Pergamon

Tetrahedron Letters 41 (2000) 6083–6087

TETRAHEDRON LETTERS

C_3-Symmetric metacyclophane-based anion receptors with three thiourea groups as linkers between aromatic groups

Kwan Hee Lee and Jong-In Hong*

School of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-742, South Korea

Received 27 April 2000; revised 5 June 2000; accepted 9 June 2000

Abstract

Neutral anion receptors based on the C_3-symmetric metacyclophane structure with three thiourea groups as linkers between aromatic groups have been prepared and examined for their anion-binding ability. The association constants of **1** and **2** with various anions were measured by the ^{1}H NMR titration method. Compound **2**, with three convergent thiourea groups pointing toward the binding cavity, showed increased binding affinities to anions and selective binding to AcO^- compared to conformationally more flexible **1**, which exhibited selective binding to $H_2PO_4^-$ in DMSO-d_6.

Keywords: anion recognition; metacyclophane; thiourea; ^{1}H NMR titration.

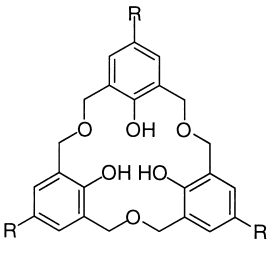
In spite of recent advances and the variety of anion receptors developed so far, the problem of achieving strong and selective anion recognition has not yet been solved, in contrast to the far more developed classical cation receptors.[1] So far, the basic strategy for the construction of anion-binding receptors has been to exploit electrostatic interactions[2] and/or hydrogen bonds,[3] or Lewis acidic metal–ligand interactions.[4] Among these noncovalent interactions, we have been interested in developing hydrogen bond-based neutral anion receptors. Owing to the relatively strong hydrogen bonding ability of urea and thiourea groups, a number of molecules possessing urea or thiourea groups have been designed as neutral receptors for various anions.[3] For strong and selective binding, these groups should be preorganized to complement the target anion and minimize intramolecular hydrogen bonding. One way to achieve this is to make cyclic receptors with urea or thiourea groups connected to rigid spacers.[3e,f] This paper describes the synthesis of C_3-symmetric metacyclophane-based anion receptors with three thiourea groups and their binding properties toward various anions in polar organic media.

We chose **1**[5] as a novel framework for anion receptors. Compound **1** can be envisioned as a hexahomooxacalix[3]arene[6] analog: six oxygens used for metal ion complexation[6b] are replaced

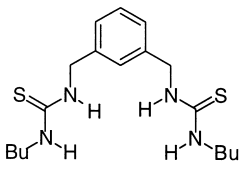
* Corresponding author. Tel: +82-2-880-6682; fax: +82-2-889-1568; e-mail: jihong@plaza.snu.ac.kr

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00966-7

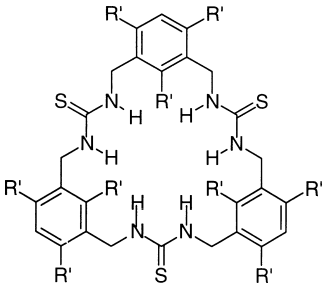
with three thiourea groups as hydrogen bond donors for anion binding; their conformational flexibility is similar.



hexahomooxacalix[3]arenes



Acyclic bis(thiourea)



1 (R' = H)
2 (R' = Et)

The judicious molecular design of artificial receptors starting from the basic skeleton of **1** is expected to lead to a very active area of anion recognition. We wanted to orient thiourea NH protons toward the macrocyclic cavity for effective anion binding. However, MM2 calculations on **1** indicate that low energy conformations within the 3 kcal/mol window are not preorganized for binding to anionic guests inside the macrocyclic cavity.[7] One way to reduce the reorganization costs of complexation and thus enhance the binding efficiency is to exploit nonbonded, conformational locking interactions.[8] The design principle comes from the conformation of hexaethylbenzene; avoidance of nonbonded interactions of the adjacent methylene hydrogens assures that the β groups alternate above (*a*) and below (*b*) the ring in a trigonally symmetric conformation (*ababab*).[2f,9] We thought that placing three ethyl groups on the 2, 4 and 6 positions of the aromatic spacer of **1** would give rise to conformationally less flexible **2**. This design would result in orienting the six thiourea NH groups of **2** preferentially toward the inner side of the bowl-shaped macrocycle. Indeed, conformational searching of **2** confirms the expected cone conformation of all conformers within the 3 kcal/mol window of the lowest energy conformer in which a cavity is formed by six inwardly predisposed NH groups for anion binding (Fig. 1).[7] Modeling also suggests that intramolecular hydrogen bonding between these groups is clearly

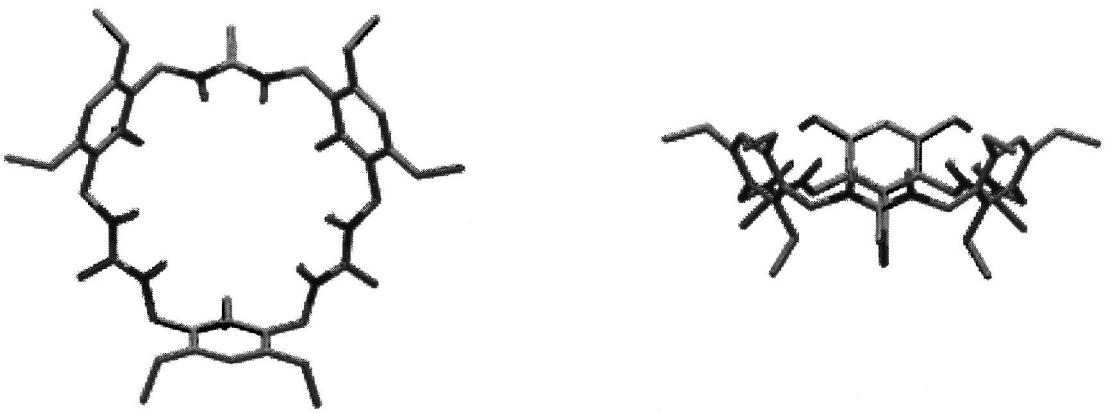
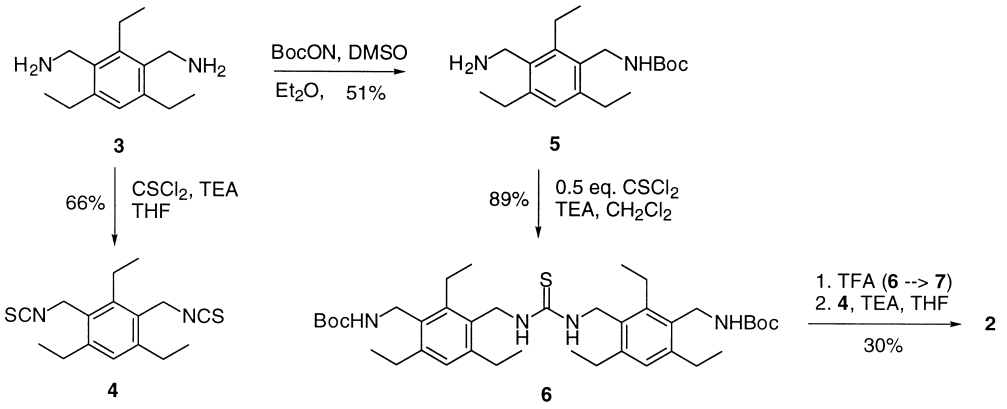


Figure 1. The energy-minimized structure of **2** (left: top view, right: side view). Hydrogens except NHs have been omitted for clarity.

impossible. A binding cavity formed by *meta*-substituted aromatics may function as a hydrophobic pocket for the nonpolar part of a substrate. From these structural features, the designed C_3 host **2** could act as an effective binder for various shapes of anions and polyatomic substrates.

The known compound **1** was prepared according to a published procedure.[5] Compound **2**[10] was obtained from 1,3-bis(aminomethyl)-2,4,6-triethylbenzene (**3**) in four steps, as shown in Scheme 1.



Scheme 1.

The bridging methylene protons (–C*H*$_2$–NHCSNH–) appearing as a broad singlet at 4.66 ppm at 30°C were split into two signals at 4.99 and 4.21 ppm at 0°C, exhibiting a large geminal coupling of 13.4 Hz at –25°C, which indicates a cone-shaped conformer as expected from conformational searching.

Addition of the tetrabutylammonium salts of anions to **1** or **2** in $CDCl_3$ and DMSO-d_6 caused substantial downfield shifts of the NH resonances in the ^{1}H NMR spectra, indicating the formation of hydrogen-bonded complexes. Aromatic proton signals of **2** experienced upfield shifts upon complexation with anions, indicating that anions should be surrounded by aromatic rings. Additionally, the bridging benzylic protons became diastereotopic (AcO^-, $\Delta\delta = 0.14$ ppm; $H_2PO_4^-$, $\Delta\delta = 0.33$ ppm; Br^-, $\Delta\delta = 0.45$ ppm: N_3^-, $\Delta\delta = 0.37$ ppm) after addition of 1 equiv. anions in $CDCl_3$, suggesting the formation of a conformationally rigid 1:1 complex with a cone conformation.

A Job titration[11] between **1** and $H_2PO_4^-$ conducted in DMSO-d_6 showed that the maximum signal change was observed at 0.5 mol fraction of **1**, indicative of 1:1 complex formation. Analysis of the ^{1}H NMR titration data gave the binding constants listed in Table 1. Compound **1** showed binding selectivities in the order $H_2PO_4^- > AcO^- > Cl^-$ in DMSO-d_6. In spite of the less basic character of $H_2PO_4^-$ compared to AcO^-, $H_2PO_4^-$ showed stronger binding to **1** than did acetate. The binding tendency of **1** for anions is similar to that of acyclic[3c] or cyclic thioureas.[3e,f] This means that although **1** has a macrocyclic structure, it seems to have a similar local conformation to acyclic 1,3-bis(thioureido)methylbenzene.[3c] Thus, we believe that the favorable binding of **1** toward $H_2PO_4^-$ can be rationalized based on the complex geometry[3c] and different solvation effects of anions by DMSO.[3f] In contrast, compound **2** showed binding selectivities in the order $AcO^- > H_2PO_4^- > Cl^- > N_3^- > Br^-$ in DMSO-d_6. Compound **2** exhibited good selectivity for AcO^- compared with $H_2PO_4^-$, which bound to **1** with a higher affinity. We assume the main reason is the different basicity between AcO^- and $H_2PO_4^-$: pK_a (AcOH) = 4.76, pK_a (H_3PO_4) = 2.16 (H_2O

Table 1
Association constants (K_a, M^{-1}) of **1** and **2** with anions in DMSO-d_6 at 25°C[a]

	1[b]	**2**[c]	acyclic bis(thiourea)[d]
$H_2PO_4^-$	800	1600	820
AcO^-	320	5300	470
Cl^-	40	95	9
N_3^-	ND[e]	30	
Br^-	ND[e]	11	

[a] Guest anions are added as their tetrabutylammonium salts except for Cl^-, which was used as tetraethylammonium salt. [**1**] = [**2**] = 3 mM in DMSO-d_6, [anion] = 35~150 mM in DMSO-d_6. [b] NH of **1** was monitored in DMSO-d_6, [c] NH and ArH of **2** were monitored in DMSO-d_6. [d] reference 3c. [e] No detectable change of ^{1}H NMR chemical shifts.

at 25°C, $I = 0$).[12] Compared to **1**, compound **2** shows a twofold increase in binding affinity for $H_2PO_4^-$ and Cl^-, and a notable 17-fold increase for AcO^- in DMSO-d_6. The higher binding affinities of **2** to anions would result from the preorganized NH groups of **2** for anion binding.

Interactions of **2** with AcO^- or $H_2PO_4^-$ were examined using the MacroModel/Batchmin V5.5 package.[7] The global minimum structures clearly demonstrate the hydrogen bonding between thiourea NHs and AcO^- oxygens or $H_2PO_4^-$ oxygens.

In summary, we have developed novel anion-binding agents (**1**, **2**) based on the C_3-symmetric metacyclophane structure with three thiourea groups as linkers between aromatic groups. The cooperative action of thiourea NHs as hydrogen bond donors toward guest anions was achieved by placing three ethyl groups on the 2, 4 and 6 positions of the aromatic spacer of **1**. Compound **2**, with three convergent thiourea groups pointing toward the binding cavity, showed increased binding affinities to anions and selective binding to AcO^- compared to conformationally more flexible **1**, which exhibited selective binding to $H_2PO_4^-$ in DMSO-d_6. Introducing other binding elements to the aromatic spacer would facilitate the rational design of more effective and selective anionophores.

Acknowledgements

This study was supported by a grant (No. HMP-97-D-4-0014) of the '97 Good Health R&D Project, Ministry of Health & Welfare and CMDS (KOSEF). K.H.L. thanks the Ministry of Education for the BK 21 postdoctoral fellowship.

References

1. (a) Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamv, J. D.; Christensen, J. J.; Sen, D. *Chem. Rev.* **1985**. *85*, 271. (b) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721. (c) Pedersen, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1021. (d) Cram, D. J.; Cram, J. M. *Science* **1974**, *183*, 803–809.
2. (a) Tabushi, I.; Kobuke, Y.; Imuta, J. *J. Am. Chem. Soc.* **1981**, *103*, 6152–6157. (b) Kuroda, Y.; Hatakeyama, H.; Seshimo, H.; Ogoshi, H. *Supramol. Chem.* **1994**, *3*, 267–271. (c) Schneider, H.-J.; Blatter, T.; Palm, B.; Pfingstag, U.; Rudiger, V.; Theis, L. *J. Am. Chem. Soc.* **1992**, *114*, 7704–7708. (d) Kral, V.; Furuta, H.; Shreder, K.; Lynch, V.; Sessler, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 1595–1607. (e) Jubian, V.; Veronese, A.; Dixon, R. P.; Hamilton,

A. D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1237–1239. (f) Metzger, A.; Lynch, V. M.; Anslyn, E. V. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 862–865. (g) Yeo, W.-S.; Hong, J.-I. *Tetrahedron Lett.* **1998**, *39*, 8137–8140. (h) Jung, Y.-G.; Yeo, W.-S.; Lee, S. B.; Hong, J.-I. *Chem. Commun.* **1997**, 1061–1062. (i) Ahn, D.-R.; Kim, T. W.; Hong, J.-I. *Tetrahedron Lett.* **1999**, *40*, 6045–6048.

3. (a) Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369–370. (b) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072–7080. (c) Nishizawa, S.; Bühlmann, P.; Iwao, M.; Umezawa, Y. *Tetrahedron Lett.* **1995**, *36*, 6483–6486. (d) Bühlmann, P.; Nishizawa, S.; Xiao, K. P.; Umezawa, Y. *Tetrahedron* **1997**, *53*, 1647–1654. (e) Tobe, Y.; Sasaki, S.; Mizuno, M.; Naemura, K. *Chem. Lett.* **1998**, *8,* 835. (f) Sasaki, S.-I.; Mizuno, M.; Naemura, K.; Tobe, Y. *J. Org. Chem.* **2000***, 65*, 275–283. (g) Scheerder, J.; Engbersen, J. F. J.; Casnati, A.; Ungaro, R.; Reinhoudt, D. N. *J. Org. Chem.* **1995***, 60*, 6448–6454. (h) Xie, H.; Yi, S.; Wu, S. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2751–2754.
4. (a) Rudkevich, D. M.; Verboom, W.; Brzozka, Z.; Palys, M. J.; Stauthamer, W. P. R. V.; van Hummel, G. J.; Franken, S. M.; Harkema, S.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, *116*, 4341–4351. (b) Eliseev, A. V.; Schneider, H.-J. *J. Chem. Soc., Chem. Commun.* **1993**, 1834–1836.
5. Gross, R.; Dürner, G.; Göbel, M. W. *Liebigs Ann. Chem.* **1994**, 49.
6. (a) Dhawan, B.; Gutsche, C. D. *J. Org. Chem.* **1983**, *48*, 1536. (b) Daitch, C. E.; Hampton, P. D.; Duesler, E. N.; Alam, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 7769–7773. (c) Tsubaki, K.; Otsubo, T.; Tanaka, K.; Fuji, K. *J. Org. Chem.* **1998**, *63*, 3260–3265.
7. MacroModel/Batchmin V5.5, employing Amber* and MM2* force-fields with GB/SA chloroform solvation model. See: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.
8. Iimori, T.; Still, W. C.; Rheingold, A. L.; Staley, D. L. *J. Am. Chem. Soc.* **1989**, *111*, 3439–3440.
9. (a) Iverson, D. J.; Hunter, G.; Blount, J. F.; Damewood, J. R.; Mislow, K. *J. Am. Chem. Soc.* **1981**, *103*, 6073–6083. (b) Stack, T. D. P.; Weigel, J. A.; Holm, R. H. *Inorg. Chem. Soc.* **1990**, *29*, 3745–3760. (c) Stack, T. D. P.; Hou, Z.; Raymond, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 6466–6467.
10. Compound **2**: mp 260–261°C; IR (KBr) 3742, 3434, 3225, 3051, 2965, 1691, 1645, 1531, 1337, 1262 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.89 (s, 3H), 4.98 (s, 6H), 4.67 (s, 12H), 2.65–2.60 (m, 18H), 1.20–1.16 (m, 27H); ^1H NMR (300 MHz, DMSO-d_6) δ 7.00 (s, 6H), 6.92 (s, 3H), 4.68 (s, 12H), 2.61–2.53 (m, 18H), 1.15–1.03 (m, 27H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.9, 143.6, 143.1, 131.5, 121.9, 41.8, 39.6, 26.3, 22.5, 16.2, 15.9; FAB-MS (*m*-NBA) *m*/*z* 787 (M^++H), FAB-HRMS (*m*-NBA) calcd for $C_{45}H_{67}N_6S_3$ $[M+H]^+$ 787.4589, found 787.4589. Compound **3**: IR (KBr) 3283, 2965, 2094, 1571, 1458, 1374, 1297 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 1H), 3.88 (s, 4H), 2.85 (q, $J=6$ Hz, 2H), 2.72 (q, $J=7.8$ Hz, 4H), 1.25 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 141.0, 136.5, 127.7, 39.3, 26.2, 22.4, 17.0, 16.2; EI-MS *m*/*z* 186, 203(M^+–NH_3); HRMS calcd for $C_{14}H_{21}N_1$ $[M–NH_3]^+$ 203.1674, found 203.1681. Compound **4**: mp: 42–44°C; IR (KBr) 2968, 2160, 2076, 1459, 1332 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (s, 1H), 4.72 (s, 4H), 2.81 (q, $J=7.8$Hz, 2H), 2.73 (q, $J=7.5$Hz, 4H), 1.26 (m, 9H); ^{13}C NMR (75 MHz $CDCl_3$) δ 144.6, 142.5, 131.3, 128.5, 128.2, 42.6, 26.5, 23.0, 16.3, 15.7; EI-MS *m*/*z* 304 (M^+); HRMS calcd for $C_{16}H_{20}N_2S_2$ $[M]^+$ 304.1607, found 304.1061. Compound **5**: mp 49–51°C; IR (KBr) 3355, 3289, 3177, 2968, 1690, 1533, 1364, 1277, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (s, 1H), 4.86 (broad, 1H), 4.30 (d, $J=4.4$ Hz, 2H), 3.81 (s, 2H), 2.77–2.58 (m, 6H), 1.40 (s, 9H), 1.22–1.13 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 142.9, 142.7, 142.1, 136.2, 131.2, 127.6, 79.3, 50.1, 38.9, 38.3, 28.4, 26.1, 22.4, 16.8, 16.2, 16.0; EI-MS *m*/*z* 303 (M^+–NH_3); HRMS calcd for $C_{19}H_{29}N_1O_2$ $[M–NH_3]^+$ 303.2198, found 303.2200. Compound **6**: mp 172–173°C; IR (KBr) 3660, 2969, 1686, 1516, 1361, 1250, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (s, 2H), 5.96 (s, 2H), 4.64 (broad, 4H), 4.43 (s, 2H), 4.04 (s, broad, 4H), 2.68–2.54 (m, 18H), 1.27(s, 18H), 1.21–1.14 (m, 18H); ^{13}C NMR (75 MHz $CDCl_3$) δ 181.6, 155.5, 144.2, 143.6, 131.5, 130.4, 127.9, 42.9, 18.4, 28.4, 26.4, 26.2, 22.8, 16.8, 16.1, 16.0; FAB-MS *m*/*z* 682 (M^+); FAB-HRMS calcd for $C_{39}H_{62}N_4O_4S$ $[M]^+$ 682.4492, found 682.4492. Compound **7**: mp 170–171°C; IR (KBr) 3583, 3960, 1675, 1200, 1137 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.19 (s, 6H), 7.18 (s, 2H), 7.03 (s, 2H), 4.63 (s, 4H), 4.03 (s, 4H), 2.74–2.58 (m, 6H), 1.17–1.06 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.7, 158.2, 144.7, 143.7, 143.1, 131.5, 127.5, 127.1, 41.8, 37.5, 25.7, 25.3, 22.3, 16.2, 15.8, 15.3; EI-MS *m*/*z* 482 $[M–2CF_3COO]^+$. HRMS calcd for $C_{29}H_{46}N_4S$ $[M–2CF_3COO]^+$ 482.3443, found 482.3440.
11. Conners, K. A. *Binding Constants*, 1st ed.; John Wiley: New York, 1987; pp. 24–28.
12. Lide, D. R. *CRC Handbook of Chemistry and Physics*; CRC Press: Cleveland, OH, 1994.