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Resolution of α-aminolactams by inclusion complexation with chiral host compounds

Zofia Urbanczyk-Lipkowska,[a,*] Noriaki Fukuda[b] and Koichi Tanaka[b,*]

[a]*Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warszawa, Poland*
[b]*Department of Chemistry and Materials Engineering, Faculty of Chemistry, Materials and Bioengineering and High Technology Research Center, Kansai University, Suita, Osaka 564-8680, Japan*

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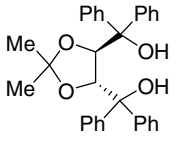
Abstract—3-Aminopiperidin-2-one and α-amino-ε-caprolactam were efficiently resolved by inclusion complexation with a chiral host compound, (*R*,*R*)-(−)-*trans*-4,5-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.5]decane. The amino substituent on the lactam ring was found to play an important role in efficient chiral recognition in the inclusion crystals.

1. Introduction

Recent interest in the preparation of enantiopure compounds has created a need for new separation methods yielding low molecular weight chiral starting compounds. One of the studied techniques is application of inclusion complexation methodology, that is, the formation of a molecular complex between a neutral chiral host and just one enantiomer from a racemate. The selectivity of this process is a derivative of host versatility, character of the guest (size, polarity, solubility, and ability of H-bond formation, etc.), and resolution conditions. In particular, chiral versatile hosts of tartaric acid origins **1** and **2** have been found a cheap and reliable selectors for resolution.[1] Moreover, these hosts can be used both in solution[2] and in the form of suspension,[3] such as in the case of the resolution of oily, racemic secondary alcohols, where high yields and ee were achieved. Herein we report a study on the resolution of racemic α-aminolactams **3**–**5** and α-methyl-lactams **6**–**8** by selective complexation with chiral hosts **1** and **2**. (*RS*)-α-Amino-ε-caprolactam **5** is widely used in organic synthesis and the resolution of its racemic mixture is of common interest. An interesting example of the resolution of (*RS*)-α-amino-ε-caprolactam **5**, by diastereomeric salt formation controlled by the dielectric constant of solution, has recently been reported.



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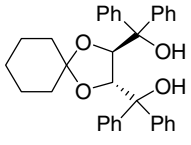

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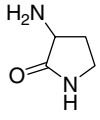

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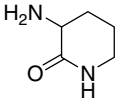

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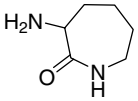

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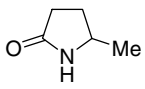

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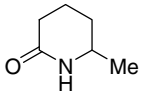

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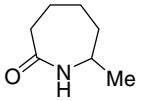

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It was shown that the chiral recognition of *N*-tosyl-(*S*)-phenylalanine can be switched between (*S*)-**5** and (*R*)-**5** by simply changing the solvent from MeOH ($\varepsilon = 33$) to an *i*-PrOH/H_2O (89:11) mixture ($\varepsilon = 25$).[4]

2. Results and discussion

A solution of (*R*,*R*)-(−)-**2** (0.66 g, 1.32 mmol) and (±)-**4** (0.30 g, 2.64 mmol) in toluene (10 ml) was kept at room

* Corresponding authors. Tel.: +48 22 343 2207; fax: +48 22 632 6681 (Z.U.-L.); tel./fax: +81 06 6339 4026 (K.T.); e-mail addresses: ocryst@icho.edu.pl; ktanaka@ipcku.kansai-u.ac.jp

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Table 1. Resolution of lactams **3**–**8** by inclusion complexation with optically active host compounds **1** and **2**

Guest	(*R*,*R*)-(−)-**1**		(*R*,*R*)-(−)-**2**	
	% ee[a]	Config.[b]	% ee	Config.
3	—	—	—	—
4	—	—	>99	(*S*)-(−)
5	>99	(*S*)-(−)	>99	(*S*)-(−)
6	4	(*S*)-(−)	9	(*S*)-(−)
7	69	(*R*)-(−)	24	(*R*)-(−)
8	5	(−)	14	(−)

[a] Enantiomeric excess was determined by HPLC.
[b] Absolute configuration was determined by comparison of the $[\alpha]_D$ sign.

temperature for several days, during which time colorless prisms of the 1:1 inclusion complex of (*R*,*R*)-(−)-**2** with (*S*)-(−)-**4** (0.37 g) were formed. From the 1:1 inclusion complex, (*S*)-(−)-**4** of >99% ee was obtained in 27% yield by silica-gel column chromatographic separation. The enantiomeric excess was determined by means of an HPLC column of Chiralpak AD-H (Daicel). Similarly, (±)-**5** was also efficiently resolved by complexation with (*R*,*R*)-(−)-**1** or (*R*,*R*)-(−)-**2** in >99% ee (Table 1). In contrast, (±)-**3** did not form any inclusion crystals with these host compounds. We next examined the resolution of methyl substituted lactams **6**–**8**. However, the resolution only occurred in the case of lactam **7** in 69% ee. These data suggested that the amino substituent of the lactam ring plays an important role in chiral recognition in inclusion crystals.

2.1. X-ray analysis

A marked difference in the enantiomeric excess between compounds **3**–**5** and **6**–**8** prompted us to analyze in detail the crystal structure of the successfully obtained crystalline complex and, in particular, the intermolecular interactions of all known crystalline complexes involving the studied hosts. Typically, hosts **1** and **2** form layered structures with the hydrophilic portion of the molecules inside and the hydrophobic portion outside of the layer. The hydrophilic part usually contains guest molecules kept by a system of hydrogen bonds between the host and the guest and, if appropriate, π–π interactions. From two sterically hindered OH groups of the host, one forms a strong intramolecular hydrogen bond. The second can act as a hydrogen bond donor to capture guest molecules. In the present case, the structure of the complex retains the above structural characteristics. The ORTEP view of the inclusion complex (*R*,*R*)-(−)-**1** and (*S*)-(−)-**5** shows guest molecules included between the two hosts belonging to the two different layers (Fig. 1). In the complex studied there is an excess of hydrogen bond donors over acceptors. Therefore, an additional intramolecular hydrogen bond is formed between an amino group and carbonyl oxygen atom of the guest molecules. Interestingly, the carbonyl group O6 atom of the α-amino-ε-caprolactam **5** is hidden between two hydrogen bond donating groups (amino and imino) and is not involved in any intermolecular H-bonding. Instead, the O3 atom of the host, which is already involved in the intramolecular H-bond, acts as an acceptor of the amide proton of the lactam. The free hydroxyl group O4 of the host forms an

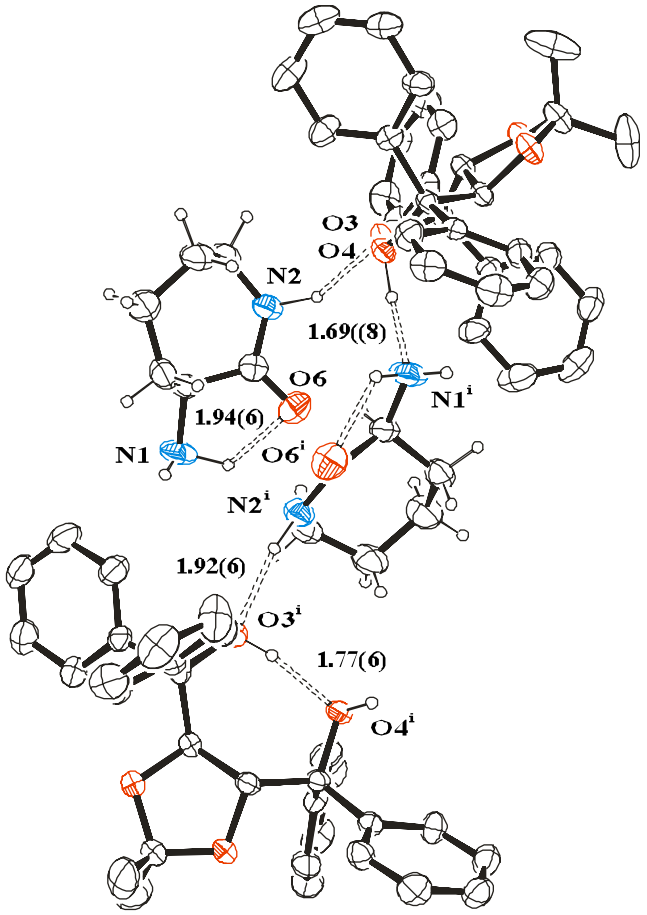

Figure 1. ORTEP view of the (1:1) complex between (*R*,*R*)-(−)-**1** and (*S*)-(−)-**5**, displaying 30% probability and H-bonding pattern: intramolecular: O3···O4 2.624(5), H3···O4 1.77(6) Å, angle N3–H3···O4 168(5)° and N1···O6 2.1…, H41···O6 1.94(6) Å, angle N1–H41···O6 115(5)°; intermolecular: N2···O3 2.895(6), H2···O3 1.92(6) Å, angle N2–H2···O3 149(6)°; O4···N1^{i} 2.725(6), H4···N2^{i} 1.69(8) Å, angle O4–H4···N1^{i} 178(7)° [i: 1 − *x*, *y* − 1/2, 1 − *z*].

H-bond with N1 of the amine group, which acts again as an acceptor (for details see Fig. 1). Furthermore, (*S*)-α-amino-ε-caprolactam molecule connects two layers of the hosts acting as hydrogen bond donor and acceptor.

Successful resolution with an inclusion complexation method requires two steps: selective recognition in solution between chiral host and one enantiomer of the guest with formation of a hetero-complex, and efficient packing of such a complex in the crystal. Both processes undergo in solution and are solvent dependent. In conclusion, it can be said that with this proton donor/acceptor ratio, the main role of the amino group is to act as an acceptor of the hydrogen bond. This facilitates the efficient chiral recognition and further stabilizes the crystal formation in toluene. The character of the cyclic lactams **6**–**8** with the methyl group is more lypophilic and therefore, the molecules have a higher affinity to solvent molecules than to the host compounds. In addition, the carbonyl group of the guests is again hidden between the methyl and imino groups and therefore, is inactive during host–guest

interactions. The absolute configuration of the α-amino-ε-caprolactam molecule determined by comparison of the known specific rotation of the free guest is in agreement with the X-ray data.

3. Experimental

Melting points were measured by Stanford Research Systems MPA-100. ^{1}H NMR spectra were obtained with a JEOL EX-270. IR spectra were recorded on a JASCO FT/IR 4100 spectrometer. Optical rotations were measured on an ATAGO AP-100 polarimeter and enantiomeric excesses were determined by HPLC on Chiralpak AD-H (Daicel).

3.1. Resolution of 3-aminopiperidin-2-one 4 by inclusion complexation with (*R*,*R*)-(−)-2

When a solution of (*R*,*R*)-(−)-**2** (0.66 g, 1.32 mmol) and (±)-**4** (0.30 g, 2.64 mmol) in toluene (10 ml) was kept at room temperature for several days, colorless prisms of the 1:1 inclusion complex of (*R*,*R*)-(−)-**2** with (*S*)-(−)-**4** (0.37 g, mp 160–166 °C) were formed. The crystals were analyzed by ^{1}H NMR spectra to determine the host–guest ratios. From the 1:1 inclusion complex, (*S*)-(−)-**4** (0.04 g, 27% yield, >99% ee) was obtained by silica-gel column chromatographic separation. The enantiomeric excess was determined by HPLC analysis with Chiralpak AD-H (Daicel Chemical Industries, Ltd); eluent, hexane/EtOH = 80/20; flow rate, 0.5 ml/min; detection, UV 220 nm; retention time, 38 min (*S*-enantiomer) and 35 min (*R*-enantiomer).

3.2. Resolution of α-amino-ε-caprolactam 5 by inclusion complexation with (*R*,*R*)-(−)-1

When a solution of (*R*,*R*)-(−)-**1** (1.21 g, 2.6 mmol) and (±)-**5** (0.66 g, 5.2 mmol) in toluene (20 ml) was kept at room temperature for several days, colorless prisms of the 1:1 inclusion complex of (*R*,*R*)-(−)-**1** with (*S*)-(−)-**5** (0.84 g, mp 162–167 °C) were formed. The crystals were analyzed by ^{1}H NMR spectra to determine the host–guest ratio. From the 1:1 inclusion complex, (*S*)-(−)-**5** (0.10 g, 30% yield, >99% ee) was obtained by silica-gel column chromatographic separation. The enantiomeric excess was determined by HPLC analysis with Chiralpak AD-H (Daicel Chemical Industries, Ltd); eluent, hexane/EtOH = 80/20; flow rate, 0.5 ml/min; detection, UV 220 nm; retention time, 31 min (*S*-enantiomer) and 33 min (*R*-enantiomer).

3.3. Resolution of 6-methyl-2-piperidone 7 by inclusion complexation with (*R*,*R*)-(−)-1

When a solution of (*R*,*R*)-(−)-**1** (0.62 g, 1.33 mmol) and (±)-**7** (0.30 g, 2.65 mmol) in toluene (10 ml) was kept at room temperature for several days, colorless prisms of the inclusion complex of (*R*,*R*)-(−)-**1** and (*R*)-(−)-**7** (0.23 g, mp 144–146 °C) were obtained. Upon heating of the inclusion complex at 210 °C in vacuo, (*R*)-(−)-**7** was obtained in 69% ee (0.016 g, 28% yield). The enantiomeric excess was determined by HPLC analysis with Chiralpak AD-H (Daicel Chemical Industries, Ltd); eluent, hexane/EtOH = 80/20; flow rate, 0.5 ml/min; detection, UV 220 nm; retention time, 17 min (*S*-enantiomer) and 15 min (*R*-enantiomer).

3.4. X-ray diffraction

A suitable crystal was mounted on a glass fiber. Data collection was performed at 295 K on a Nonius BV MACH diffractometer with graphite monochromated CuKα ($\lambda = 1.54178$ Å). The structure was solved with direct methods using the SHELXS97[5] and refined with SHELXL97[6] software. Refinement was performed anisotropically for all non-hydrogen atoms using the full-matrix least-squares method. In general, hydrogen atoms were assigned to idealized positions and were allowed to ride with thermal parameters fixed at $1.2U_{eq}$ of the parent atom. Hydroxyl group H-atoms were localized from $\Delta\rho$ maps and refined. The residual electron densities were of no chemical significance. *Crystal data*: (1:1) Inclusion complex of (*R*,*R*)-(−)-**1** and (*S*)-(−)-**5**: $C_{37}H_{42}N_2O_5$ $F_w = 599.77$; monoclinic space group $P2_1$, $a = 9.719(2)$, $b = 9.763(2)$, $c = 17.583(4)$ Å, $\beta = 100.66(3)°$, $V = 1639.6(6)$ Å^3, $Z = 2$, $D_c = 1.205$, $F(0\,0\,0) = 1272$. 3487 reflections collected in the θ-range 5.61–74.05°, 3385 unique [R(int) = 0.04]. Final R index $R_1 = 0.0490$ [1891 reflections with $I > 2\sigma(I)$], and for all data $wR = 0.1540$, $S = 1.053$; Flack parameter −0.1(4).

CCDC-643247, contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at 'http://www.ccdc.cam.ac.uk/conts/retrieving.html' [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam.sc.uk].

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