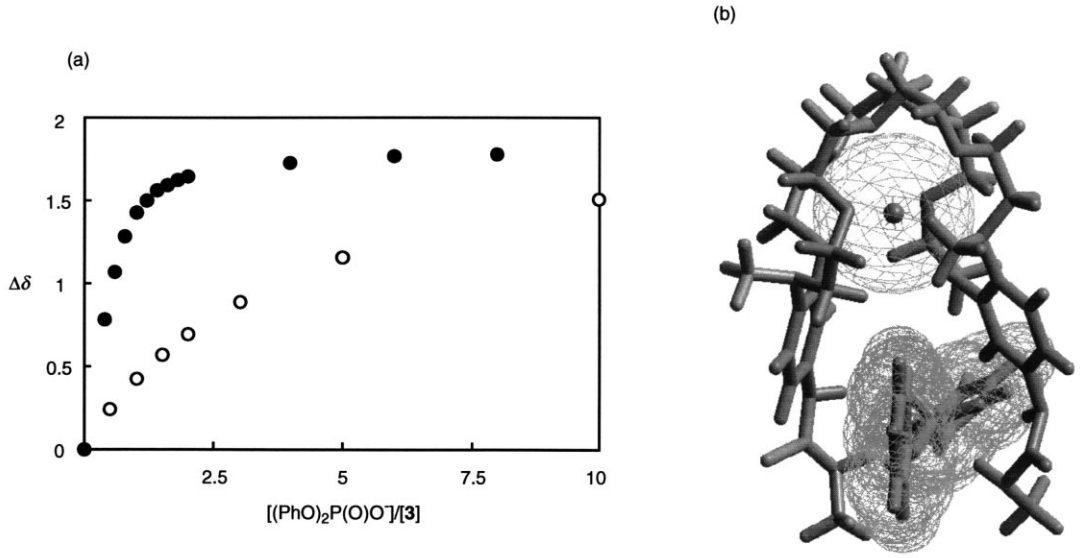


Figure 1. (a) Titration plots of Ar-N*H*C(S) resonance of **3** upon addition of $(PhO)_2P(O)O^-$ in CD_3CN: (●) **3**+K^+ (3 equiv.); (○) **3**; [**3**] = 2.0 mM at 297 K; (b) an energy-minimized complex structure [**3**-K^+-$(PhO)_2P(O)O^-$]

investigated the cation-facilitated binding with anions. Fig. 1(a) shows the results of titration in which the shifts of Ar-N*H*-C(S) resonances were monitored as a function of the incremental amounts of $(PhO)_2P(O)O^-$ in the absence and presence of 3 equiv. of K^+. Clearly, the presence of K^+ caused a much more rapid shift in the resonance than did only system **3**. The analysis of the binding curves led us to consider two stepwise complexations as follows: $H+G \rightleftarrows HG$ (K_1), $HG+G \rightleftarrows HGG$ (K_2), $[H_0]=[H]+[HG]+[HGG]$, wherein [H] and [G] refer to the system **3** and anion, respectively. A nonlinear curve-fitting procedure[14] based on the complexation modes could fully reproduce the experimental data to estimate each association constant (K_1 and K_2). The values as well as the result of the case with I^- are summarized in Table 1. System **3** shows high selectivity for an oxoanion such as $(PhO)_2P(O)O^-$, as comparing with $K_1 \times K_2$, which is suggestive of a significant binding by the thiourea units. Therefore, an efficient cooperative complexation of K^+ and $(PhO)_2P(O)O^-$ was obtained; the K_1 value of the phosphate ion increased remarkably by a factor of 19 upon the presence of K^+, being 9,200 M^{-1}. Although similar positive cooperative binding was also observed in the case of I^-, by adding the cation there was a considerable increase in 1:1 stoichiometric recognition with $(PhO)_2P(O)O^-$ over I^-, with the selectivity of 130-fold. This was taken as indication that a certain K^+-assisted organization of the receptors favored the ditopic binding with the phosphate ion, accompanying an increase in acidity of the thiourea protons. The binding ability toward the phosphate ion could also be accelerated with added Cs^+ as a tetraphenylborate salt (CsTPB)[15] (see Table 1). However, because of the greater ionic size of Cs^+ the effect was not as strong as that in the case of K^+.

As a control experiment, when **8**, lacking the crowned cavity, was used for the complexation event, there was not such significant cooperative binding behavior. The energy-minimized molecular model[16] (Fig. 1(b)) has implied that **3** binds simultaneously K^+ and $(PhO)_2P(O)O^-$ in an induced fit fashion where the distance between the encapsulated ions is ca. 6.3 Å. The value would provide a significant electrostatic interaction. Presently, we are attempting to obtain an X-ray crystal structure of the **3**-K^+-$(PhO)_2P(O)O^-$ complex to clarify such result.

Table 1
Association constants (K_1 and K_2/M^{-1})[a] for **3** with anions in the absence and presence of metal ions in CD_3CN at 297 K

	$(PhO)_2P(O)O^{-}$[b]		I^{-}[c]	
	K_1	K_2	K_1	K_2
3	490	110	< 10	< 3
3 $(+K^+)$[d]	9,200	15	69	31
3 $(+Cs^+)$[d]	3,200	24	–[e]	–[e]

[a]The data were averaged over at least three runs (errors < 14%). [b](Et_4N) salt. [c](n-Bu_4N) salt. [d]Titrations were carried out in the presence of 3 equiv. of KTCPB and CsTPB, respectively. [e]Values not determined.

In conclusion, the results described in this paper lead us to suggest a new approach to a multi-site receptor for cooperative ion-pair binding. Most notably, use of K^+ remarkably enhanced the binding ability of the phosphate ion at two thiourea units. This feature may be applicable to an artificial catalysis enabling hydrolyzation of phosphate diesters;[17] the corresponding cation-regulated catalytic systems are possible by modifying this receptor. Of course, the synthetic availability of the synthon **1** could allow us to develop other cooperative or allosteric systems. Extensive efforts are being directed toward this end.

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11. ^{1}H NMR (400 MHz, CD_3CN, TMS) δ 7.78 (dd, J = 9.0, 2.6 Hz, 2H), 7.63 (d, J = 2.6 Hz, 2H), 6.81 (d, J = 9.0 Hz, 2H), 4.16–4.14 (m, 4H), 3.83–3.81 (m, 4H), 3.70 (t, J = 5.8 Hz, 4H), 3.65–3.63 (m, 4H), 3.62–3.59 (m, 4H), 3.55 (t, J = 5.8 Hz, 4H), 3.52–3.50 (m, 4H), 3.48–3.46 (m, 4H), 2.97 (s, 6H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 148.5, 147.6, 139.5, 118.5, 114.8, 107.5, 70.8, 70.7, 70.6, 70.5, 70.4, 69.3, 68.0, 54.0, 40.8; MS-EI *m*/*z* 652 $[M]^+$. Anal. calcd for $C_{30}H_{44}N_4O_{12}$: C, 55.21; H, 6.80; N, 8.58. Found: C, 55.02; H, 6.74; N, 8.49.
12. ^{1}H NMR (400 MHz, CD_3CN, TMS) δ 7.92 (s, 2H), 6.86 (d, J = 8.3 Hz, 2H), 6.76 (s, 2H), 6.70 (dd, J = 8.4, 2.2 Hz, 2H), 6.45–6.44 (m, 2H), 4.07–4.05 (m, 4H), 3.81–3.79 (m, 4H), 3.67–3.59 (m, 12H), 3.55–3.51 (m, 8H), 3.21 (t, J = 6.2 Hz, 4H), 2.94 (d, J = 4.5 Hz, 6H), 2.78 (s, 6H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 182.0, 151.7, 141.6, 128.7, 118.8, 118.5, 110.7, 70.7, 70.6, 70.4, 69.8, 69.5, 67.7, 54.2, 40.3, 32.1; MS-EI *m*/*z* 740 $[M+2H]^+$. Anal. calcd for $C_{34}H_{54}N_6O_8S_2 \cdot 0.5H_2O$: C, 54.60; H, 7.41; N, 11.24. Found: C, 54.53; H, 7.29; N, 11.13.
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