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Synthesis of *N*-substituted cyclic triglycines and their response to metal ions

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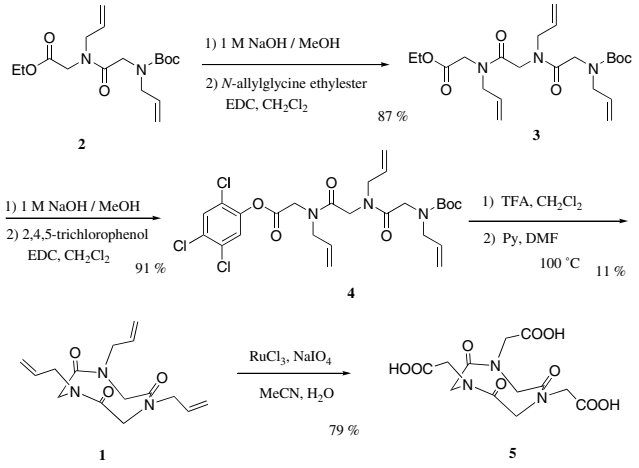
Abstract—*N*,*N*′,*N*″-Trisubstituted-*cyclo*-triglycines were synthesized. The major conformation of these compounds has C_3 symmetry, and the carbonyl groups and substituents on the nitrogen are inclined in the same direction. Their response to various metal ions was estimated by constructing ion-selective electrodes. Two of them responded selectively to Ca^{2+} over other cations, demonstrating that *N*,*N*′,*N*″-trisubstituted-*cyclo*-triglycines provide a new scaffold to act as host molecules.

Cyclic peptides are attractive candidates for artificial receptors because they have a rigid peptide backbone that forms a cavity and provides binding sites suitable for guest molecules. The conformations of *N*-methylated cyclic glycine oligomers have been investigated over the past two decades.[1–5] NMR measurements indicate that di, tri, and tetramers have a rigid conformation, but pentamers or larger have multiple major conformations.[1,2] We focused on the cyclic trimer, which has a C_3 symmetry conformation (crown conformation) elucidated by NMR[1,2] and X-ray crystallography studies.[3] The *N*-methyl groups in the cyclic trimers are inclined in the same direction and the mutual distance between the carbonyl groups was comparable to the distance of phenolic oxygen in calix[4]arene. Thus, we hypothesized that *N*-substituted cyclic triglycines could act as host molecules. In this communication, we describe the synthesis of some *N*-substituted cyclic triglycines and estimate their response to various metal ions by constructing ion-selective electrodes.[6–9]

We chose *N*,*N*′,*N*″-triallyl-*cyclo*-triglycine **1** as a scaffold for the various functionalized host molecules. The scaffold **1** was prepared by simple condensation (shown in Scheme 1). Starting from Boc-protected dipeptide **2**,[10]



Scheme 1. Synthesis of *N*,*N*′,*N*″-trisubstituted-*cyclo*-triglycine.

the ester group in **2** was hydrolyzed and coupled with Boc-protected *N*-allylglycine ethylester to afford **3**. Following Titlestead's procedure,[2] the ethyl ester in **3** was converted to 2,4,5-trichlorophenol ester **4**. The activated ester **4** was slowly added to the mixture of pyridine and dimethylformamide using a syringe pump under diluted conditions. The cyclic tripeptide **1** was isolated in 11% yield along with 22% of *N*,*N*′-diallyldiketopiperazine (cyclic dimer). A substantial amount of cyclic hexamer was detected in the crude product by

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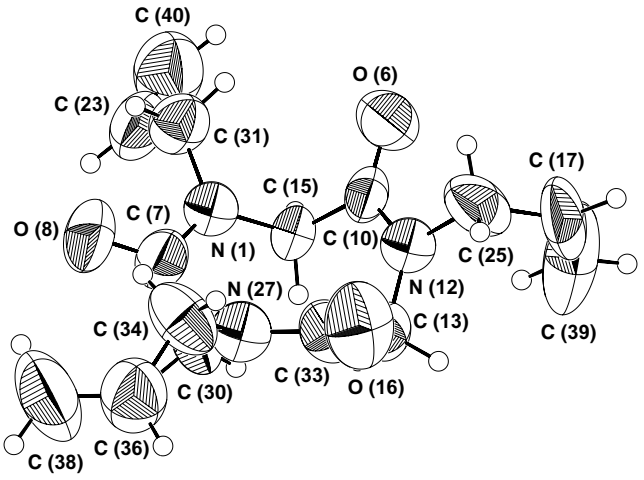
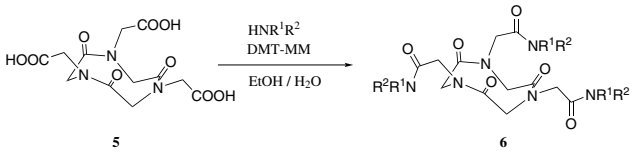
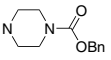
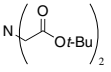
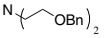


Figure 1. X-ray structure of **1**.



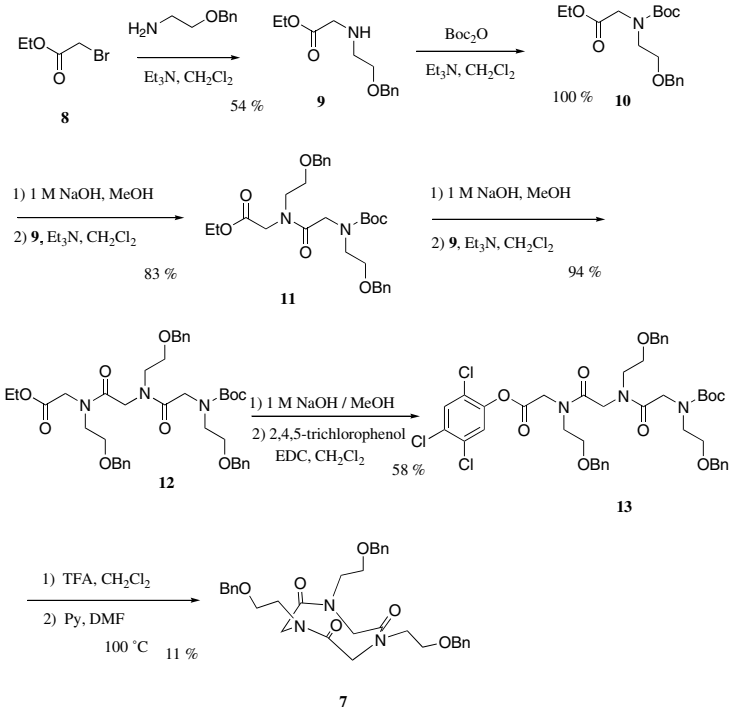
5 **6**

compound	NR^1R^2	yield
6a	$N(C_{10}H_{21})_2$	20
6b		14
6c		23
6d		36
6e		12

Scheme 2. Condensation of **5** with secondary amines.

mass spectroscopy, but the hexamer was not isolated. The ^1H and ^{13}C NMR spectra of **1** indicate that the major conformation was the expected crown form along with some boat form (6%; crown to boat ratio 16:1) in $CDCl_3$. The crown to boat ratio depends on the solvent (52:1 in DMSO-d_6 and 38:1 in D_2O[11]). X-ray crystallography of **1** indicates the crown form[12] (Fig. 1), which is almost identical to the conformation simulated by the conformational analysis using MacroModel software.[13] The double bonds in **1** were oxidatively cleaved to afford the tricarboxylic acid **5**. The conformation of **5** had the crown form, and the boat form of **5** could not be detected by NMR analysis in D_2O. Finally, some secondary amines were condensed to explore their potential utility as a scaffold for the ionophores. Many attempts to obtain the amides **6** using common dehydrating reagents such as EDC[14] or PyBOP[15] failed, due to the insolubility of **5** in aprotic solvent. The expected product was isolated when DMT-MM[16] was used as a dehydrating reagent, which can be used in protic solvent (Scheme 2). The compound **7**, having *N*-benzyloxyethyl groups, was synthesized in the same manner as above (Scheme 3).

The potentiometric ion-selectivity coefficients of the electrodes[17] based on these synthetic compounds are shown in Figure 2. The selectivity coefficients against



8 **9** **10** **11** **12** **13** **7**

Scheme 3. Synthesis of *N*,*N*′,*N*″-tribenzyloxyethyl-*cyclo*-triglycine.

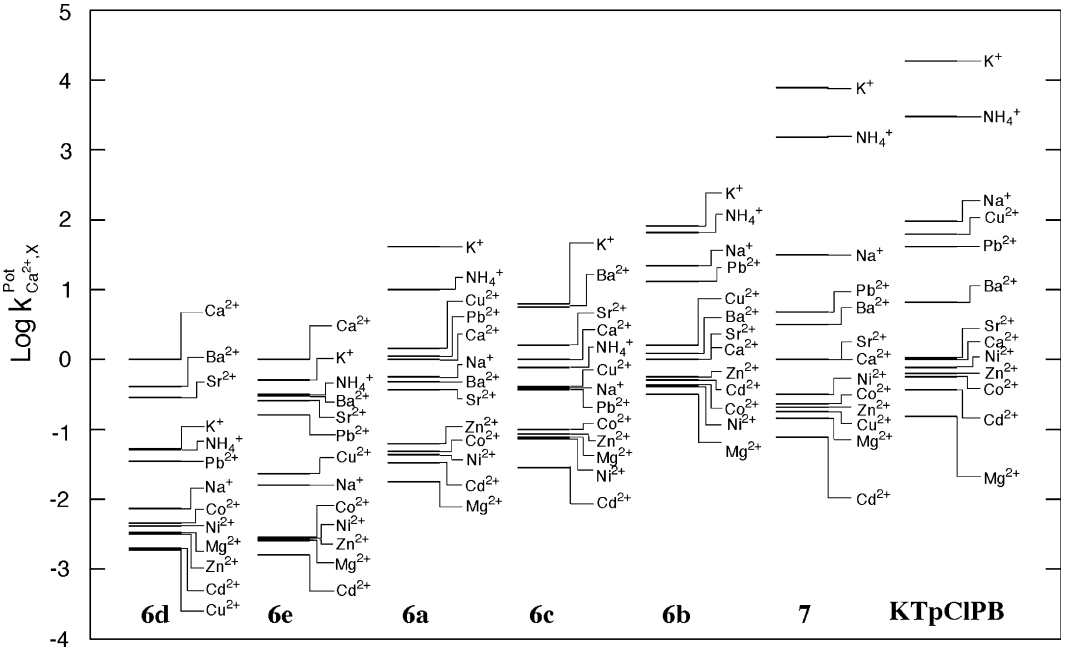


Figure 2. Selectivity coefficients of electrodes.

various inorganic cations were compared. For comparison, we examined the selectivity coefficients of the electrode based on an ion exchanger, potassium tetrakis(*p*-chlorophenyl)borate (KTpClPB), which responds to inorganic cations based on their lipophilic properties.[6,9] In contrast to KTpClPB-based electrode, the electrodes made from **6d** and **6e** responded more strongly to Ca^{2+} compared to other cations, including alkali metal ions such as Na^+ and K^+. The didecylcarbamoylmethyl derivative **6a** had less affinity for Ca^{2+}. These results indicate that some of the benzylic oxygens of **6d** and **6e** preferentially provide a coordinating site for Ca^{2+}. In particular, the electrode using **6d** had high affinity for Ca^{2+}, enhancing the ion selectivity of Ca^{2+} against K^+. Based on the molecular modeling of **6e**, one or two benzylic oxygens are outside of the cavity in some rotational isomers of amide linkage, which might result in the lower Ca^{2+}/K^+ selectivity of **6e**. Compounds **6c** and **6b** had much worse selectivity for Ca^{2+}, probably due to the presence of several coordination sites, resulting in low recognition of specific metal cations. The calibration graphs for Ca^{2+} are shown in Figure 3.[18] The slope and the detection limit of the electrode using **6d** were 28 mV/decade and 1×10^{-5} mol/L, respectively, performing the best among the various compounds examined in the present study. However, the sensitivity and the selectivity of the present electrode could not exceed those of Ca^{2+}-selective electrodes so far developed.[7]

In summary, we synthesized some *N*,*N*′,*N*″-tricarbamoyloxy triglycines. Compounds **6d** and **6e** had high affinity for Ca^{2+}, demonstrating that the *N*,*N*′,*N*″-trisubstituted triglycines provide a new scaffold to act as host molecules. A combinatorial approach to discover better host molecules using this scaffold is under investigation.

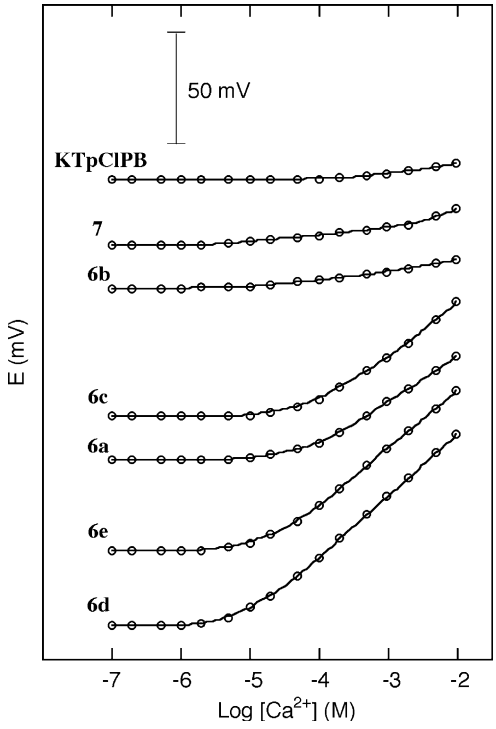


Figure 3. Calibration plots for Ca^{2+}.

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References and notes

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11. Kraemer et al.[4] reported a similar phenomenon. They described that polar solvent stabilized the dipole moment of the crown form.
12. Crystallographic data (excluding structure factors) for **1** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-220730. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
13. A Monte Carlo conformational search employing the AMBER force field included with MacroModel software (v. 6.0).
14. EDC: *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride.
15. PyBOP: 1*H*-Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, see Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 205–208.
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17. Sensor membranes of the electrodes were prepared as reported previously,[6–9] by incorporating 1 mg ionophore, 50 mol% KTpClPB relative to the ionophore, 60 μL *o*-nitrophenyl octyl ether (NPOE), and 30 mg poly(vinyl chloride). A sensor membrane based on an ion exchanger alone was composed of 0.5 mg KTpClPB, 60 μL NPOE, and 30 mg poly(vinyl chloride). The selectivity coefficients of the electrodes were determined using a separate solution method[6,8] with the respective chloride salts at 0.1 M, except for Pb^{2+}, for which we used the acetate salt. To cross-check the values of the selectivity coefficients, we measured the coefficients for **6d** against several metal cations using a matched potential method[6,9] (Mg^{2+} −2.7; Sr^{2+} −0.6; Ba^{2+} −0.3; Na^{+} −2.7; K^{+} −2.0). These values were similar to those obtained using the separate solution method. With the matched potential method, we used a fixed concentration (1.0×10^{-4} M) of $CaCl_2$ as the background. The selectivity coefficients were calculated from the concentration of the interfering ions that induced the same amount of potential change as that induced by increasing the concentration of $CaCl_2$ to 2.0×10^{-4} M. This measurement was performed in the presence of 0.1 M Tris–HCl (pH 7) to maintain a constant ionic strength.
18. Measurements were performed at room temperature (approximately 25 °C) in 0.1 M Tris–HCl (pH 7) to adjust the ionic strength of the solution.