Enantioselective Carboxylate Receptor Using Glycoluril Molecular Scaffold

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We have introduced a new enantioselective receptor **1** by incorporation of chiral building blocks to the previously reported carboxylate selective receptor **2**. Binding studies carried out using ^{1}H NMR revealed that the receptor **1** showed moderate enantioselectivity with a general preference for D-amino acids and a highest enantioselectivity for leucine among the amino acids we investigated.

Key Words : Glycoluril, Enantioselection, Amino acids

Introduction

Enantioselective recognition is one of the most fundamental and significant process in natural systems.[1] However, enantioselective recognition still remains a major challenge for host-guest chemist.[2] The ability to discriminate between enantiomers using synthetic receptors would allow the understanding of biochemical systems and contribute to the development of pharmaceuticals, enantioselective sensors, catalysts and separation of racemates.[3] Amino acids are attractive targets for the enantioselective recognition because of their biological significance and practical importance.[4] One of the methods to accomplish enantioselection has been the introduction of chiral moiety near binding site.[5] Interactions between chiral group in the receptor and chiral substrate give discrimination of enantiomers.

In an effort to produce simple enantioselective receptors for carboxylate derivatives such as amino acids, we have developed the receptor **1**. The receptor **1** was modified from the receptor **2** which showed good affinities for Y shaped anions such as acetate and benzoate.[6] ^{1}H NMR studies revealed that the tweezer-type receptor **2** had a hydrogen bond arrangement required for carboxylate through two amide hydrogen bonds. When chiral building blocks are incorporated in the receptor **2**, the new receptor **1** with chiral groups near binding site might discriminate between enantiomeric guests due to side chain interactions as shown in Figure 1. Binding studies carried out using ^{1}H NMR revealed that the receptor **1** showed moderate enantioselectivity with a general preference for D-amino acids and the highest enantioselectivity for leucine among the amino acids we investigated.

Results and Discussion

The synthetic procedure of compound **1** is summarized in Scheme 1. The synthesis started from the reaction between 4-methoxybenzylamine and potassium cyanate in water. This reaction gave the product **4** in 61% yield.[7] Then the compound **4** was refluxed with benzil in benzene under TFA catalyst with Dean stark apparatus to give para-methoxybenzyl protected glycoluril **5** in 74% yield. Reaction of the compound **5** with methyl bromoacetate afforded the compound **6** in 52% yield. Hydrolysis of compound **6** with 10 equivalents of lithium hydroxide in methanol gave the dicarboxylic acid **7** in 77% yield. Treatment of the hydrolyzed compound with oxalyl chloride to give diacid chloride **8** and the reaction between L-alanine methyl ester and diacid chloride **8** gave the desired compound **1** in 37% yield.

In case of the receptor **2**, downfield shifts in both the amide N-H hydrogen and CH_2 hydrogen peaks next to amides were utilized for the ^{1}H NMR titration. However, we could not clearly identify N-H hydrogen and CH_2 hydrogen peaks in the receptor **1**, as they were mixed with other peaks.

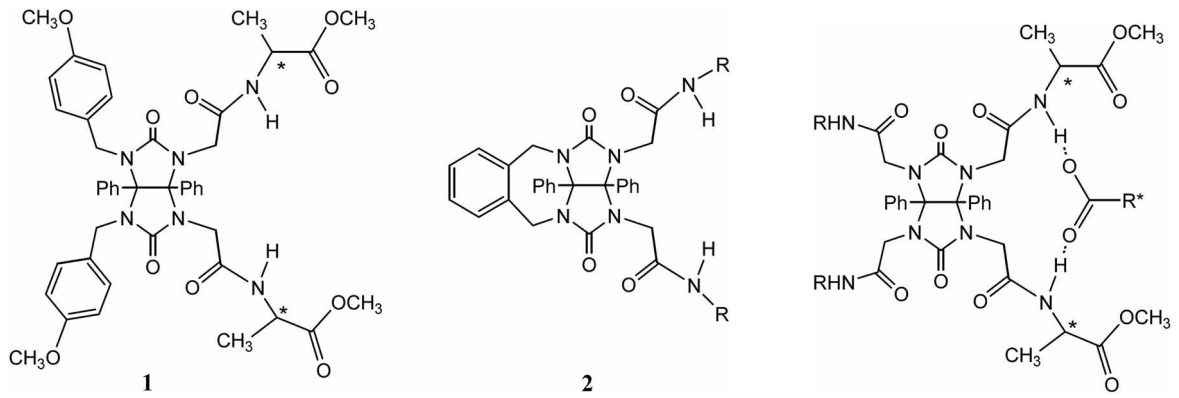
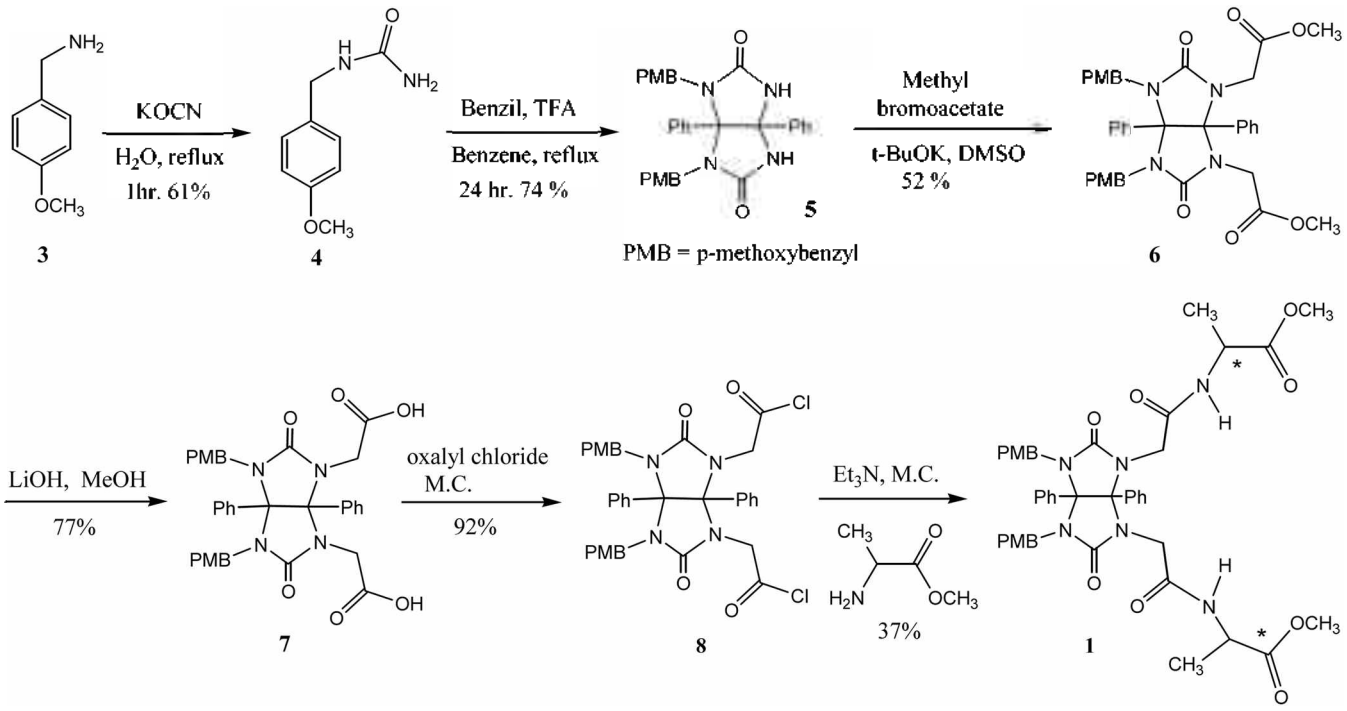


Figure 1. The proposed binding of carboxylates in various amino acids by the receptor **1**. R* represents a chiral group.



Scheme 1. The synthetic procedure for the receptor **1**.

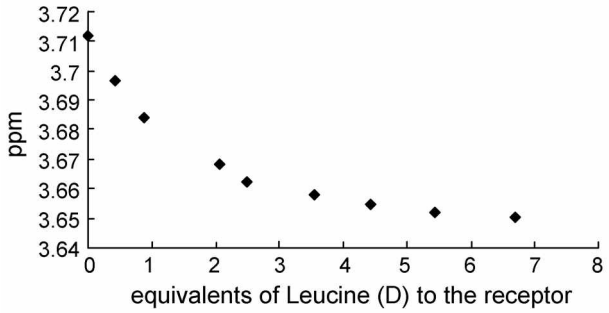


Figure 2. Changes in the ester -OCH_3 protons in the receptor 1 with increasing concentrations of N-Boc-D-Lecine.

Therefore, we utilized ester -OCH_3 peak in the receptor **1**. The -OCH_3 group is located near to amino acids when amino acids bind to the receptor **1**.

The tetrabutylammomium carboxylate salts of *N*-protected amino acids were prepared by neutralizing the corresponding *N*-protected amino acid with 1.0 M tetrabutylammonium hydroxide in methanol solution, followed by vacuum-drying at 40-50 °C for 24 h. The addition of tetrabutylammonium carboxylate salts of various *N*-protected amino acids to the solution of receptor **1** in CD_3CN resulted in upfield shifts in ester -OCH_3 peak. For example, the ester -OCH_3 peak in the receptor **1** moved upfield from 3.71 ppm to 3.65 ppm for 7 equivalents of N-Boc-D-leucine. No further shifts were observed (Fig. 2). Although the amount of shift was small, it was consistent phenomena for all the amino acids we investigated. In case of N-Boc-L-leucine, 9 equivalents of amino acid were required to obtain saturation point. The saturation point was also 3.65 ppm for N-Boc-L-leucine. The association constants calculated from NMR titration

Table 1. Binding constants (K_{ass}) for the 1 : 1 complexes formed between the receptor **1** and tetrabutylammonium carboxylate salts of various *N*-protected amino acids in CD_3CN

Entry	Substrate	K_{ass} (M^{-1})
1	N-Boc-D-Leu-CO_2^- NBu_4^+	$8.9 \times 10^2 \pm 35$
2	N-Boc-L- Leu-CO_2^- NBu_4^+	$2.5 \times 10^2 \pm 12$
3	N-Boc-D-Gln-CO_2^- NBu_4^+	$7.2 \times 10 \pm 2$
4	N-Boc-L-Gln-CO_2^- NBu_4^+	$4.2 \times 10^2 \pm 3$
5	N-Boc-D-Phe-CO_2^- NBu_4^+	$8.0 \times 10^2 \pm 98$
6	N-Boc-L-Phe-CO_2^- NBu_4^+	$6.0 \times 10^2 \pm 30$
7	N-Boc-D-Val-CO_2^- NBu_4^+	$6.0 \times 10^2 \pm 36$
8	N-Boc-L-Val-CO_2^- NBu_4^+	$2.5 \times 10^2 \pm 12$
9	N-Boc-D-Ala-CO_2^- NBu_4^+	$5.7 \times 10^2 \pm 23$
10	N-Boc-L-Ala-CO_2^- NBu_4^+	$4.3 \times 10^2 \pm 21$
11	N-Boc-D-Trp-CO_2^- NBu_4^+	$2.7 \times 10^2 \pm 19$
12	N-Boc-L-Trp-CO_2^- NBu_4^+	$2.4 \times 10^2 \pm 12$

gave $8.9 \times 10^2 \pm 35$ for N-Boc-D-leucine and $2.5 \times 10^2 \pm 12$ for N-Boc-L-leucine.[8] Binding studies with chiral receptor **1** and a range of *N*-protected amino acid derivatives as tetrabutylammonium carboxylate salts in CD_3CN were carried out and the results are summarized in Table 1. From the experiments, the receptor **1** has a moderate selectivity for different amino acids. The highest selectivity is observed between N-Boc-D-leucine and N-Boc-L-valine. N-Boc-D-leucine binds to the receptor **1** about 3.7 times stronger than N-Boc-L-valine. In addition, the chiral receptor **1** shows moderate enantioselectivity with general preference for D-amino acids. Among the amino acids we investigated, amino acid with bulky side chain showed better selectivity. N-Boc-leucine (D/L = 3.6) showed the highest enantioselectivity

while N-Boc-alanine showed almost no selectivity (D/L = 1.3)

Conclusion

We have prepared a new receptor **1**, which is moderately enantioselective for a range of N-protected amino acids. The receptor **1** showed a preference for D-amino acids and amino acid with bulky side chain such as leucine showed better selectivity.

Experimental Section

General methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Flash chromatography were carried out on silicagel 60 (230-400 mesh ASTM; Merck). Thin layer chromatography (TLC) was carried out using Merck 60F254 plates with thickness 0.25 mm. Preparative TLC was performed using merck 60 F254 plates with thickness of 1 mm.

^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker 200 MHz or 500 MHz NMR. Chemical shift were given in parts per million and coupling constants (J) in hertz. Mass spectra were obtained using a JMS-HX 110A/110A Tandem Mass Spectrometer.

Compound 4: To a solution of 4.7 mL 4-methoxybenzylamine in 40 mL distilled water was added 4.2 g potassium cyanate and refluxed for an hour. After the reaction mixture was cooled to 0 °C and 8 mL HCl was added. Filtration of white precipitate gave 4.02 g (61%) of product. ^{1}H NMR ($CDCl_3$) 7.20 (d, 2H, J = 8.0), 6.84 (d, 2H, J = 8.0), 4.75 (s, 1H), 4.30 (s, 2H), 4.27 (d, 2H), ^{13}C NMR (DMSO-d_6) δ 159.52, 158.93, 133.65, 129.20, 114.48, 55.90, 43.16 HRMS (FAB) calculated for $C_9H_{12}N_2O_4H^+$; 181.0977 found for 181.0976.

Compound 5: To a solution of 2.7 g of compound **4** and 1.6 g benzil in 30 mL benzene was added 2.3 mL trifluoroacetic acid. The reaction mixture was refluxed under Dean-stark apparatus for 24 hours. The precipitated solid was filtered and washed with ethanol. 3.0 g (74%) of product was obtained. ^{1}H NMR ($CDCl_3$) 6.96 (m, 18H) 5.54 (s, 2H), 4.37 (d, 2H, J = 16.0), 3.89 (d, 2H, J = 16.0), 3.74 (s, 6H) ^{13}C NMR (DMSO-d_6) δ 159.79, 158.80, 138.79, 133.82, 131.81, 129.86, 129.18, 129.05, 128.89, 128.76, 128.25, 127.99, 114.19, 91.21, 81.33, 55.84, 45.11 HRMS (FAB) calculated for $C_{32}H_{30}N_4O_4H^+$: 535.2345 found for 535.2394.

Compound 6: To a solution of 1 g of glycoluril **5** in 20 mL DMSO was added 525 mg potassium tert-butoxide and stirred for 10 min. Then 430 μL of methybromoacetate was added to the reaction mixture and stirred for 12 hr at room temperature. The reaction mixture was poured into 20 mL of distilled water. The precipitated solid was filtered and washed with 10 mL of water 5 times. The solid was chromatographed with 1% methanol to give 660 mg of oily product **6** in 52% yield. ^{1}H NMR ($CDCl_3$) 6.96 (m, 18H), 4.41 (d, 2H, J = 16), 4.11 (d, 2H, J = 18), 3.89 (d, 2H, J = 16), 3.79 (s, 6H), 3.74 (s, 6H), 3.65 (d, 2H, J = 18), ^{13}C NMR ($CDCl_3$) δ 169.68, 159.62, 158.94, 132.04, 131.88, 130.29, 129.67, 129.56, 129.20, 129.11, 128.68, 128.55, 128.21, 114.14, 90.46, 87.18, 55.54, 52.96, 46.15, 43.56 HRMS (ESI) calculated $C_{38}H_{38}N_4O_8H^+$: 679.2768 found for 679.2791

Compound 7: To a solution of 660 mg of compound **6** in 30 mL methanol was added 407 mg of lithium hydroxide and stirred 8 hr. The solvent of reaction mixture was removed in vacuo and the residue was dissolved in 10 mL of water. The undissolved solid was removed by filtration and the filtrate was treated with concentrated 12% HCl until Ph reached 2. The filtration of evaporated solid gave 490 mg of compound 7 in 77% yield. ^{1}H NMR ($CDCl_3$) 6.94 (m, 18H), 4.36 (d, 2H, J = 16), 4.19 (d, 2H, J = 18), 3.90 (d, 2H, J = 16), 3.73 (d, 2H, J = 18), 3.69 (s, 6H), ^{13}C NMR (DMSO-d_6) $_d$ 170.58, 158.99, 157.93, 132.70, 1432.26, 130.39, 129.62, 128.94, 128.63, 128.33, 128.18, 127.96, 113.41, 88.72, 86.62, 54.99, 44.51, 43.23 HRMS (ESI) calculated $C_{36}H_{34}N_4O_8H^+$: 651.2455 found for 651.2433.

Compound 1: To a suspension of 470 mg of compound **7** in 15 mL of dichloromethane was added 2 mL of oxalyl chloride and 30 microliter of 5 % DMF in dichloromethane. The reaction mixture was stirred for overnight. Evaporation of the solvent in vacuo gave 460 mg of the compound **8** in 92 % yield. To a solution of 450 mg of compound **8** in 10 mL of dichloromethane was added 456 mg of L-alanine methyl ester hydrochloride and 911 microliter of triethylamine. The reaction mixture was stirred for 12 hr at room temperature. Evaporation of the solvent from the reaction mixture and silica gel chromatography with 2% methanol in dichloromethane gave 200 mg of product **1** in 37% yield. ^{1}H NMR (CD_3CN) 7.03 (m, 20H), 4.67 (d, 1H, J = 18), 4.47 (m, 2H), 4.21 (d, 1H, J = 18), 4.08 (d, 1H, J = 16), 3.90 (d, 1H, J = 16), 3.73 (m, 16H), 1.36 (d, 6H, J = 8), ^{13}C NMR (DMSO-d_6) δ 173.64, 173.02, 168.32, 168.06, 159.77, 159.77, 159.57, 158.52, 158.47, 132.25, 132.20, 130.42, 130.39, 129.57, 129.21, 128.97, 128.70, 128.30, 128.04, 127.85, 127.80, 113.54, 113.44, 89.17, 87.45, 54.80, 54.74, 52.14, 52.08, 51.84, 48.16, 48.01, 45.16, 44.69, 44.34, 17.08, 16.78 HRMS (ESI) calculated $C_{44}H_{48}N_6O_{10}H^+$: 821.3510 found for 821.3512.

Preparation of tetrabutylammomium carboxylate salts. The tetrabutylammomium carboxylate salts of *N*-protected amino acids were prepared by neutralizing the 100 mg of the corresponding *N*-protected amino acid with 1 equivalent of 1.0 M tetrabutylammonium hydroxide in methanol solution, followed by vaccum-drying at 40-50 °C for 24 h.

Preparation of NMR-titration solutions. The solution of receptors as 4 mM in CD_3CN was titrated by adding known quantities of concentrated solution (400 mM) of anions in the form of their tetrabutylammonium salts. All titrations were repeated at least once to get consistent values.

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