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Enantiomeric discrimination by novel optically active isocyanurates having peripheral amino acid units

Hiroshi Sugimoto,* Yuuka Yamane and Shohei Inoue

Department of Industrial Chemistry, Faculty of Engineering, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

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Abstract

Chiral discrimination of enantiomers by a novel optically active isocyanurate **3** was demonstrated by ^{1}H NMR. Compound **3** was considered to be more flexible and mobile in solution than the linear amino acid oligomer **6** as shown by ^{1}H NMR, and thus considered to be unfavorable for precise molecular recognition. However, in the spectrum of **3** and racemic binaphthol **4** at the molar ratio of 2:3 in $CDCl_3$, the signal assignable to the O*H* groups of binaphthol shifted downfield from that of binaphthol alone and split in two singlets, indicating that **3** distinguished the enantiomers of **4**. In sharp contrast to **3**, methoxycarbonyl-L-leucine methyl ester **5**, a model compound composed of one amino acid unit in **3c**, did not discriminate the enantiomers of **4**, indicating that it is necessary for three L-amino acid units to be organized on the isocyanurate framework in order to recognize the enantiomers of **4**.

1. Introduction

Highly selective molecular recognition, especially chiral recognition, by enzymes is of great significance in vital systems. Taking into account the structural features of enzymes, model molecules have been designed so that the stereogenic centers, e.g. from the amino acid units, introduced into the backbone and/or periphery should be arranged at definite distances and orientations to provide a rigid structure. For this purpose, an α-helix is a preferable 3-dimensional conformation.[1] The widely studied chiral molecules, other than artificial polypeptide-organized molecules, for chiral recognition and/or asymmetric catalysis are chiral crown ethers[2] and cyclodextrins,[3] which are rigid cyclic compounds and have a cavity for inclusion of appropriate guest molecules.[4] On the other hand, molecules having stereogenic centers on flexible auxiliaries have been less studied, since their mobility is considered to be disadvantageous to precise molecular recognition.

We have recently focused our interest on the synthesis and utility of novel enzyme models based on isocyanurate. Isocyanurate is a suitable framework molecule for designing host molecules to

* Corresponding author. Fax: +81-3-5261-4631; e-mail: hrssgmt@ci.kagu.sut.ac.jp

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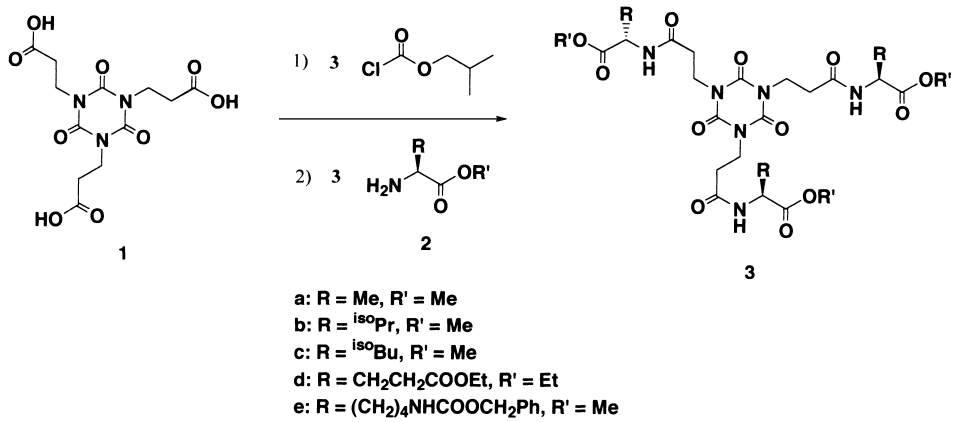
realize chiral recognition, since we consider that multi stereogenic centers on the *N*-substituents are organized on an inflexible six-membered isocyanurate ring and then work cooperatively. In the present study, novel optically active isocyanurates having three amino acid units **3a–e** were synthesized. Compound **3** is expected to distinguish one antipode of a racemic substrate from the other when the functional groups on the isocyanurate ring and amino acid moieties appropriately change their conformation in dynamic recognition system in order to serve as binding sites in the interaction with substrates.

2. Results and discussion

2.1. Synthesis of isocyanurates having three amino acid units 3

Isocyanurates having three amino acid units **3a–e** were synthesized from tris(2-carboxyethyl)isocyanurate **1** and the corresponding amino esters **2a–e** by the formation of amide bonds between -COOH groups of **1** and -NH_2 groups of **2** via mixed acid anhydrides (Scheme 1).



Scheme 1.

For example, the white powder obtained after the reaction between **1** and **2c** was the desired isocyanurate **3c** as evidenced by ^{1}H NMR measurement. The signal due to COO*H* group of **1** was observed to disappear and the signal due to the N*H* group originating from **2c** decreased in relative intensity. In the IR spectrum of the product, a new absorption band at 1647 cm^{-1} which is assignable to the absorption of C=O stretching vibration of the amide bond formed by the reaction of **1** and **2c** was observed. The results of ^{13}C NMR, elemental analysis, and molecular mass analysis as well as ^{1}H NMR and IR showed that the white powder obtained was the desired isocyanurate having three L-leucine units **3c**. Since **3c** has three asymmetric carbons in the molecule, **3c** had a specific rotation ($[\alpha]_D^{23.1}$) of +8.0 deg. ($c = 2.3$ g/100 mL, $CHCl_3$; Table 1, run 3). The reaction of **1** with L-alanine methyl ester **2a**, L-valine methyl ester **2b**, L-glutamic acid diethyl ester **2d**, and L-lysine methyl ester with the ε-amino group protected with benzyloxycarbonyl group **2e** gave the corresponding isocyanurates **3a**, **3b**, **3d** and **3e**. They were characterized by ^{1}H and ^{13}C NMR, IR, and mass spectra. The yields and specific rotations are shown in Table 1, runs 1, 2, 4 and 5.

Table 1
Synthesis of optically active isocyanurates (**3**) from tris(2-carboxyethyl)isocyanurate (**1**) and amino acid esters (**2**). Yield and specific rotation of **3**

Run	**3**	Yield in %	Specific Rotation[a]		
			c in g/100mL	Temp in °C	$[\alpha]_D$ in deg
1	**a**	15	1.6	23.1	+9.3
2	**b**	56	1.1	22.3	+24.6
3	**c**	69	2.3	25.2	+8.0
4	**d**	56	2.1	22.6	+26.5
5	**e**	63	1.7	22.7	+19.4

[a] In $CHCl_3$; Sample cell length = 50 mm.

2.2. Chiral recognition by isocyanurates having three amino acid units **3**

To investigate the interaction between the novel optically active isocyanurate having three L-amino acid units **3** and racemic guest compound, ^{1}H NMR studies were performed for the mixture of **3c** and racemic binaphthol **4**. When a mixture of **3c** and racemic **4** at the molar ratio of 2:3 in $CDCl_3$ ([**3c**] = 62.5 mmol/L) was subjected to ^{1}H NMR measurement at room temperature, the signal assignable to the O*H* groups of **4** clearly shifted to the downfield region from that observed for **4** alone (δ 5.03 ppm; Fig. 1 (B)) and split into two singlets (δ 5.48 and 5.59 ppm; Fig. 1 (C)).

This observation indicates that the OH groups of **4** participated in the interaction, such as hydrogen bonding, with **3c**. On the other hand, the upfield shift from 6.95 (Fig. 1 (A)) to 6.51 (Fig. 1 (C)) ppm was observed for the signal due to the N*H* groups of **3c**, indicating that the N*H* groups were under the shielding effect of the naphthyl groups of **4** or that intra- and/or intermolecular hydrogen bonds among the amide groups of **3c** were broken in the presence of **4**. All the results mentioned as above show that a possible interaction exists between the amide C=O groups of **3c** and the OH groups of **4**. Three amino acid arms of **3c** appeared to be equivalent in the ^{1}H NMR spectrum for the mixture of **3c** and **4**, indicating that conformational change of **3c** and/or migratory interaction of amino acid arms of **3c** with OH groups of **4** took place more quickly than NMR time scale in solution at room temperature.[5]

In the case where (*R*)-**4** in place of racemic **4** was present with **3c** in $CDCl_3$ under similar conditions, a signal due to the O*H* groups appeared at δ 5.55 ppm (Fig. 1 (D)), while the ^{1}H NMR spectrum for the mixture of **3c** and (*S*)-**4** showed an O*H* signal at δ 5.64 ppm. These observations indicate that **3c** in solution interacted with both of (*R*)-**4** and (*S*)-**4** and gave a set of diastereoisomeric complexes, where the O*H* groups in **3c–(*R*)-4** and **3c–(*S*)-4** complexes were located in sufficiently different environments to show their ^{1}H NMR signals at different chemical shift. Consequently, **3c** is considered to discriminate the ***R*-form and the *S*-form of 4** spectroscopically.[6]

The association constants for the **3c**–(*R*)-**4** and **3c**–(*S*)-**4** systems were determined from the chemical shift values for ^{1}H NMR signals due to O*H* of (*R*)- and (*S*)-**4** in the presence of **3c** in

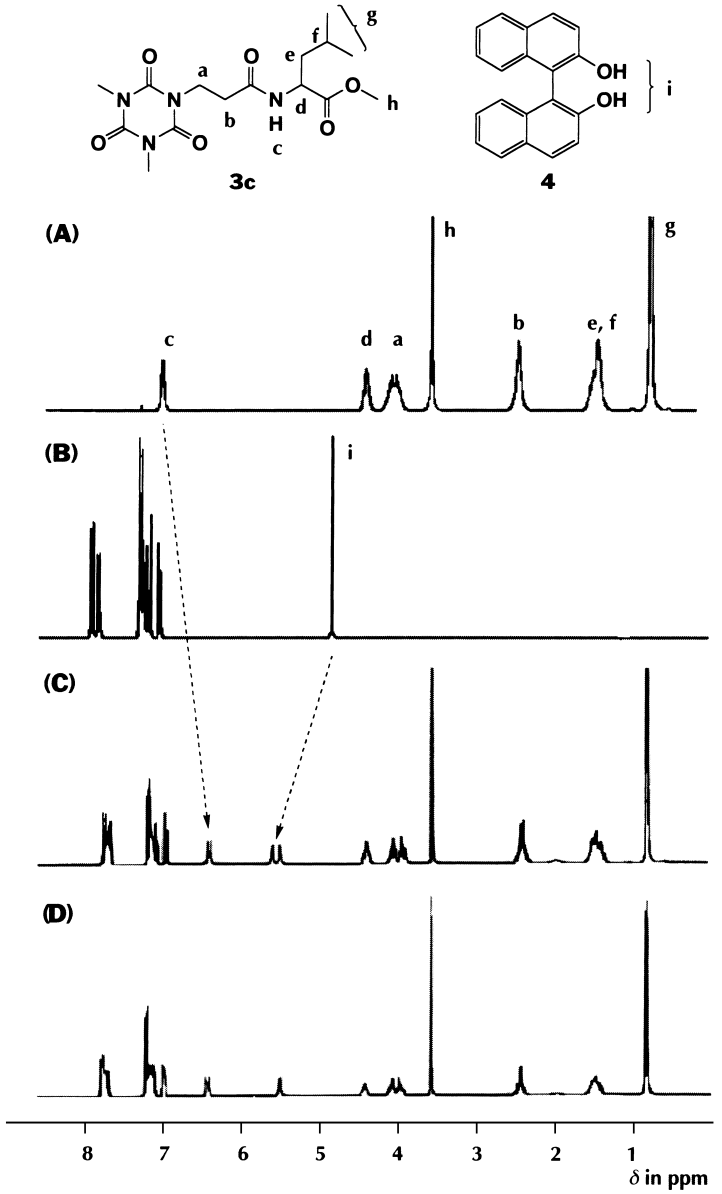
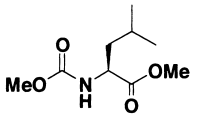


Figure 1. ^{1}H NMR spectra in $CDCl_3$ at 23°C of (A) isocyanurate (**3c**) ([**3c**]$_0$ = 0.05 M), (B) binaphthol (**4**) ([**4**]$_0$ = 0.075 M), (C) a mixture of **3c** and racemic **4** ([**4**]$_0$ = 0.075 mol/L, [**3C**]$_0$/[**4**]$_0$ = 2/3, and (D) a mixture of **3c** and (*R*)-**4** ([**4**]$_0$ = 0.075 mol/L, [**3c**]$_0$/[(*R*)-**4**]$_0$ = 2/3)

$CDCl_3$ ([**4**]$_0$ = 0.075 M, [**3c**]$_0$/[**4**]$_0$ = 2/3, 30°C). The value of the association constant (K) for the **3c**–(*R*)-**4** system (402 L mol^{-1}) is not so much different from that for the **3c**–(*S*)-**4** system ($K_{\mathbf{3c–S4}}$ = 319 L mol^{-1}). This result indicates that the **3c**–(*R*)-**4** complex has a similar stability to that the **3c**–(*S*)-**4** complex, and thus the observed difference in the chemical shift values due to O*H* signals in for the **3c**–(*R*)-**4** and **3c**–(*S*)-**4** systems are attributed the different structures of diastereoisomeric complexes.

Contrary to the above as observed for the **3c**–**4** system, the ^{1}H NMR spectrum for the mixture of methoxycarbonyl-L-leucine methyl ester **5**, a model compound of one amino acid unit in **3c**, and racemic **4** showed a singlet signal due to the O*H* groups of **4**, with a slight downfield shift, at δ 5.28 ppm.



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This means that it is of much importance for three L-leucine units to be organized on the isocyanurate framework to recognize the enantiomers of **4**, resulting that their O*H* signals appears at different chemical shifts.

As the temperature was raised, the split ^{1}H NMR signals due to O*H* groups of **4** in the presence of **3c** were observed to shift towards the original position at δ 5.03 ppm where the one singlet signal appeared in the absence of **3c** (Fig. 2).

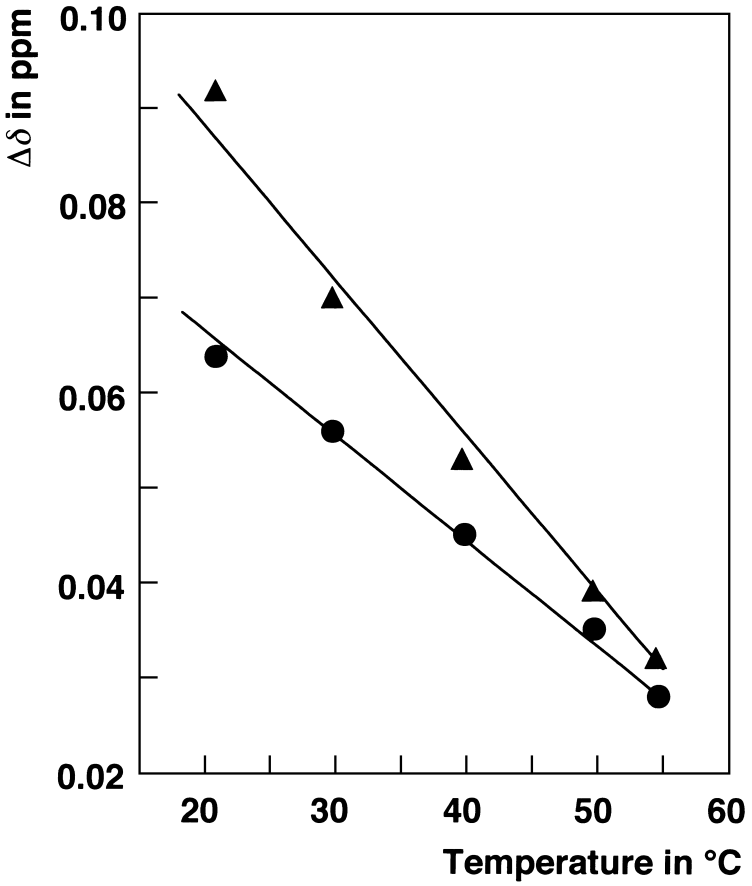
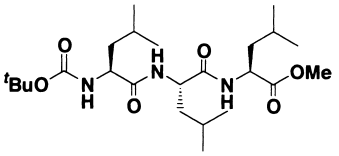


Figure 2. ^{1}H NMR profiles in $CDCl_3$ of isocyanurate (**3c**)-binaphthol (**4**) (▲) and tripeptide (**5**)-**4** (●) mixtures. Relationships between the difference of the chemical shifts duo to the split O*H* signals of **4** and the temperature

The separation ($\Delta\delta$) of diastereoisomeric O*H* signals was 0.03 ppm at 55°C, which was 0.05 and 0.09 ppm at 40 and 21°C, respectively. In contrast, a linear trimer of L-leucine **6**, which was also found to distinguish enantiomers of **4** at room temperature, showed similar temperature dependence.



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The change in the $\Delta\delta$ value was smaller than that observed for **3c**–**4** system. This result indicates that conformational change of **3c** occurred more easily than that of **6**. However, it is a very important result that more flexible, and thus dynamic **3c** in solution discriminates between enantiomers of **4**. This fact provides the possibility that **3c** readily adapts its structure to guest molecules.

Similar to **3c**, **3a**, **3b** and **3d** distinguished enantiomers of **4** under identical conditions as shown by the two singlets in the ^{1}H NMR spectra. In sharp contrast, **3e** could not distinguish an enantiomer of **4** from the other (Table 2).

Table 2
Chemical shift values of ^{1}H NMR signals due to O*H* groups of binaphthol (**4**) in the presence of optically active isocyanurates (**3**)

Run	**3**	δ in ppm[a]	
1	**a**	5.46	5.53
2	**b**	5.64	5.70
3	**c**	5.48	5.59
4	**d**	5.64	5.69
5	**e**	5.86	

[a] Chemical shift values of OH signals of **4**.

3. Conclusion

The present study demonstrated an interesting example of chiral recognition by the conformationally dynamic chiral isocyanurates **3**. Although **3** was more flexible and mobile in solution than the linear amino acid oligomer **6** as shown by the ^{1}H NMR studies, and thus considered to be unfavorable for precise molecular recognition, **3** sufficiently resolved two signals assignable to enantiomeric O*H* groups of binaphthol **4** on ^{1}H NMR spectra. This result encourages the design of chiral host molecules from flexible building blocks.

Chiral recognition of other racemic guest molecules by **3** is under investigation.

4. Experimental

Materials. Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl in a nitrogen atmosphere. Dimethylformamide (DMF) was distilled over CaH_2 under reduced pressure in a nitrogen atmosphere. Dichloromethane (CH_2Cl_2) was washed successively with concentrated H_2SO_4, water, and aqueous $NaHCO_3$, dried over $CaCl_2$, and distilled over CaH_2 under nitrogen. Deuterated chloroform ($CDCl_3$) was distilled over CaH_2 in a nitrogen atmosphere. *N*-Methylmorphorine was used as obtained.

Amino acid derivatives, purchased from Sigma, were used as obtained. 1,1′-Bi-2-naphthol (binaphthol; **4**), purchased from Tokyo Chemical Industry, was recrystallized from benzene.

Methoxycarbonyl-L-leucine methyl ester **5** was synthesized from methyl (*S*)-2-isocyanato-4-methylpentanoate[7] and large excess methanol. A linear trimer of L-leucine, *N*-*tert*-butyloxycarbonyl-L-leucyl-L-leucyl-L-leucine methyl ester **6**, was prepared by the reaction between L-leucine methyl ester and *N*-*tert*-butyloxycarbonyl-L-leucyl-L-leucine, which was obtained by the hydrogenation of *N*-*tert*-butyloxycarbonyl-L-leucyl-L-leucine benzyl ester synthesized from *N*-*tert*-butyloxycarbonyl-L-leucine and L-leucine benzyl ester.[8]

4.1. Synthesis of optically active isocyanurate *3*

Isocyanurate having three L-leucine units **3c** was synthesized as follows:[9] To a THF solution (100 mL) of tris(2-carboxyethyl)isocyanurate (**1**, 6.9 g; 20 mmol), *N*-methylmorphorine (6.7 mL; 60 mmol), and isobutyl chloroformate (8.0 mL; 60 mmol) at –15°C under dry nitrogen, a DMF solution (80 mL) of L-leucine methyl ester (**2c**: 13.0 g; 72 mmol) and *N*-methylmorphorine (8.1 mL; 72 mmol) was added (Scheme 1). The resulting mixture was stirred for 30 min at –15°C and for 15 h at room temperature, from which the volatile fraction was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), then washed successively with 5% $NaHCO_3$ aq., water, 1N aq. HCl, and water. The organic layer was separated and evaporated to dryness to give a light yellow powder. White gel formed after the addition of methanol to the powder was collected by filtration and dried under reduced pressure, affording **3c** as white powder (10.0 g; yield 69%). ^{1}H NMR ($CDCl_3$; ppm): δ 0.85 (d, 18H, $CH_2CH(CH_3)_2$), 1.37–1.61 (m, 9H, $CH_2CH(CH_3)_2$ and $CH_2CH(CH_3)_2$), 2.38–2.55 (m, 6H, NCH_2CH_2), 3.61(s, 9H, OCH_3), 3.94–4.19 (m, 6H, NCH_2CH_2), 4.45–4.51 (m, 3H, NHCH(*iso*Bu)CO), 6.95 (d, 3H, NHCH(*iso*Bu)CO). IR (KBr; cm^{-1}): 1743 (O–C=O), 1689 (NHC=O), 1647 (NC(=O)N). Elemental analysis: calcd H 7.49%, C 54.53%, N 11.56%, O 26.42%; obsd H 7.53%, C 54.00%, N 11.60%, O 26.87%. FAB-MS for $C_{33}H_{55}N_6O_{12}$ (MH): m/z 727.

Other optically active isocyanurates, **3a**, **3b**, **3d** and **3e**, were synthesized from **1** and the corresponding **2** and characterized similarly to the above procedure for **3c**.

Compound **3a**: ^{1}H NMR ($CDCl_3$; ppm): δ 1.35 (d, 3H, CH_3), 2.46–2.66 (m, 6H, NCH_2CH_2), 3.70 (s, 9H, OCH_3), 4.06–4.42 (m, 6H, NCH_2CH_2), 4.47–4.58 (m, 3H, $NHCH(CH_3)CO$), 6.62 (d, 3H, $NHCH(CH_3)CO$). IR (KBr; cm^{-1}): 1736 (O–C=O), 1693 (NHC=O), 1643 (NC(=O)N). Elemental analysis: calcd H 6.04%, C 48.59%, N 13.88%, O 31.49%; obsd H 6.08%, C 48.00%, N 13.99%, O 31.93%. FAB-MS for $C_{24}H_{37}N_6O_{12}$ (MH): m/z 601.

Compound **3b**: ^{1}H NMR ($CDCl_3$; ppm): δ 0.93 (d, 18H, $CH(CH_3)_2$), 2.09–2.19 61 (m, 3H, $CH(CH_3)_2$) 2.54–2.75 (m, 6H, NCH_2CH_2), 3.73 (s, 9H, OCH_3), 4.13–4.33 (m, 6H, NCH_2CH_2), 4.49–4.52 (m, 3H, NHCH(*iso*Pr)CO), 6.44 (d, 3H, NHCH(*iso*Pr)CO). IR (KBr; cm^{-1}): 1,743 (O–C=O), 1,689 (NHC=O), 1,647 (NC(=O)N). FAB-MS for $C_{30}H_{49}N_6O_{12}$ (MH): m/z 685.

Compound **3d**: ^{1}H NMR ($CDCl_3$; ppm): δ 1.12–1.28 (m, 18H, OCH_2CH_3), 1.83–2.18 (m, 6H, $CHCH_2CH_2COOEt$), 2.22–2.41 (m, 6H, $CHCH_2CH_2COOEt$), 2.43–2.63 (m, 6H, NCH_2CH_2), 4.01–4.24 (m, 18H, NCH_2CH_2 and OCH_2CH_3), 4.43–4.52 (m, 3H, $NHCH(CH_2CH_2COOEt)CO$), 6.91 (d, 3H, $NHCH(isoBu)CO$). IR (KBr; cm^{-1}): 1751 (O–C=O), 1689 (NHC=O), 1643 (NC(=O)N). Elemental analysis: calcd H 6.71%, C 51.99%, N 9.33%, O 31.97%; obsd H 6.75%, C 51.97%, N 9.14%, O 32.14%. FAB-MS for $C_{39}H_{61}N_6O_{18}$ (MH): m/z 901.

Compound **3e**: ^{1}H NMR ($CDCl_3$; ppm): δ 1.16–1.79 (m, 18H, $NHCH(CH_2CH_2CH_2CH_2N)CO$), 2.32–2.58 (m, 6H, NCH_2CH_2), 3.02–3.16 (m, 18H, $NHCH(CH_2CH_2CH_2CH_2NHCOOCH_2Ph)CO$), 3.61 (s, 9H, OCH_3), 3.96–4.20 (m, 6H, NCH_2CH_2), 4.37–4.47 (m, 3H, $NHCH(CH_2CH_2CH_2CH_2NHCOOCH_2Ph)CO$), 4.99 (s, 6H, OCH_2Ph), 5.13 (br, 3H, $CH_2CH_2CH_2CH_2NHCOOCH_2Ph$) 6.73 (d, 3H, $NHCH(CH_2CH_2CH_2CH_2NHCOOCH_2Ph)CO$). IR (KBr; cm^{-1}): 1748 (O–C=O), 1692 (NHC=O), 1642 (NC(=O)N).

4.2. Measurements

^{1}H NMR measurements were performed using $CDCl_3$ as solvent at 22°C on a Bruker type DPX-400 spectrometer, where the chemical shifts were determined with respect to TMS (δ 0.00 ppm) as internal standard. IR spectra were recorded on a HORIBA FT-210 spectrometer. Mass spectra were recorded on a JEOL JMS-SX102A spectrometer. Optical rotations were measured on a HORIBA High Sensitive Polarimeter SEPA-300.

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5. Other guest compounds so far examined, such as borneol, menthol, methyl mandelate, binaphtynlamine, *N*-cbz-phenylalanine benzyl ester, showed downfield shift and/or broardening of their signals in the presence of **3** in ^{1}H NMR measurement, however, the signals due to *R*-form and *S*-form were not separately observed at different chemical shifts.
6. Discrimination of enantiomers in ^{1}H NMR spectra was reported by using chiral compounds such as 2,2,2-trifluoro-1-(9-anthryl)ethanol,[a] dihydoroquinine,[b] and some amides having aromatic groups,[c] as resolving agent.

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