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# Effective receptors for fluoride and acetate ions: synthesis and binding study of pyrrole- and cystine-based cyclopeptido-mimetics

Yanhua Zhang,[a] Zhenming Yin,[a,b] Jiaqi He[a] and Jin-Pei Cheng[a,*]

[a]*Department of Chemistry, State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China*
[b]*College of Chemistry and Life Science, Tianjin Normal University, Tianjin 300074, China*

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**Abstract**—Two conformationally constrained pseudo-cyclopeptides (**1**, **2**) consisting of pyrrole-, pyridine-, and cystine-moieties were designed and synthesized as neutral receptors for anionic guests. The anion recognition abilities of these two receptors were examined photometrically in acetonitrile solution. The UV–vis study revealed that the [1+1] receptor (**1**) formed 1:1 complexes with anions, whereas the [2+2] receptor (**2**) led to 1:2 mode binding with anions. Both receptors displayed good affinity and selectivity for fluoride and acetate ions.


Anion recognition has recently become a hot theme in supramolecular chemistry due primarily to its important roles in life sciences and in many medical and environmental settings.[1] A number of neutral receptors containing amide,[2] urea/thiourea,[3] or pyrrole[4] groups were developed by virtue of their H-bonding capacity of the N-residing electron pairs. Amongst them, cyclic peptide should be of particular interest because it belongs to a family of natural macrocycles that are well-known for their importance in life processes and are expected to provide more relevant understandings on related functions.[5] In this connection, several anion recognition studies were reported recently. Ranganathan et al. found that the aromatic-bridged cystine-containing pseudo-cyclopeptide was an effective receptor for l,ω-alkane dicarboxylates.[6] Kubik et al. showed that the L-proline and 6-aminopicolinic acid-based cyclopeptide mimics were able to bind halides and sulfate in aqueous mixture.[7] Ungaro and co-workers observed that peptidocalix[4]arene can bind well with carboxylates.[8] Yang and Wu developed a class of cyclic hexapeptides that showed binding preference for chloride ion.[9] In our earlier work, we found that calix[4]arene-based cyclopeptides can effectively bind with *p*-nitrophenyl phosphate and a cystine-based pseudo-cyclopeptide is a good amphi-binding receptor.[10]

Despite these remarkable achievements, development of neutral receptors of anions is realized to be quite slow compared to the ocean of literature works on cation recognition. Thus, design of conformational constrained models capable of effective and selective binding of anions remains to be highly significant. In the present work, we designed and obtained two new constrained peptidomimetics by jointly incorporating three conformational rigid structures such as pyrrole, cystine, and pyridine motifs into the macrocyclic backbone. We found that the produced [1+1] type and [2+2] type pseudo-cyclopeptides (**1** and **2**) were very good anion receptors with special preference in binding with fluoride and acetate ions in polar solvent such as acetonitrile.

The synthesis of compounds **1** and **2** is outlined in Scheme 1. Catalytic hydrogenation of oxime **3**[11] with Pd/C in the presence of hydrochloric acid yielded amine **4**, which was then N-protected with di-*tert*-butyl-dicarbonate ($Boc_2O$) under basic conditions and followed by saponification to afford amino acid **5**. Condensation of 1 equiv of L-cystine dimethyl ester and 2 equiv of **5** by *N*,*N*′-dicyclohexylcarbodiimide (DCC) in the presence of 4-dimethylaminopyridine (DMAP) generated linear peptide **6**. The macrocyclic receptors **1** and **2** were obtained by the reaction of N-deprotected peptide **6**

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* Corresponding author. E-mail: chengjp@most.cn

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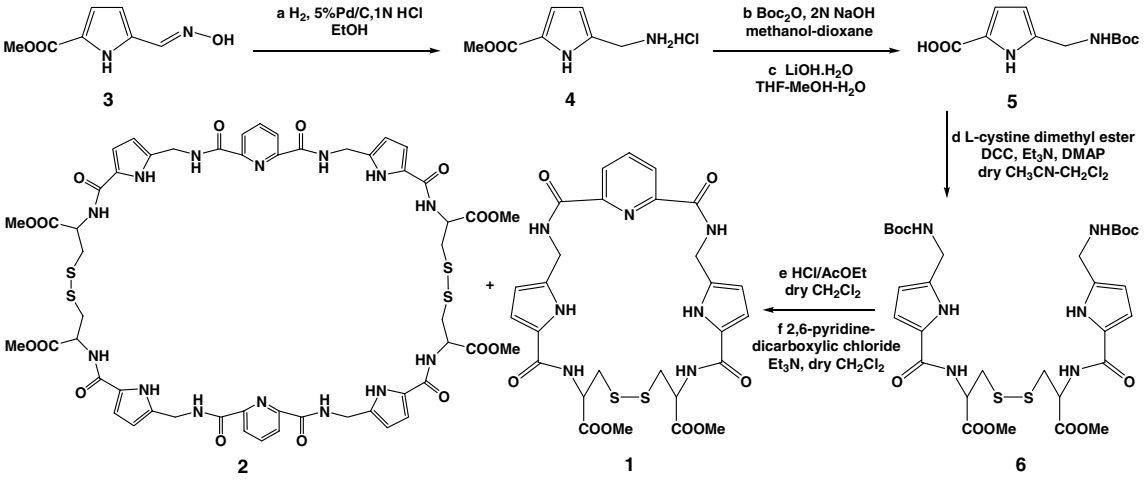


**Scheme 1.** Synthetic routes to target compounds **1** and **2**.

with 2,6-pyridine dicarboxylic chloride in the presence of triethylamine in dry dichloromethane under highly diluted conditions. The crude products were then purified by column chromatography.[12]

Preliminary examination of anion binding properties of **1** and **2** were conducted in DMSO-$d_6$ first by $^1$H NMR method. Significant weakening and downfield shifting of the NH signals were observed upon addition of small aliquots of $F^-$ or $AcO^-$ solution. When excess amount of anions was added, the NH signals disappeared completely. This indicated that receptors **1** and **2** bind very effectively with these anions and that the binding should be resulted from hydrogen bonding interactions.

For a more precise evaluation of the binding constants of receptors **1** and **2** with anionic guests, UV–vis titrations were carried out in acetonitrile.[13] The UV–vis absorption changes of receptor **1** upon aliquot additions of fluoride ion are shown in Figure 1. The absorption peak at 266 nm was observed to decrease rapidly to its limiting value with a small red shift when 1 equiv fluoride was added. No further change of UV–vis spectrum was detected when fluoride ion was added in excess. This kind of titration curve suggests the formation of a 1:1 type complex between **1** and the fluoride ion. A similar pattern of spectrum change was observed when $AcO^-$ was added. In comparison, in the case of $Cl^-$, the UV spectrum of **1** corresponded relatively slowly and also to a less magnitude when the anion was added, indicating that receptor **1** can bind, but less efficiently, with the chloride ion. On the other hand, no obvious change could be found when $Br^-$ ion was added in excess. This is probably due to the differences in their size and H-bonding effect, or the combination of the two. The large UV–vis spectrum changes obtained upon additions of $F^-$ and $AcO^-$ are understandable because the negative charges on these anions are more centralized and both the $F^-$ and $AcO^-$ ions have better hydrogen bond-

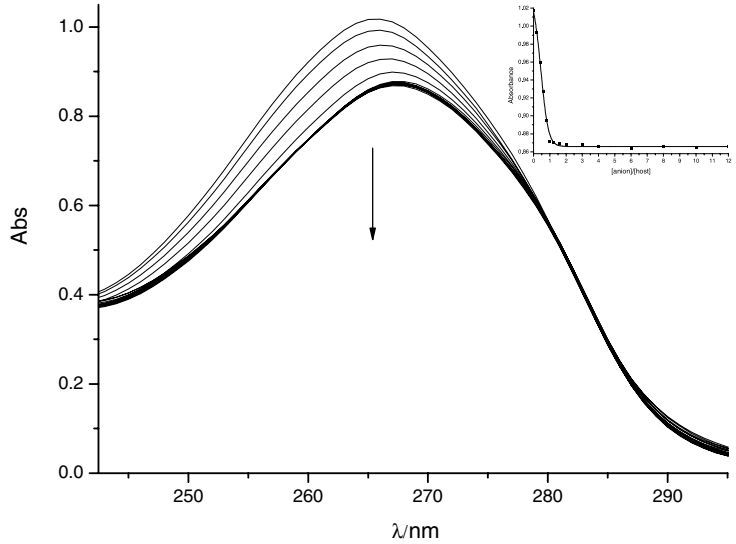


**Figure 1.** The UV–vis spectrum changes of receptor **1** ($2.5 \times 10^{-5}$ M) upon addition of fluoride (equiv of anion: 0, 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.6, 2, 3, 4, 6, 8, 10, and 12) in $CH_3CN$. Inset: UV–vis spectra titration curve of receptor **1** with $F^-$.

ing abilities compared to that of the other anions examined.[14]

The titration curves of **1** upon addition of dihydrogen phosphate appeared to be somewhat different (Fig. 2). When small aliquots of $H_2PO_4^-$ (<1 equiv) were consecutively added, the absorption peak of **1** at 266 nm decreased gradually and meanwhile red-shifted to 269 nm with an isosbestic point at 268 nm (Fig. 3). This suggests the formation of a 1:1 type host–guest complex. However, aggregation had probably occurred when $H_2PO_4^-$ was added in excess, and the titration profile became complicated due likely to the biphasic behavior.[4c,15]

Additions of $F^-$ or $AcO^-$ ions to an acetonitrile solution of cyclopeptide **2** also resulted in immediate decrease of its UV absorption at 267 nm. It is worthy of noting that the absorption approached its limiting value only when about 2 equiv of anions was added, this suggests that receptor **2** and the $F^-$ or $AcO^-$ anion should have formed a 1:2 stoichiometry complex (Fig. 4).

With the stoichiometry of the complex between receptor and anionic guest in hand, the association constants ($K_{ass}$) were then calculated from the UV–vis titration experiments. For the 1:1 stoichiometry complexes, the association constants of the **1**-$F^-$, **1**-$AcO^-$ and **1**-$Cl^-$ complexes were measured, respectively, as $1.43 \times 10^7\ M^{-1}$, $6.87 \times 10^6\ M^{-1}$, and $1.25 \times 10^4\ M^{-1}$ by nonlinear curve-fitting procedure.[16] In the case of 1:2 complexation, the $K_{ass}$ values for receptor **2** with $F^-$, $AcO^-$, and $Cl^-$ were evaluated to be $7.84 \times 10^9\ M^{-2}$, $1.06 \times 10^{10}\ M^{-2}$, and $4.13 \times 10^8\ M^{-2}$, respectively,

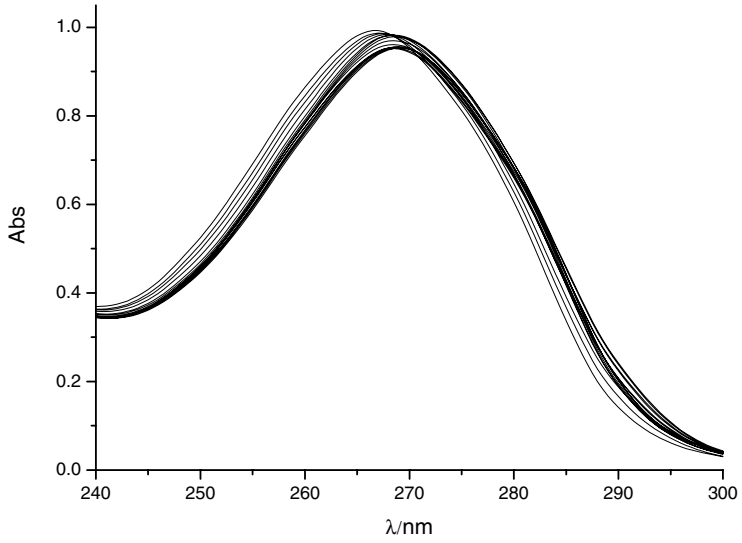


**Figure 2.** The UV–vis spectrum changes of receptor **1** ($2.5 \times 10^{-5}$ M) upon addition of dihydrogen phosphate (equiv of anion: 0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.6, 2, 3, 4, 6, 8, 10, and 12) in $CH_3CN$.

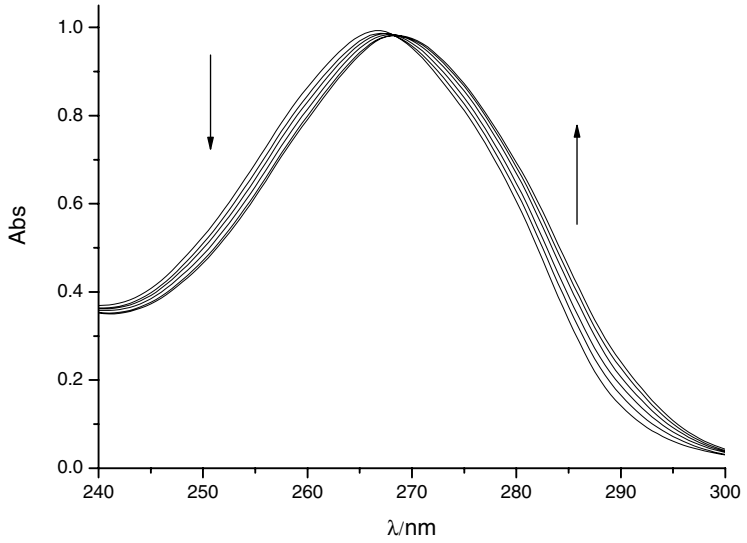


**Figure 3.** The UV–vis spectrum changes of receptor **1** ($2.5 \times 10^{-5}$ M) upon addition of dihydrogen phosphate (equiv of anions: 0, 0.2, 0.4, 0.6, 0.8, and 1) in $CH_3CN$.

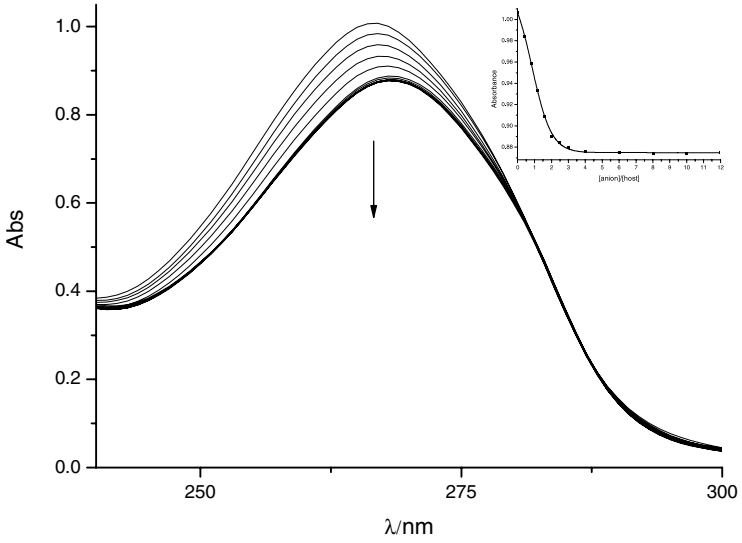


**Figure 4.** The UV–vis spectrum changes of receptor **2** ($1.25 \times 10^{-5}$ M) upon addition of acetate (equiv of anion: 0, 0.4, 0.8, 1.2, 1.6, 2, 2.5, 3, 4, 6, 8, 10, and 12) in $CH_3CN$. Inset: UV–vis spectra titration curve of receptor **2** with $AcO^-$.

following the standard procedure in the literature.[17] These data reveal that receptors **1** and **2** both have high affinity and good selectivity toward fluoride and acetate ions. The results also demonstrates that receptor **1** has a much better anion binding ability than that of the acyclic pyrrolic amide-based receptors reported earlier,[18] and this should not be of surprise because suitably constrained cyclic cavity is known to provide better geometry for hosting anions of relevant size. It is also noted that peptide **1** is a much better fluoride and acetate receptor than the simpler cystine-bearing pseudo-cyclopeptide ($K_{ass} = 418\ M^{-1}$ for $F^-$ and $112\ M^{-1}$ for $AcO^-$[10b]). This can be understood because introduction of an additional pyrrole structure into the backbone of the macrocycle not only further constrains the receptor's conformational freedom, but also promotes a more effective anion binding site by virtue of the pyrrole-NH hydrogen bonds whose importance has already been demonstrated by the preliminary NMR experiments of this work.

In conclusion, we have developed two new pseudo-cyclopeptides by incorporating several H-bond donating and conformationally constrained structures (pyrrole, pyridine, and cystine) into the macrocycle backbone. The UV–vis titration experiments demonstrated that the smaller [1+1] receptor (**1**) formed 1:1 type complexes and the larger [2+2] receptor (**2**) formed 1:2 type complexes with anions. The derived association constants revealed that both receptors possessed good affinity and selectivity for fluoride and acetate ions in acetonitrile via multi-hydrogen-bonding interactions.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.066.

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12. Data for compound **1**: Yield 18%; $^{1}$H NMR (400 MHz, DMSO-$d_6$, TMS): $\delta$ 2.86–2.92, 3.16–3.20 (m, 4H, –$CH_2$–), 3.63 (s, 6H, –$CH_3$), 4.46–4.57 (m, 4H, –$CH_2$–), 4.86–4.90 (m, 2H, –CH–), 6.02 (s, 2H, 3-$C_4H_2N$), 6.72 (s, 2H, 4-$C_4H_2N$), 8.12–8.20 (m, 3H, pyridine-CH), 8.26 (d, 2H, $J = 8.8$ Hz, NH), 9.49 (t, 2H, $J = 5.6$ Hz, NH), 11.38 (s, 2H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 36.1, 51.5, 52.9, 60.5, 108.8, 111.8, 125.4, 125.2, 133.6, 139.9, 149.7, 160.9, 163.1, 172.0; HRMS (ESI) $m/z$: $[M+H]^+$ calcd for $C_{27}H_{30}N_7O_8S_2$, 644.1592; found, 644.1593. Compound **2**: Yield 6.2%; $^{1}$H NMR (400 MHz, DMSO-$d_6$, TMS): $\delta$ 2.87–2.92, 3.15–3.20 (m, 4H, –$CH_2$–), 3.64 (s, 6H, –$CH_3$), 4.45–4.58 (m, 4H, –$CH_2$–), 4.85–4.91 (m, 2H, –CH–), 6.02 (s, 2H, 3-$C_4H_2N$), 6.72 (s, 2H, 4-$C_4H_2N$), 8.11–8.24 (m, 3H, pyridine-H), 8.37 (d, 2H, $J = 8.4$ Hz, NH), 9.46 (t, 2H, $J = 5.2$ Hz, NH), 11.38 (s, 2H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 36.2, 40.7, 51.6, 52.9, 108.8, 111.8, 125.1, 125.6, 133.7, 139.9, 149.8, 160.9, 163.8, 172.0; HRMS (ESI) $m/z$: $[M+H]^+$ calcd for $C_{54}H_{59}N_{14}O_{16}S_4$, 1287.3111; found, 1287.3118.
13. The counter ion is tetrabutylammonium (TBA). The solvent acetonitrile used in the titration experiments was refluxed and distilled from alkaline $KMnO_4$, followed by fractional distillation from phosphorous pentoxide before use.
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