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Asymmetric recognition of 1-arylethylamines by (*R*)-phenylglycyl-(*R*)-phenylglycine and its mechanism

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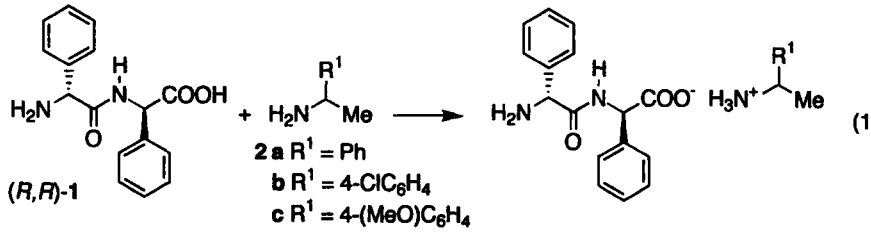
Abstract: An unprotected dipeptide, (*R*)-phenylglycyl-(*R*)-phenylglycine, which is insoluble in water, was shown to be an excellent resolving reagent for racemic 1-arylethylamines. By simply stirring the mixture of the dipeptide and racemic 1-phenylethylamine in presence of water, asymmetric recognition occurred to give a salt of (*S*)-1-phenylethylamine (95% ee) and the dipeptide. X-Ray crystallographic study of the salt elucidated the crystal structure of the diastereomeric salt, where hydrogen bonding and hydrophobic interaction between the dipeptide and amines play important roles in the construction of layers.

Introduction

Resolution of amines has a long history and numerous resolving reagents have been developed.[1] *N*-Protected chiral amino acids react with racemic amines to form the corresponding diastereomeric salts, which have been utilized for the resolution of several amines.[2] In the reverse sense, some chiral amines were used as resolving reagents for racemic *N*-protected amino acids such as phenylglycine.[3] However little attention has been paid to the use of dipeptides for resolution except for *N*-protected aspartylphenylalanine esters, which have a carboxyl group in the side-chain.[4] In the course of our studies on crystal engineering of dipeptides and their related compounds, it was found that (*R*)-phenylglycyl-(*R*)-phenylglycine molecules (*R,R*)-**1** construct a layer structure and alkyl phenyl sulfoxides are included with high enantioselectiviy in the void between the layers.[5] Furthermore, asymmetric salt formation of (*R,R*)-**1** with amines was investigated and we wish to report that (*R,R*)-**1** has a good ability to resolve racemic 1-arylethylamines (eq. 1).



Results and discussion

To a suspension of (*R,R*)-**1** in water was added racemic amine ($R^1CH(R^2)NH_2$; 2 molar equivalents), and the resulting mixture was stirred for 24 h. An insoluble salt was isolated by filtration, washed with benzene, and dried *in vacuo*. After the insoluble salt was again dissolved in aqueous sodium hydroxide, the liberated amine was extracted with dichloromethane. After benzoylation or acetylation, its enantiomeric excess was determined by chiral HPLC analysis.

The results using various amines are summarized in Table 1. The resolution was efficiently performed below 15°C (entries 1–3). In the case of 1-phenylethylamine **2a**, the corresponding amide was obtained

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Table 1. Resolution of asymmetric recognition of amines by (*R*,*R*)-**1**[a]

entry	amine $R^1CH(R^2)NH_2$ R^1	R^2		yield[d] / %	e.e.[e] / %
1	Ph	CH_3	**2a**[b]	86	92(*S*)
2[f]				83	95(*S*)
3[g]				90	63(*S*)
4	4-ClC_6H_4	CH_3	**2b**[b]	96	88(*S*)
5	4-$CH_3OC_6H_4$	CH_3	**2c**[b]	87	85(*S*)
6	Ph	CH_2CH_3	**2d**[c]	28	0
7	Ph	$CH_2CH_2CH_3$	**2e**[b]	69	27(*S*)
8	Ph	$CH_2CH(CH_3)_2$	**2f**[b]	90	28(*S*)
9	Cyclohexyl	CH_3	**2g**[b]	88	29(*S*)
10	Bz	CH_3	**2h**[b]	86	22(*R*)

[a] The mixture of (*R*,*R*)-**1** (0.5 mmol), amine (1.1 mmol), and water (1 mL) was stirred for 24 h at 15 °C. [b] The amine was isolated as an benzoyl derivative (see Experimental section). [c] The liberated amine was derived to the acetylamide using acetic anhydride. [d] Yield means mol% of the obtained amide based on the amount of the dipeptide. [e] Enantiomeric excess (e.e.) of the amide was determined by a chiral HPLC analysis (Daicel chiral cel OD). [f] at 8 °C. [g] at 30 °C.

in 83% yield based on the starting dipeptide, and the enantioselectivity of the liberated **2a** was very high (95% ee; *S*-form). 1-(4-Chlorophenyl)ethylamine **2b** and 1-(4-methoxyphenyl)ethylamine **2c** were resolved in 89% ee (*S*-form) and 85% ee (*S*-form) by (*R*,*R*)-**1**, respectively (entries 4 and 5).

Recently, Kinbara *et al.* interpreted the *p*-substituent effect on the resolution of 1-arylethylamines using mandelic acid, which is an oxygenated analogue of phenylglycine.[6] Since matching of molecular length between mandelic acid and 1-arylethylamines is important to the formation of the insoluble diastereomeric salts, 1-(4-methoxyphenyl)ethylamine is not resolved by (*R*)-mandelic acid. In contrast, the present resolution using (*R*,*R*)-**1** seems to be tolerant to the *p*-substituent of the 1-arylethylamine.

For racemic amines having ethyl, propyl, or isobutyl group, the yield of the corresponding amide was not only low but also the resolution efficiency was poor (entries 6–8). Similarly, 1-alkylethylamines (**2g** and **2h**) were not resolved effectively (entries 9 and 10).

Fortunately, we obtained a single crystal of the salt of (*S*)-**2a** and (*R*,*R*)-**1**, which was suitable for X-ray crystallography. The ORTEP view of crystal structure is shown in Figure 1. The salt is consisted of (*R*,*R*)-**1**, (*S*)-**2a**, and water. A perspective view (Figure 2) and its schematic representation (Figure 3) show that the remarkable feature of the crystal is the stacking of unique wavy sheets. Notably, two wavy sheets that are C_2 symmetric each other interlock by edge-to-face interaction between phenyl groups to form a flat layer. The resulting flat layers further stack to construct the crystal.

In addition to the salt formation between the amino group of (*S*)-**2a** and the carboxyl group of (*R*,*R*)-**1**, the following two hydrophobic interactions play an important role in the crystal packing: (1) the edge-to-face interaction between the benzene ring of (*S*)-**2a** and that of (*R*,*R*)-**1**, (2) the closed contact between methyl group of (*S*)-**2a** and the benzene ring of (*R*,*R*)-**1**. This effective three-point interaction is likely to explain high asymmetric recognition of **2a** by (*R*,*R*)-**1**. As for some longer alkyl groups such as ethyl, propyl, and *sec*-butyl groups, packing between the alkyl and the benzene ring of (*R*,*R*)-**1** does not match for the last interaction that are essential for the asymmetric recognition (*vide supra*).

As seen in Figure 4, the wavy sheet is formed *via* six sets of hydrogen bonding. The salt formation between the amino group of (*S*)-**2** and the carboxyl group of (*R*,*R*)-**1** is observed to contribute the

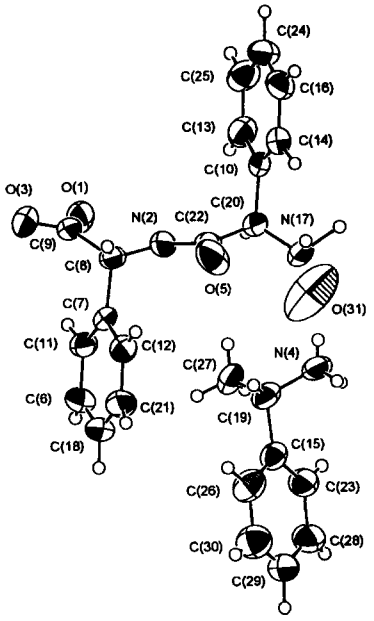

Figure 1. ORTEP drawing of the salt.

linkage along the b axis (N^4–O^1 and N^4–O^{*3}, 2.76 and 2.80 Å respectively). This is probably because the amino group of **2** is more basic than that of (*R*,*R*)-**1**.

The amino group of the dipeptide is bound to a water molecule with the 2.92 and 3.05 Å distances (N^{17}–O^{31} and N^{17}–O^{*31} respectively) to construct the linkage along the b axis. In addition, there are two sets of hydrogen bonding along the c axis between the amine and the amino group and between the carboxyl group and water (N^4–N^{17} and O^3–O^{31}, 2.92 and 2.91 Å respectively). As a result, a hydrogen bonding network constructs a wavy sheet structure (see Figs 2 and 3).

In summary, we revealed the asymmetric recognition of various amines with the simple dipeptide (*R*,*R*)-**1** and interaction between the dipeptide and an amine was clarified based on the crystal structure of the salts. These results suggest that the dipeptide serves as an excellent resolving agent for racemic amines.

Experimental

^{1}H-NMR Spectra were recorded on a Hitachi R-600 at 60 MHz or Varian Gemini 2000 at 300 MHz. The infrared spectra were recorded on a JASCO Herschel FT/IR-350. (*R*)-Phenylglycine (99% ee) was purchased from Tokyo Kasei Kogyo. Racemic amines were prepared from ketones and formamide according to the Leuckart reaction in the literature methods.[7]

Synthesis of (R)*-phenylglycyl-*(R)*-phenylglycine* (R,R)*-1*

Protection of the carboxylic group of (*R*)-phenylglycine was proceeded with benzyl alcohol in the presence of *p*-toluenesulfonic acid. On the other hand, protection of its amine group was performed by benzyloxycarbonyl chloride (Z-Chloride). Then the Z-protected (*R*)-phenylglycine and (*R*)-phenylglycine benzyl ester were coupled with DCC and HOBt. (*R*,*R*)-**1** was prepared by hydrogenation of the protected dipeptide (palladium black as a catalyst). All steps proceeded in excellent yield.

(*R*,*R*)-**1**: white powder, m.p. 220–223°C (decomp.), $[\alpha]_D^{25}=-137.2$ (c=0.99, 0.2M HCl) IR (KBr): 3370, 3300, 1676, 1560, 1508 cm^{-1}. ^{1}H-NMR (300 MHz: DCl+D_2O): 5.24 (s, 1H, NC*H*CO), 5.50 (s, 1H, NC*H*CO), 7.41–7.46 (m, 5H, Ph), 7.53 (s, br, 5H, Ph).

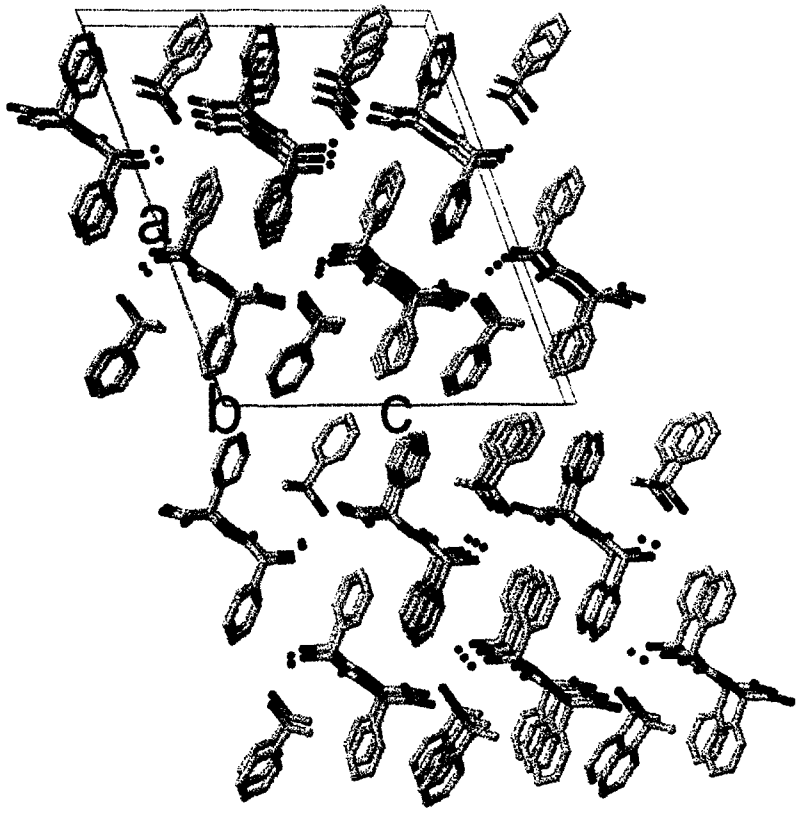

Figure 2. A perspective view of crystal packing.

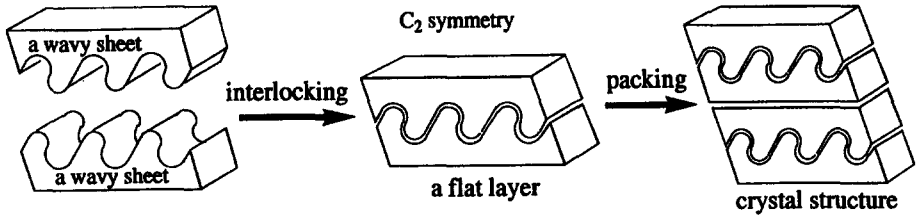

Figure 3. Schematic representation of crystal packing in the salt [(*R*,*R*)-**1**+(*S*)-**2a**+H_2O]

General procedure for the optical resolution

To a suspension of (*R*,*R*)-**1** (0.50 mmol) in water (1.0 ml) was added amine (1.1 mmol), the resulting mixture was stirred for 24 h at 15°C. The insoluble salt was filtered and washed with benzene (60 ml). The insoluble salt was dissolved in 0.4 M aqueous solution of sodium hydroxide, and extraction with dichloromethane (30 ml×2) was performed. After the combined organic layers were dried over potassium carbonate, benzoyl chloride (0.5 ml) and triethylamine (5 ml) were added. For acetylation, acetic anhydride (1.0 ml) was used instead of benzoyl chloride (0.5 ml). The mixture was stirred for 12 h at room temperature and then an aqueous solution of sodium hydroxide (0.4 M) was added. The mixture was extracted with dichloromethane (30 ml×2). The combined organic layers were dried over potassium carbonate, and concentrated under a reduced pressure. Column chromatography of the

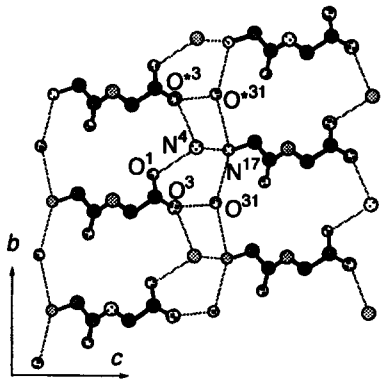

Figure 4. Hydrogen bond network (b-c plane). For clarity, alkyl and aryl groups were omitted.

residue on silica gel (eluent; benzene (100 ml), and then 25:1 chloroform/methanol (80 ml)) afforded the corresponding amide.

Enantiomeric excess of amines was determined by chiral HPLC: Column, Daicel Chiralcel OD (ϕ 4.6×250 mm). Absolute configuration was determined by comparison of the optical rotation with that reported in the literature.[8] Analytical conditions and retention time are following:

Benzoylated **2a**; eluent, hexane/2-propanol (9:1); flow rate, 0.7 ml/min, $t_R(R)$=18 min, $t_R(S)$=24 min.

Benzoylated **2b**; eluent, hexane/2-propanol (9:1); flow rate, 0.7 ml/min, $t_R(R)$=17 min, $t_R(S)$=28 min.

Benzoylated **2c**; eluent, hexane/2-propanol (9:1); flow rate, 0.7 ml/min, $t_R(R)$=22 min, $t_R(S)$=32 min.

Acetylated **2d**; eluent, hexane/2-propanol (30:1); flow rate, 0.9 ml/min, $t_R(R)$=35 min, $t_R(S)$=43 min.

Benzoylated **2e**; eluent, hexane/2-propanol (9:1); flow rate, 0.7 ml/min, $t_R(R)$=16 min, $t_R(S)$=21 min.

Benzoylated **2f**; eluent, hexane/2-propanol (9:1); flow rate, 0.5 ml/min, $t_R(R)$=16 min, $t_R(S)$=23 min.

Benzoylated **2g**; eluent, hexane/2-propanol (9:1); flow rate, 0.7 ml/min, $t_R(R)$=14 min, $t_R(S)$=21 min.

Benzoylated **2h**; eluent, hexane/2-propanol (9:1); flow rate, 0.5 ml/min, $t_R(R)$=24 min, $t_R(S)$=28 min.

Crystal data and structure refinement

(*R*,*R*)-**1** was dissolved in 0.1 M HCl and the pH to 6.5 was adjusted with 0.1 M NaOH. To the resulting (*R*,*R*)-**1** solution was added (*S*)-1-phenylethylamine, the mixture was allowed to stand for several weeks to afford colorless plate crystals.

Crystal data for the amine salt

$C_{24}H_{29}N_3O_4$, M 423.51. Crystal size 0.45×0.15×0.12 mm. Crystal system—monoclinic, space group A2 (No 5), a=22.068(6) Å, b=5.738(2) Å, c=18.790(5) Å, β=110.31(2)°, V=2231(1) Å^3, Z=4, D_{calcd}=1.26, η=6.648 cm^{-1}, F(000)=903, temperature 298 K. A Mac Science MXC18 four-circle diffractometer with graphite monochromated Cu Kα (λ=1.54178 Å) radiation was used. 2459 Reflections measured, 2325 independent. The structure was solved and refined by a computer program package; CRYSTAN-GM Ver. 6.2.1 from MAC Science Co. Ltd. *R*=0.0551 (1940 reflections with Fo>3σ(Fo)), *Rw*=0.0588, structure solved by direct methods (SIR 92[9] on a computer program package), 382 parameters, with heavy atoms refined anisotropically, residual electron density 0.24/−0.26. Further detail data have been deposited with the Cambridge Crystallographic Data Centre.[10]

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