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Inclusion of aliphatic alcohols in pockets of (*S*)-threonyl-(*S*)-phenylglycine using grinding method

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ABSTRACT

Inclusion compounds of a dipeptide, (*S*)-threonyl-(*S*)-phenylglycine (Thr-Phg), with several aliphatic alcohols were easily prepared by grinding them in a mortar. Thr-Phg molecules arranged in antiparallel to construct a sheet, and guest alcohols were accommodated in a chiral pocket between the sheets. 3-Butyn-2-ol and 2-butanol were included with moderate enantioselectivity, 57% ee (*R*) and 49% ee (*R*), respectively. The role of the hydroxy group of Thr-Phg is not only to construct the unique pocket but also to capture guest alcohols by hydrogen bonding.

1. Introduction

Optical resolution of neutral compounds by crystal lattice inclusion attracts significant attention due to its high efficiency and simplicity.[1] Inclusion phenomena using chiral host compounds, such as bile acid derivatives,[2] brucine,[3] and tartaric acid derivatives,[4] have been applied for chiral discrimination of racemic alcohols. Recently, two-component supramolecular hosts resolved secondary alcohol with high enantioselectivities.[5] On the other hand, dipeptides recognized substrates stereoselectively just like enzymes do in their own cavity in nature. For example, we reported (*R*)-naphthylglycyl-(*R*)-phenylglycine, which is composed of non-natural amino acids, forms a pocket cavity and included allylic alcohols and β-hydroxyesters.[6] Görbitz reported inclusion compounds of natural dipeptides, such as Ala-Val, Ala-Phe, Val-Phe, Leu-Phe, Leu-Leu, and Leu-Val, with small alcohols.[7] Thus, it has been reported that these dipeptides having alkyl or phenyl groups could include alcohol guests.

We are interested in the functional group of a side chain and how it affects inclusion ability. Although threonine, which has a hydroxy group, acts as an active point in enzymes, dipeptides containing threonine have never been reported as inclusion compounds of alcohols. We report that (*S*)-threonyl-(*S*)-phenylglycine (Thr-Phg) includes several alcohols with moderate enantioselectivity. Interestingly, amorphous Thr-Phg was crystallized with guest alcohols by using a grinding method (Fig. 1). In these crystals, a unique pocket was constructed by the phenyl group of Phg and hydrogen-bonded hydroxyethyl group of Thr. At the same time, the hydroxy group of Thr captured guest alcohols by a hydrogen bond between the dipeptide sheet structures.

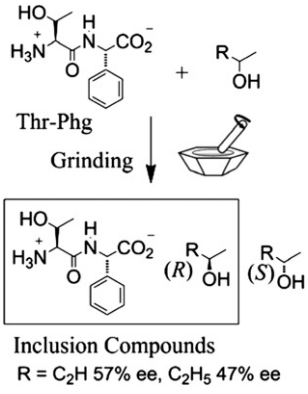

Fig. 1. Structure of (*S*)-threonyl-(*S*)-phenylglycine (Thr-Phg) and schematic drawing of enantiomeric inclusion of racemic alcohols.

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2. Results and discussion

2.1. Preparation of inclusion using grinding method

Recently, a grinding method has often been applied for preparing co-crystals.[8] We reported that dipeptides included sulfoxides by using a grinding method.[9] Thr-Phg (0.5 mmol) was mixed in the guest alcohol (0.5 mL) using a mortal for about 30 min until the liquid evaporated. The resulting solid was analyzed using a powder X-ray diffractometer (PXRD). Fig. 2 shows the change in powder X-ray diffraction patterns of Thr-Phg samples mixed with 2-butanol. Thr-Phg is an amorphous solid; but interestingly, the inclusion compounds created using a grinding method crystallized. The pattern of inclusion compound created using the grinding method was identical to that of single crystals (Fig. 2b and c). In other words, the crystallization process of amorphous Thr-Phg into crystalline inclusion compounds would be essential for this inclusion phenomenon.

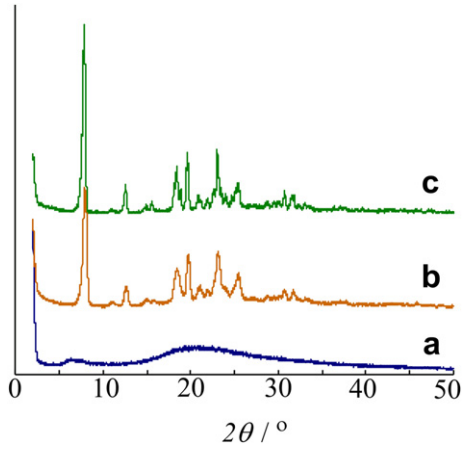


Fig. 2. Powder X-ray diffraction patterns (a) Thr-Phg only (amorphous). (b) Grinding sample of Thr-Phg with 2-butanol. (c) Single crystals of Thr-Phg with 2-butanol.

The results are summarized in Table 1. A series of the inclusion compounds have a strong diffraction peak in the lower 2θ range, which was assigned as the layer distance (LD in Table 1). The peak corresponds to the diffraction plane of the dipeptide backbone in the crystals (vide infra). Ratios of guest (alcohol) to host (Thr-Phg) were determined using ^{1}H NMR. When an alcohol was *racemic*, the included alcohol was recovered by thermal decomposition using a glass tube oven apparatus. After the alcohol was reacted with phenylisocyanate to transform the *N*-phenylcarbamate, the enantiomeric excess of the carbamate was estimated using chiral HPLC with chiralcel OD-H or AD-H.

An inclusion compound of methanol was unstable and showed a low guest/host ratio (entry 1). The inclusion compound released included methanol within several hours because it would be too small to fill up the Thr-Phg cavity. Primary and secondary alcohols from ethanol to butanol formed inclusion compounds with Thr-Phg, where (*R*)-form (49% ee) of 2-butanol was included preferably (entries 2–7). Other alcohols having four carbon atoms, 3-buten-2-ol and 3-butyn-2-ol, were included in 39% ee (*R*) and 57% ee (*R*), respectively (entries 8 and 9). However tertiary alcohol (2-methyl-2-propanol) was not included at all (entry 10). Concerning C5- and C6-alcohols, 2-pentanol, and cyclohexanol were included, where 2-pentanol was recognized in 32% ee (*R*) (entries 11 and 12). In addition, all of these inclusion compounds had the similar interlayer distances (10.6–12.5 Å).

Table 1
Inclusion of alcohols by grinding

Entry	Guest	Guest/Host	ee %	LDA/Å[a]
1	Methanol	0.9	—	10.8
2	Ethanol	0.53	—	10.6
3	1-Propanol	0.55	—	11.0
4	2-Propanol	0.65	—	11.1
5	1-Butanol	0.70	—	11.4
6	2-Methyl-1-propanol	0.66	—	11.3
7	2-Butanol	0.91	49 (*R*)	11.3
8	3-Buten-2-ol	0.48	39 (*R*)	11.1
9	3-Butyn-2-ol	0.68	57 (*R*)	11.3
10	2-Methyl-2-propanol	0.00	—	—
11	2-Pentanol	0.83	32 (*R*)	11.8
12	Cyclohexanol	0.80[b]	—	12.5

[a] LD is an interlayer distance measured by PXRD.
[b] Washed with methanol.

2.2. Crystal structure of inclusion compounds with alcohols

Single crystals of the inclusion compound with 1-propanol, 2-propanol, 2-butanol, and cyclohexanol were prepared using a crystallization method from a methanol solution of Thr-Phg containing the guest alcohol and analyzed using single-crystal X-ray crystallography. Fig. 3 shows a typical crystal structure of an inclusion

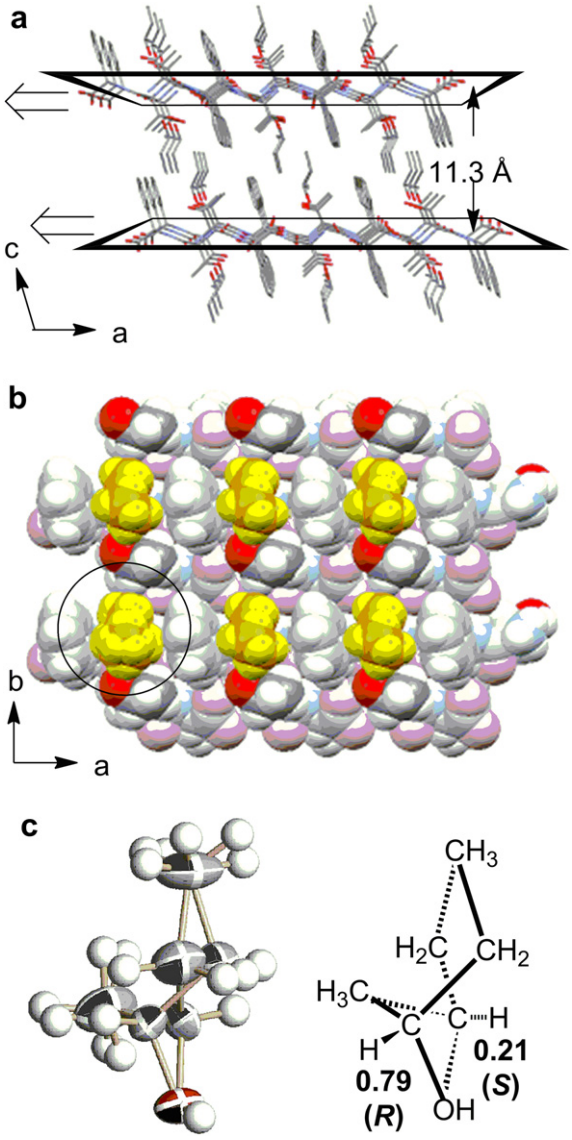
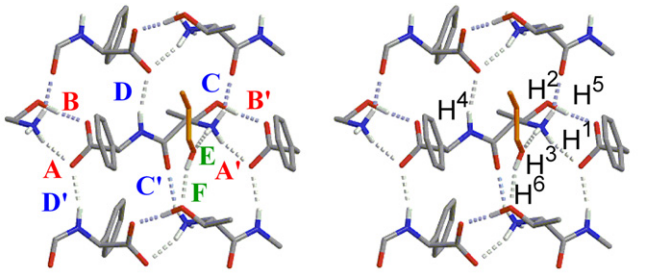


Fig. 3. Crystal structure of inclusion compounds of Thr-Phg with 2-butanol. Only (*R*)-2-butanol is shown. (a) Layer structure of inclusion compound. (b) Pocket cavities on sheet and disorder structure of 2-butanol is only shown in circle. Alcohols are in yellow and oxygen atoms bound with alcohols are shown in red. (c) Disorder structure of 2-butanol in inclusion cavity.

compound with 2-butanol. Dipeptide molecules assembled to form sheet structures, and the interlayer distance (11.3 Å) corresponded to layer distances (LD=11.3 Å) estimated using PXRD. Interestingly, a unique pocket was constructed by the 1-hydroxyethyl and phenyl groups of Thr-Phg between these sheet structures (Fig. 3b). In *racemic* 2-butanol, both enantiomers were included at the same position in the cavity, where 2-butanol was observed as a disorder structure with the ratio of *R*/*S*=79:21 (Fig. 3c). As a result, 2-butanol was included in 58% ee (*R*) in the single crystals. The enantiomeric excess agreed rather well with the value (49% ee), which was obtained using the grinding method. This result suggested that the solid obtained by the grinding method as well as the crystallization method was almost thermodynamic stable and less affected by a kinetic factor.

Other inclusion compounds of 1-propanol, 2-propanol, and cyclohexanol have a quite similar sheet structure. Fig. 4 illustrates the hydrogen-bonding network of these inclusion compounds, and the corresponding hydrogen-bonding distances for all the analyzed inclusion compounds resembled each other.



Guest	A/Å	B/Å	C/Å	D/Å	E/Å	F/Å
1-PrOH	2.78	2.68	2.76	2.96	2.72	2.74
2-PrOH	2.79	2.69	2.75	2.96	2.73	2.74
2-BuOH	2.73	2.68	2.75	2.95	2.73	2.73
c-$C_6H_{11}OH$	2.80	2.69	2.76	2.96	2.72	2.74

Fig. 4. Stereoview of Thr-Phg with 1-propanol (colored in orange) and hydrogen-bonding distances in four analyzed inclusion crystals.

The zwitterionic Thr-Phg molecule made a strong hydrogen bond between the first ammonio proton (H^1) and the nearby carboxylate of the other Thr-Phg (bond A: COO···H^1–N: 2.73–2.80 Å) with the help of coulombic interaction. Simultaneously, a hydroxy group of Thr connected with the same carboxyl group of the dipeptides (bond B: COO···H^5–O: 2.68–2.69 Å). The collaborated hydrogen bonds (A and B in Fig. 4) connected to Thr-Phg to form a one-dimensional ribbon. Similar double hydrogen bonds were observed in the Ser-Ala crystals (bond A: 2.72 Å, bond B: 2.62 Å)[10a] and the Ser-Asn monohydrate crystals (bond A: 2.80 Å, bond B: 2.64 Å).[10b] Just like the antiparallel sheet structure of polypeptides, these dipeptide ribbons were arranged in antiparallel by a hydrogen-bonding network (C and D in Fig. 4). The second ammonio proton (H^2) of Thr-Phg bonded to an oxygen atom of amide (bond C: COO···H^2–N, 2.75–2.76 Å) and an amide proton (H^4) connected to the carboxyl group (bond D: N–H^4···O=C, 2.95–2.96 Å). These hydrogen bonds take part in the construction of the sheet structure. In addition, the alcohol guest in the cavity was effectively caught by duplicated hydrogen bonds (E and F in Fig. 4). Specifically, a hydroxy group of the alcohol guest linked to both the third ammonio proton (H^3) of Thr (bond E: N–H^3···O, 2.72–2.73 Å) and the hydroxy oxygen atom of Thr (bond F: O–H^6···O, 2.73–2.74 Å). These hydrogen-bonding distances between host and guest were close to those of Ser-Asn monohydrate, where the hydrogen-bonding network of the dipeptide was quite different.[10b] In the crystals, the hydroxy group of the water linked to both the third ammonio proton of Ser (bond E: 2.75 Å) and the hydroxy oxygen atom of Ser (bond F: 2.78 Å). As mentioned above, all protic hydrogen atoms of inclusion compounds form hydrogen bonds in crystals. Judging from the similarity of the four analyzed inclusion compounds, this sheet structure of Thr-Phg has generality to some extent.

2.3. Crystal structure of chiral pockets

Fig. 5 shows alcohol guests in cavities surrounded by side chains of four Thr-Phg molecules. These pockets are common to the four inclusion compounds. The walls of the pocket consisted of two phenyl groups and two 1-hydroxyethyl groups. Alcohol guests were captured in the cavity by hydrogen bonds E and F in Fig. 4. In these inclusion cavities of Thr-Phg, primary, and secondary alcohols are clipped between two phenyl rings. Therefore, tertiary alcohol, such as 2-methyl-2-propanol was too bulky to fit in the cavity (entry 10 in Table 1).

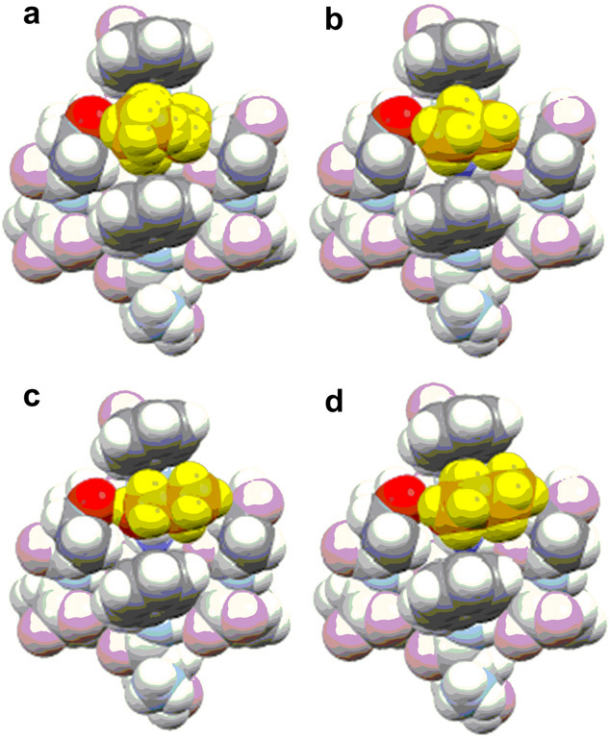


Fig. 5. Crystal structure of pocket cavities with four alcohols. (a) 2-Butanol (disordered structure). (b) 2-Propanol. (c) 1-Propanol. (d) Cyclohexanol. Alcohols are in yellow and oxygen atoms bound with alcohols are shown in red.

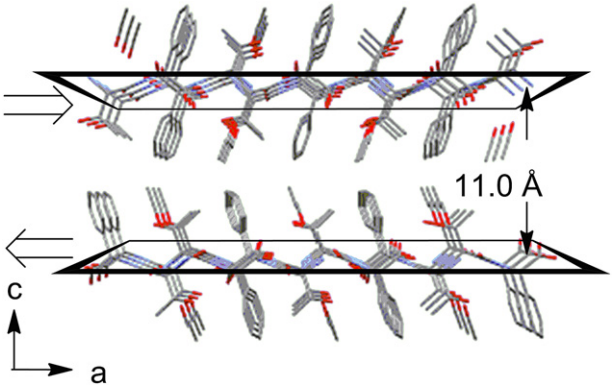


Fig. 6. Crystal structure of inclusion compounds of Thr-Phg with 1-propanol. Stacking mode is antiparallel.

Although the sheet structures of these inclusion compounds are quite similar, two different stacking modes of the dipeptide sheet were observed. Crystals including 2-butanol and 2-propanol have the space group $P2_1$, where the dipeptides pile up in the same direction (arrows in Fig. 3a). However, crystals including 1-propanol and cyclohexanol became the space group $P2_12_12_1$, where the dipeptides sheets stacked in the opposite direction, as shown by the arrows in Fig. 6. It is noteworthy that all dipeptide sheet structures resembled each other even though the stacking mode of the sheets was different. Similar guest-induced alternative stacking of dipeptides was observed in Lue-Ala with alkyl methyl sulfoxides.[11]

3. Conclusions

In summary, Thr-Phg as a new host dipeptide formed inclusion compounds with several aliphatic alcohols. These inclusion compounds were prepared easily and rapidly using a grinding method. In these inclusion compounds, Thr-Phg molecules were arranged in antiparallel to construct a monolayer sheet. The chiral recognition site of Thr-Phg discriminated *racemic* secondary alcohol, such as 2-butanol, 3-buten-2-ol, and 3-butyn-2-ol, in modest enantioselectivity (up to 57%). The hydroxy group of guest alcohols was trapped between $^{+}NH_3$ of Thr-Phg and OH of the neighboring Thr-Phg through hydrogen bonds in a pocket cavity. It is noteworthy that the hydroxy group of Thr-Phg played an important role in not only constructing a unique pocket but in also capturing guest alcohols. We succeeded in applying a hydroxy group of threonine to make a cavity suitable for the alcohol guests. Further investigation of molecular recognition using dipeptides containing threonine is in progress.

4. Experimental

4.1. General methods

NMR spectra were recorded at 300 MHz for ^{1}H NMR and 75.5 MHz for ^{13}C NMR. Melting points (decomposition) were measured on a TG-DTA. Both of (*S*)-threonine and (*S*)-phenylglycine (99% ee) were purchased from Tokyo Chemical Industry. Elemental analyses and high-resolution mass spectroscopy (HRMS) were performed at Chemical Analysis Center, Chiba University. The HRMS spectra using electrospray ionization (ESI) were obtained on a Thermo Scientific Exactive spectrometer. Powder X-ray diffractions were obtained with a MAC Science MXP diffractometer using graphite-monochromated Cu Kα radiation (30 kV, 200 mA). The spectra were measured at room temperature between 2° and 50° in the $2\theta/\theta$-scan mode with steps of 0.01° in 2θ and 4° min^{-1}.

4.2. Synthesis of Thr-Phg

The preparation of (*S*)-threonyl-(*S*)-phenylglycine [Thr-Phg] was usual synthesis procedure described in the previous paper.[7] According to the EDC/HOBt method,[12] coupling between (*S*)-*N*-(benzyloxycarbonyl)threonine[13] and (*S*)-phenylglycine benzyl ester *p*-toluenesulfonate[14] provided the protected dipeptide (80% yield). The deprotection by hydrogenolysis proceeded in the presence of Pd black to afford Thr-Phg quantitatively. Thr-Phg: white solid, mp 145.8–146.2 °C; $[\alpha]_{D^{25}}$ +114.09 (*c* 0.10, MeOH); ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm)=7.27–7.47 (m, 5H), 5.28 (s, 1H), 4.11 (m, 1H), 3.76 (d, *J*=6.0 Hz, 1H), 1.32 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (D_2O, 75.5 MHz): δ (ppm)=176.0, 167.0, 138.0, 129.1, 128.3, 127.4, 66.3, 60.0, 58.7, 18.7; IR (KBr) 3365, 1618, 1387, 1113, 698 (cm^{-1}). Anal. Calcd for $C_{12}H_{16}N_2O_4\cdot0.15H_2O\cdot0.05CH_3OH$: C, 56.41; H, 6.48; N, 10.92. Found: C, 56.71; H, 6.39; N, 10.63. HRMS (ESI) calcd for $C_{12}H_{16}N_2O_4Na$ $(M+Na)^+$ 275.1002, found 275.0996.

4.3. Preparation of inclusion compound of Thr-Phg by grinding method

Thr-Phg (0.50 mmol) and alcohol (0.3 mL) were mixed in an agate mortar until an excessive amount of alcohol evaporated. After addition of alcohol (0.2 mL), the similar mixing was performed. It took about 30 min. The residual solids are collected and analyzed. The ratios of guest/host were determined by ^{1}H NMR. After included alcohol was recovered by thermal decomposition of using a glass tube oven apparatus, the alcohol was reacted with phenylisocyanate to transform the *N*-phenylcarbamate. The enantiomeric excess was estimated as the *N*-phenylcarbamate by a chiral HPLC equipped with chiralcel OD-H or AD-H.

2-Butyl phenylcarbamate: HPLC (OD-H) eluent, hexane/2-propanol (9:1), flow rate=1.0 mL/min, t_R (*S*)=6.8 min, t_R (*R*)=13.0 min.

3-Buten-2-yl phenylcarbamate: HPLC (AD-H) eluent, hexane/2-propanol (9:1), flow rate=0.5 mL/min, t_R (*R*)=13.9 min, t_R (*S*)=15.5 min.

3-Butyn-2-yl phenylcarbamate: HPLC eluent (AD-H), hexane/2-propanol (9:1), flow rate=0.5 mL/min, t_R (*R*)=18.3 min, t_R (*S*)=23.2 min.

2-Pentyl phenylcarbamate: HPLC (OD-H) eluent, hexane/2-propanol (9:1), flow rate=1.0 mL/min, t_R (*S*)=6.1 min, t_R (*R*)=11.6 min.

4.4. Single-crystal X-ray analysis for inclusion compound of Thr-Phg

As a diffusion method, the alcohol guest (3.5 mL) was placed on a methanol (0.5 mL)/water (0.3 mL) solution of Thr-Phg (0.10 mmol) in a slender test tube. The samples were allowed to stand for several days to form the desirable single crystals in the interface between host and guest solutions. HRMS (ESI) of inclusion compounds detected not the host-guest complex but Thr-Phg.

Thr-Phg·1-PrOH: colorless crystal, mp 143.5–144.6 °C; ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm)=7.26–7.47 (m, 5H), 5.26 (s, 1H), 4.18 (m, 1H), 3.82 (d, *J*=5.1 Hz, 1H), 3.52 (t, *J*=6.9 Hz, 2H), 1.55 (m, 2H), 1.35 (d, *J*=6.3 Hz, 3H), 0.92 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (D_2O, 75.5 MHz): δ (ppm)=176.0, 167.0, 138.0, 129.1, 128.3, 127.4, 66.3, 63.7, 60.0, 58.7, 24.7, 18.7, 9.7. Powder X-ray analysis [Å(I/I_0)] 11.0 (1.00), 5.9 (0.12), 4.7 (0.28), 4.5 (0.17), 4.4 (0.22), 4.2 (0.19), 3.9 (0.17), 3.8 (0.21), 3.7 (0.16), 3.4 (0.17), 3.2 (0.12), 3.1 (0.14), 3.0 (0.12). Anal. Calcd for $C_{12}H_{16}N_2O_4\cdot0.7(C_3H_8O)\cdot0.5H_2O$: C, 55.84; H, 7.46; N, 9.24. Found: C, 55.85; H, 7.19; N, 9.27. HRMS (ESI) calcd for $C_{12}H_{16}N_2O_4Na$ $(M[Thr\text{-}Phg]+Na)^+$ 275.1002, found 275.1001.

Thr-Phg·2-PrOH: colorless crystal, mp 143.9–144.4 °C; ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm)=7.21–7.47 (m, 5H), 5.28 (s, 1H), 4.12 (m, 1H), 3.93 (m, 1H), 3.76 (d, *J*=3.0 Hz, 1H), 1.33 (d, *J*=6.0 Hz, 3H), 1.15 (d, *J*=6.3 Hz, 6H); ^{13}C NMR (D_2O, 75.5 MHz): δ (ppm)=176.0, 167.0, 138.0, 129.1, 128.3, 127.4, 66.3, 64.3, 60.0, 58.6, 23.8, 18.7. Powder X-ray analysis [Å(I/I_0)] 11.0 (1.00), 7.0 (0.19), 5.7 (0.10), 5.1 (0.11), 5.0 (0.11), 4.7 (0.27), 4.5 (0.35), 4.2 (0.27), 4.0 (0.15), 3.8 (0.33), 3.7 (0.18), 3.5 (0.16), 3.1 (0.13), 3.0 (0.10), 2.8 (0.11). Anal. Calcd for $C_{12}H_{16}N_2O_4\cdot0.9(C_3H_8O)\cdot0.44H_2O$: C, 56.18; H, 7.72; N, 8.91. Found: C, 56.18; H, 7.91; N, 9.11. HRMS (ESI) calcd for $C_{12}H_{16}N_2O_4Na$ $(M[Thr\text{-}Phg]+Na)^+$ 275.1002, found 275.0998.

Thr-Phg·2-BuOH: colorless crystal, mp 147.3–147.8 °C; ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm)=7.23–7.47 (m, 5H), 5.28 (s, 1H), 4.11 (m, 1H), 3.76 (d, *J*=5.7 Hz, 1H), 3.63 (m, 1H), 1.44 (m, 2H), 1.33 (d, *J*=6.3 Hz, 3H), 1.13 (d, *J*=6.3 Hz, 3H), 0.91 (t, 3H); ^{13}C NMR (D_2O, 75.5 MHz): δ (ppm)=176.0, 167.0, 138.0, 129.1, 128.3, 127.4, 69.5, 66.3, 60.0, 58.6, 30.9, 21.4, 18.7, 9.3. Powder X-ray analysis [Å(I/I_0)] 11.2 (1.00), 7.0 (0.20), 4.8 (0.29), 4.5 (0.41), 4.2 (0.19), 4.1 (0.16), 3.9 (0.20), 3.8 (0.45), 3.7 (0.18), 3.6 (0.18), 3.5 (0.26), 3.1 (0.13), 3.0 (0.11), 3.0 (0.11), 2.9 (0.15), 2.8 (0.17). Anal. Calcd for $C_{12}H_{16}N_2O_4\cdot0.95(C_4H_{10}O)\cdot0.19H_2O$: C, 58.19; H, 8.00; N, 8.59. Found: C, 58.19; H,

8.02; N, 8.64. HRMS (ESI) calcd for $C_{12}H_{16}N_2O_4Na$ (M[Thr-Phg]+Na)$^+$ 275.1002, found 275.1001.

Thr-Phg·cyclohexanol: colorless crystal, mp 151.1–151.4 °C; ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm)=7.24–7.46 (m, 5H), 5.29 (s, 1H), 4.12 (m, J=6.3 Hz, 1H), 3.75 (d, J=6.0 Hz, 1H), 3.52 (m, 1H), 1.86 (m, 2H), 1.74 (m, 2H), 1.58 (m, 1H), 1.35 (d, J=6.3 Hz, 3H), 1.33 (d, J=6.3 Hz, 1H), 1.14–1.28 (m, 4H); ^{13}C NMR (D_2O, 75.5 MHz): δ (ppm)=176.0, 167.0, 138.0, 129.1, 128.3, 127.4, 70.4, 66.3, 60.0, 58.6, 34.4, 25.0, 23.9, 18.7. Anal. Calcd for $C_{12}H_{16}N_2O_4\cdot 0.97(C_6H_{12}O)\cdot 0.10H_2O$: C, 60.94; H, 7.99; N, 7.98. Found: C, 60.79; H, 8.00; N, 7.95. HRMS (ESI) calcd for $C_{12}H_{16}N_2O_4Na$ (M[Thr-Phg]+Na)$^+$ 275.1002, found 275.0999.

4.5. Crystallograpic data for inclusion compounds

Data collection was performed on a Bruker APEXII CCD diffractometer with graphite-monochromated Mo Kα (λ=0.71073) radiation. The structures were solved by a direct method SHELXS-97[15] and refined by SHELXL-97[16] in a computer program package from Bruker AXS. Hydrogen atoms were calculated in appropriate position.

The inclusion compound of 1-propanol: $C_{15}H_{24}N_2O_5$, M_r=312.36, crystal dimensions 0.22×0.10×0.05 mm, orthorhombic, space group $P2_12_12_1$, T=173 K, a=8.4963(13) Å, b=9.1018(14) Å, c=22.062 (4) Å, V=1706.1(5) Å^3, Z=4, D_c=1.216 g cm^{-3}, μ=0.091 mm^{-1}, 4386 reflections collected, 1342 (R_{int}=0.0370) independent reflections, 208 refined parameters, R_1 ($I>2.0\sigma(I)$)=0.0304, wR_2 (all data)=0.0644, with heavy atoms refined anisotropically, residual electron density 0.087/−0.112.

The inclusion compound of 2-propanol: $C_{15}H_{24}N_2O_5$, M_r=312.36, crystal dimensions 0.32×0.20×0.08 mm, monoclinic, space group $P2_1$, T=173 K, a=8.5868(11) Å, b=9.0737(11) Å, c=11.3196(14) Å, β=103.465(2)°, V=857.71(18) Å^3, Z=2, D_c=1.209 g cm^{-3}, μ=0.091 mm^{-1}, 4810 reflections collected, 3292 (R_{int}=0.0180) independent reflections, 206 refined parameters, R_1 ($I>2.0\sigma(I)$)=0.0411, wR_2 (all data)=0.0984, with heavy atoms refined anisotropically, residual electron density 0.352/−0.208.

The inclusion compound of 2-butanol: $C_{16}H_{26}N_2O_5$, M_r=326.39, crystal dimensions 0.40×0.23×0.16 mm, monoclinic, space group $P2_1$, T=173 K, a=8.5632(18) Å, b=9.0563(19) Å, c=11.866(3) Å, β=107.598(2)°, V=877.1(3) Å^3, Z=2, D_c=1.236 g cm^{-3}, μ=0.092 mm^{-1}, 4972 reflections collected, 3510 (R_{int}=0.0259) independent reflections, 233 refined parameters, R_1 ($I>2.0\sigma(I)$)=0.0394, wR_2 (all data)=0.0975, with heavy atoms refined anisotropically, residual electron density 0.583/−0.319.

The inclusion compound of cyclohexanol: $C_{18}H_{28}N_2O_5$, M_r=352.42, crystal dimensions 0.37×0.29×0.12 mm, orthorhombic, space group $P2_12_12_1$, T=173 K, a=8.5464(9) Å, b=9.0873(9) Å, c=25.045(3) Å, V=1945.1(3) Å^3, Z=4, D_c=1.203 g cm^{-3}, μ=0.088 mm^{-1}, 10938 reflections collected, 4399 (R_{int}=0.0316) independent reflections, 231 refined parameters, R_1 ($I>2.0\sigma(I)$)=0.0369, wR_2 (all data)=0.0834, with heavy atoms refined anisotropically, residual electron density 0.213/−0.185.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 801221-801224. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail:deposit@ccdc.cam.ac.uk].

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References and notes

1. *Separations and Reactions in Organic Supramolecular Chemistry; Perspectives in Supramolecular Chemistry*; Toda, F., Bishop, R., Eds.; John Wiley: West Sussex, U.K, 2004; Vol. 8.
2. (a) Aburaya, K.; Murai, T.; Hisaki, I.; Tohnai, N.; Miyata, M. *Chem. Lett.* **2008**, *37*, 1224–1225; (b) Kato, K.; Aburaya, K.; Miyake, Y.; Sada, K.; Tohnai, N.; Miyata, M. *Chem. Commun.* **2003**, 2872–2873; (c) Aoki, Y.; Hishikawa, Y.; Sada, K.; Miyata, M. *Enantiomer* **2000**, *5*, 95–104; (d) Briozzo, P.; Kondo, T.; Sada, K.; Miyata, M.; Miki, K. *Acta Crystallogr., Sect. B* **1996**, *52*, 728–733; (e) Sada, K.; Kondo, T.; Miyata, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2655–2656.
3. (a) Toda, F.; Tanaka, K.; Mori, K. *Chem. Lett.* **1983**, 827–830; (b) Toda, F.; Tanaka, K.; Ueda, H. *Tetrahedron Lett.* **1981**, *22*, 4669–4672.
4. (a) Tanaka, K.; Honke, S.; Urbanczyk-Lipkowska, Z.; Toda, F. *Eur. J. Org. Chem.* **2000**, 3171–3176; (b) Kassai, C.; Juvancz, Z.; Bálint, J.; Fogassy, E.; Kozma, D. *Tetrahedron* **2000**, *56*, 8355–8359.
5. (a) Kodama, K.; Kobayashi, Y.; Saigo, K. *Cryst. Growth Des.* **2007**, *4*, 263–272; (b) Kodama, K.; Kobayashi, Y.; Saigo, K. *Chem.—Eur. J.* **2007**, *13*, 2144–2152; (c) Imai, Y.; Kawaguchi, K.; Sato, T.; Kuroda, R.; Matsubara, Y. *Tetrahedron Lett.* **2006**, *47*, 7885–7888; (d) Imai, Y.; Takeshita, M.; Sato, T.; Kuroda, R. *Chem. Commun.* **2006**, 1070–1072; (e) Imai, Y.; Sato, T.; Kuroda, R. *Chem. Commun.* **2005**, 3289–3291; (f) Kobayashi, Y.; Kodama, K.; Saigo, K. *Org. Lett.* **2004**, *6*, 2941–2944; (g) Sada, K.; Shiomi, N.; Miyata, M. *J. Am. Chem. Soc.* **1998**, *120*, 10543–10544.
6. (a) Akazome, M.; Takahashi, T.; Ogura, K. *J. Org. Chem.* **1999**, *64*, 2293–2300; (b) Akazome, M.; Sumikawa, A.; Sonobe, R.; Ogura, K. *Chem. Lett.* **1996**, 995–996.
7. (a) Görbitz, C. H. *Acta Crystallogr., Sect. B* **2002**, *58*, 849–854; (b) Görbitz, C. H. *Acta Crystallogr., Sect. C* **1999**, *55*, 2171–2177; (c) Görbitz, C. H. *Acta Crystallogr., Sect. C* **1999**, *55*, 670–672; (d) Görbitz, C. H. *Acta Crystallogr., Sect. B* **1999**, *55*, 104–113; (e) Görbitz, C. H. *Acta Chem. Scand.* **1998**, *52*, 1343–1349.
8. Friščič, T.; Jones, W. *Cryst. Growth Des.* **2009**, *9*, 1621–1637.
9. Akazome, M.; Ueno, Y.; Ooiso, H.; Ogura, K. *J. Org. Chem.* **2000**, *65*, 68–76.
10. (a) Görbitz, C. H. *Acta Crystallogr., Sect. C* **2000**, *56*, 500–502; (b) Görbitz, C. H. *Acta Crystallogr., Sect. C* **2008**, *64*, o171–o176.
11. Akazome, M.; Hirabayashi, A.; Kataoka, K.; Nomura, S.; Ogura, K. *Tetrahedron* **2005**, *61*, 1107–1113.
12. Nozaki, S.; Muramatsu, I. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2165–2168.
13. Doyle, F. P.; Fosker, G. R.; Nayler, J. H.; Smith, H. *J. Chem. Soc.* **1962**, 1440–1445.
14. Zervas, L.; Winitz, M.; Greenstein, J. P. *J. Org. Chem.* **1957**, *22*, 1515–1521.
15. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122 SHELXS97.
16. Sheldrick, G. M. *SHELXTL Version 5.10*; Bruker AXS: Madison, Wisconsin, USA, 1997.