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# Polymethylene-bridged Cystine–Glycine-containing Cyclopeptides as Hydrogen-bonding Electroneutral Anion Receptors: Design, Synthesis, and Halide Ion Recognition

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**Two conformationally constrained polymethylene-bridged cystine–glycine-based cyclopeptides (3 and 5) were synthesized as hydrogen-bonding electroneutral anion receptors by the conventional solution method. Both solution conformation and NMR titration studies showed that cyclopeptide 3 was an efficient receptor for selective recognition of halide ions, whereas cyclopeptide 5 failed to bind any halide ion.**

*Keywords*: Pseudo-cyclopeptides; Electroneutral receptor; Halide ions; Recognition

Host–guest complexation is widely observed in many biological processes such as ion transfer, enzyme catalysis and enzyme inhibition [1]. In past years, numerous artificial receptors for cationic species have been explored, and consequently cation recognition is now a well-developed area in supramolecular chemistry. By contrast, the recognition of anions, despite their very important roles in chemistry, environment science and biology, has received scant attention until recently [2–5]. Considering the intense activity and the literature that has accumulated over the past two decades in the field of supramolecular chemistry, it is surprising to find only a handful of designs for cyclic anion receptors and even fewer for neutral cyclic anion hosts [6–8]. Most of the anion hosts studied are primarily protonated mono- or polycyclic amines [9–11]. These positively charged anion receptors operate mainly through electrostatic forces, and sometimes together with $N^+—H\cdots X^-$ hydrogen bonds. However, in nature, it is the neutral anion-binding proteins composed of L-amino acid residues that regulate the transport of anions, and the interactions are largely through hydrogen bonds [12–14]. In this connection, the idea of using amino acid-based macrocycles with multiple hydrogen-bonding functions appears to be an exciting possibility to create neutral receptors that would not only be close to natural systems but also show good selectivity in multifunctional anion complexation. In this respect, it is noted that so far only a few amino acid-based cyclic oligoureas and cyclophanes have been reported as artificial anion receptors in the literature [15–17].

Following our recent findings on the binding properties of conformationally constrained cyclopeptides [18–20], here we report the synthesis and anion recognition study of two cystine–glycine-containing pseudo-cyclopeptides (**3** and **5**, Scheme 1), in which the multiple amide groups are expected to play important roles in anion recognition. The choice of cystine residue was based on the consideration that the presence of S—S linkage and the **1**, ω-diamine moieties would facilitate formation of the cyclic structure. To avoid the possible racemization in synthesis, the achiral glycine was used as another starting material. In view of the molecular symmetry, adipoyl chloride was used as the final ring closure element.

The synthesis of cyclopeptides **3** and **5** was carried out by conventional solution methods with a *tert*-butyloxycarbonyl (Boc) group to protect the amino group, a methyl ester to protect the carboxyl group,

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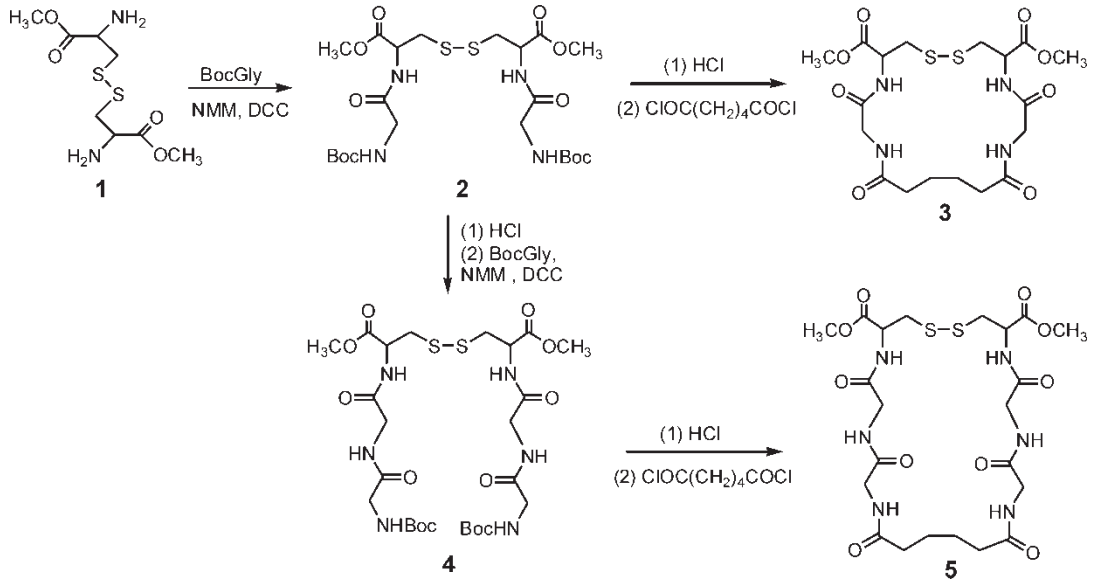


SCHEME 1 Synthesis of cystine–glycine-containing pseudo-cyclopeptides **3** and **5** (NMM = *N*-methylmorphine).



and 1,3-dicyclohexylcarbodiimide (DCC) as the coupling reagent (Scheme 1). Reaction of C-protected cystine **1** with Boc-glycine provided bis-glycine-cystine peptide **2**. After removal of the Boc group with HCl/AcOEt, the diamine was reacted with adipoyl chloride in very dilute $CH_2Cl_2$ to yield cyclopeptide **3** through [1 + 1] cyclization in good yield. The above diamine was further reacted with Boc-glycine to yield bis(glycineglycine)–cystine peptide **4**. Finally, deprotection of **4** and then condensation with adipoyl chloride afforded cyclopeptide **5** through [1 + 1] cyclization. These products were identified by IR, $^1$H NMR, and FAB-MS.[†]

The solution-state conformation of cyclopeptides **3** and **5** was analysed by $^1$H NMR, FT-IR and 2D NMR studies (NOESY, Fig. 1, NOE interactions are shown as cross-links). The presence of only a single set of resonance for the cystine, glycine and adipoyl units in the $^1$H NMR spectra of **3**, **5** indicates the highly $C_2$ symmetrical nature of the macrocycles. In the NOESY NMR spectrum of **3** (Fig. 1a), strong cross-peaks were observed both between Cys NH and Cys $C^{\alpha}H$, $C^{\beta}H$ and between Gly NH and $C^{\alpha}H$, $C^{\beta}H$ of the adipoyl unit, indicating that all amide NHs were oriented into the interior of the ring. Meanwhile, the observation also suggests that no intramolecular hydrogen bonds are formed, which is further supported by the FT-IR spectrum in $CDCl_3$, wherein two types of non-H-bonded, free amide N–H stretches are shown at 3684 $cm^{-1}$ and 3621 $cm^{-1}$, respectively. The $C_2$ symmetrical structure of **3**, having four hydrogen-bonding amide functions with NHs orienting inward (Fig. 2a), appears to be suitable for the molecular recognition of anionic substrates with spherical shapes, such as halide ions. However, for **5**, apart from similar NOE interactions of Cys NHs and Gly NHs to adjacent CH, the cross-peaks between Gly NHs and adjacent Gly $C^{\alpha}H$ were also observed (Fig. 1b), indicating Gly NHs, adjacent to the cystine unit, orient outwards, and Gly carbonyl, adjacent to the adipoyl unit, orients inwards (Fig. 2b). Obviously, this conformation is unfavourable for anion recognition due to the electrostatic repulsion of the two carbonyl O atoms with the anion.

The NMR titration method [21] is known to be very useful in binding constant determinations for anion-host complexes, and so it was applied in the present work. Addition of halide ions [as tetrabutyl-ammonium (TBA) salts] to the $CDCl_3$ solution of **3** ($1.3 \times 10^{-2}$ $M^{-1}$, 20°C) resulted in a considerable downfield shift of all NH protons, indicating effective host–guest recognition involving N–H$\cdots X^-$ hydrogen-bonding interactions. Interestingly, compound **3**, only sparingly soluble in $CDCl_3$, was found to go rapidly into solution following the addition of

[†]**3**: Yield 35(; mp 169–173°C; $^1$H NMR $\delta$ (300 MHz, DMSO-$d_6$), 8.36 (d, 2H, $J$ = 8.1, Cys NH), 8.06 (t, 2H, Gly NH), 4.62 (m, 2H, Cys $H^{\alpha}$), 3.77 (t, 4H, Gly $H^{\alpha}$), 3.65 (s, 6H, Cys $OCH_3$), 3.06 (m, 4H, Cys $H^{\beta}$), 2.17 (br, 4H, $CH_2$), 1.56 (br, 4H, $CH_2$); FT-IR (KBr, $cm^{-1}$), 3262, 1740, 1648; FAB-MS ($m/z$): 493 $[M + 1]^+$. **5**: Yield 8(; mp 173–177°C; $^1$H NMR $\delta$ (300 MHz, DMSO-$d_6$), 8.36 (d, 2H, $J$ = 8.4, Cys NH), 8.19 (t, 2H, Gly NH), 8.14 (t, 2H, Gly NH), 4.61 (t, 2H, Cys $H^{\alpha}$), 3.76 (t, 4H, Gly $H^{\alpha}$), 3.68 (t, 4H, Gly $H^{\alpha}$), 3.65 (s, 6H, Cys $OCH_3$), 3.01 (m, 4H, Cys $H^{\beta}$), 2.15 (br, 4H, $CH_2$), 1.54 (br, 4H, $CH_2$); FT-IR (KBr, $cm^{-1}$), 3257, 1747, 1640; FAB-MS ($m/z$): 607 $[M + 1]^+$.

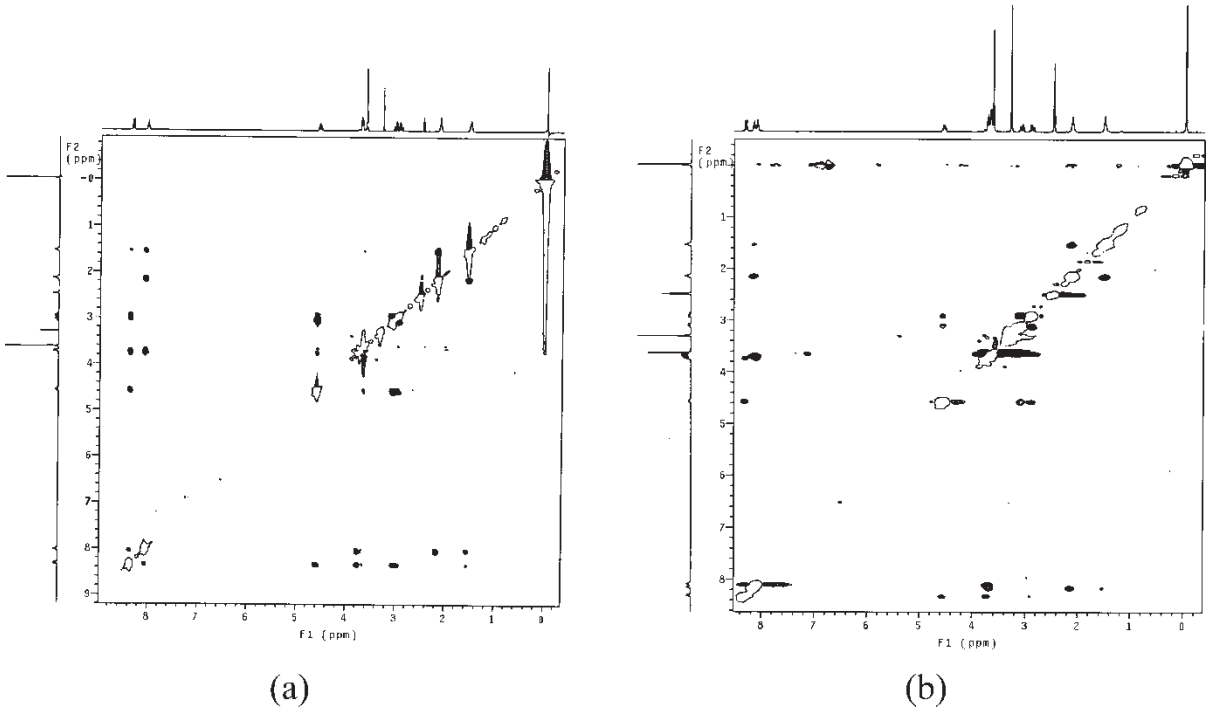


FIGURE 1 NOESY spectra of cyclopeptides **3** (a) and **5** (b).

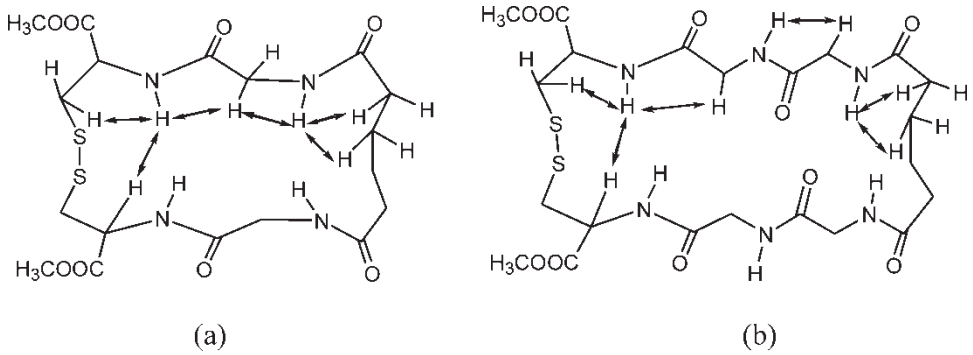


FIGURE 2 Solution conformations of cyclopeptides **3** (a) and **5** (b). NOE interactions are indicated by double-headed arrows.

halide TBA salts, further indicating the host–guest recognition. Figure 3a shows the $^1$H NMR change caused by addition of $Et_4N^+Cl^-$ to the $CDCl_3$ solution of **3**, which revealed significantly large downfield shifts once $Et_4N^+Cl^-$ was added. Further addition resulted in saturation of the chemical shift changes. The Job plot (Fig. 3b) is symmetrical and shows a maximum at a mole ratio of 0.5 of $[Cl^-]$ and $[Cl^-] + [\mathbf{3}]$, suggesting that the receptor **3** forms 1:1 stoichiometric complexes with the chloride ion [22]. Similar situations were also observed for other halide ions.

Binding studies[‡] with halide ions showed that although macrocycle **3** showed good affinity with $F^-$, $Cl^-$ and $Br^-$ and low affinity with $I^-$, macrocycle **5** failed to bind any of the halide ions. Macrocycle **5** is too insoluble in $CDCl_3$, and no $^1$H NMR signals were observed. The addition of a large amount of TBA salt did not improve its solubility, indicating the strong self-aggregation in $CDCl_3$ through intermolecular hydrogen bonds. Although macrocycle **5** is soluble in DMSO, no chemical shift change was observed even if a large amount of TBA salt was added. This is consistent with the above solution conformation analysis. The association constant ($K_a$) for **3** with $F^-$, $Cl^-$, $Br^-$ and $I^-$ TBA salts was measured as shown in Table I. It is noteworthy that the best binding was

[‡]The association constant ($K_a$) was obtained by using the following equation: $K_a = \alpha\{(1-\alpha)([G]-\alpha[H])\}$, where i$\alpha = (\delta - \delta_0)/(\delta_{max} - \delta_0)$, $\delta_0$ is the initial chemical shift (host alone), $\delta$ is the chemical shift at each titration point, and $\delta_{max}$ is the chemical shift when the receptor is entirely bound. [G] and [H] are the concentrations of guest and host, respectively, at each titration point (see [9]).

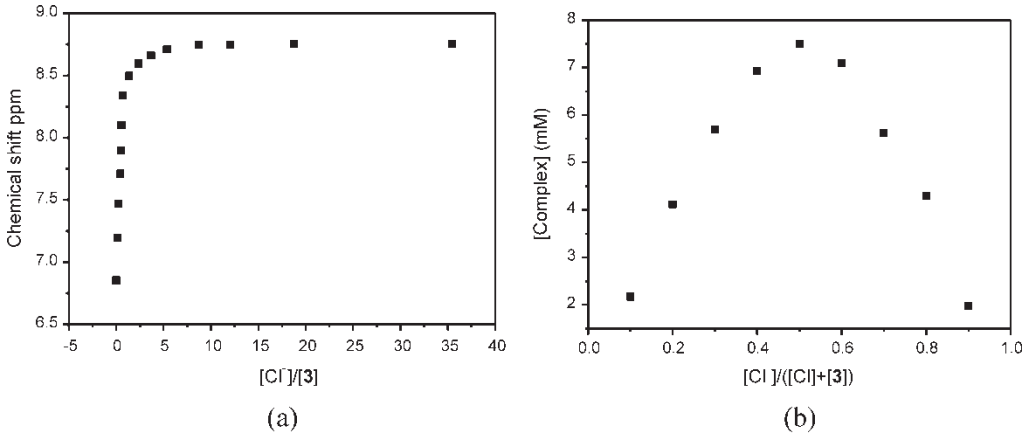


FIGURE 3 (a) Changes in the $^1$H NMR chemical shift of the Cys NH protons on the cyclopeptide **3** observed in the presence of varying mole ratios of $TBA^+Cl^-$ in $CDCl_3$. (b) Job plots showing that a 1:1 complex is formed.

TABLE I Association constants ($K_a$) and binding free energies ($\Delta G^o$) for 1:1 complexes of receptors **3** with halide ions in $CDCl_3$ at 298 K

| | $F^-$ | $Cl^-$ | $Br^-$ | $I^-$ |
|---|---|---|---|---|
| $K_a$ ($dm^3\,mol^{-1}$)* | $4.44\times10^2$ | $9.91\times10^2$ | $1.91\times10^2$ | 80 |
| $\Delta G^o_{298}$ ($kcal\,mol^{-1}$) | −3.59 | −4.07 | −3.09 | −2.58 |

*Errors are estimated to be <10%.

found with $Cl^-$ ($K_a = 9.91\times10^2\,m^{-1}$), with values 2, 5 and 12 times that for $F^-$, $Br^-$ and $I^-$, respectively, indicating that besides hydrogen bonds, there are still other factors to influence the binding. Interestingly, the result is contrary to our previous report on a pyridine-bearing cyclopeptide with a 25-membered ring, wherein $Cl^-$ was shown to have lower binding than $F^-$ and $Br^-$ [20]. The ring size of **3**, a 20-membered ring, may play an important role in $Cl^-$ recognition.

In summary, we have designed and synthesized two polymethylene-bridged cystine–glycine-based cyclopeptides **3** and **5**, and found that cyclopeptide **3** is an efficient receptor for selective recognition of halide ions, whereas cyclopeptide **5** failed to bind any halide ion.

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## *References*

[1] Dugas, H. *Bioorganic Chemistry;*, 3rd Ed. Springer-Verlag: New York, 1996.
[2] Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486–516.
[3] Gale, P. A. *Coord. Chem. Rev.* **2001**, *213*, 79–128.
[4] Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609–1646.
[5] Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, Germany, 1995.
[6] Bisson, A. P.; Lynch, V. M.; Monahan, M. K. C.; Anslyn, E. V. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2340–2342.
[7] Gale, P. A.; Sesser, J. L.; Kral, V.; Lynch, V. J. *Am. Chem. Soc.* **1996**, *118*, 5140–5141.
[8] Kelly-Rowley, A. M.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **1995**, *117*, 3438–3447.
[9] Hosseini, M. W.; Lehn, J.-M. *Helv. Chim. Acta* **1988**, *71*, 749–756.
[10] Hosseini, M. W.; Lehn, J.-M. *J. Am. Chem. Soc.* **1982**, *104*, 3525–3527.
[11] Kimura, E.; Sakonaka, A.; Yatsunami, T.; Kodama, M. *J. Am. Chem. Soc.* **1981**, *103*, 3041–3045.
[12] He, J. J.; Quiocho, F. A. *Science* **1991**, *251*, 1479–1481.
[13] Kanyo, Z. F.; Christianson, D. W. *J. Biol. Chem.* **1991**, *266*, 4246–4250.
[14] Luecke, H.; Quiocho, F. A. *Nature* **1990**, *347*, 402–406.
[15] Ranganathan, D.; Lakshmi, C.; Karle, I. L. *J. Am. Chem. Soc.* **1999**, *121*, 6103–6107.
[16] Ranganathan, D.; Lakshmi, C. *Chem. Commun.* **2001**, 1250–1251.
[17] Ranganathan, D.; Haridas, V.; Karkle, I. L. *J. Am. Chem. Soc.* **1998**, *120*, 2695–2702.
[18] Mu, L.; Cheng, J.-P.; Huang, H.; Lu, J.; Hu, X. *Synth. Commun.* **1998**, *28*, 3091–3096.
[19] Hu, X.; Chan, A. S. C.; Han, X.; He, J.; Cheng, J.-P. *Tetrahedron Lett.* **1999**, *40*, 7115–7118.
[20] Huang, H.; Mu, L.; He, J.; Cheng, J.-P. *Tetrahedron Lett.* **2002**, *43*, 2255–2258.
[21] Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072–7080, and references therein.
[22] Snellink-Ruël, B. H. M.; Antonisse, M. M. G.; Engbersen, J. F. J.; Timmerman, P.; Reinhoudt, D. N. *Eur. J. Org. Chem.* **2000**, 165–170.