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Optically Active *Anti* Head-to-head Coumarin Dimer. A New Agent for the Determination of Enantiomeric Excess of Amines and Alcohols

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The enantiomeric excess of chiral amines was successfully determined by ^{1}H NMR spectral and/or HPLC analysis of the diastereomeric diamides derived from optically active *anti* head-to-head coumarin dimer and the amines by lactone-ring-opening reaction without any condensing agent. This procedure also proved to be applicable to chiral alcohols.

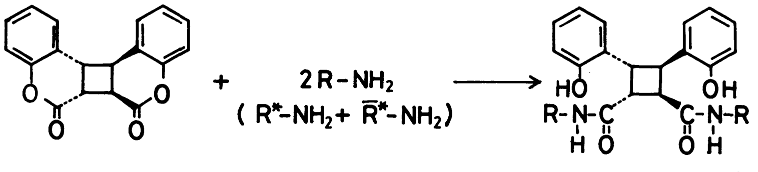
Methods for determining the enantiomeric excess of a chiral amine or alcohol include NMR spectral analysis using a chiral lanthanoid shift reagent[1] and chromatographic or NMR spectral analysis of a mixture of the diastereomeric amides or esters obtained by the reaction of an amine or alcohol with an optically active derivatizing agent such as 2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid,[2] 1-(1-naphthyl)ethyl isocyanate,[3] and 2-[1-(9-anthryl)-2,2,2-trifluoroethoxy] acetic acid.[4] The latter method gives more accurate values than the former and is applicable to the chromatographic separation of the diastereomers. The former method is more convenient and advantageous in the recovery of the amine or alcohol.

In the previous paper[5] it was shown that *anti* head-to-head coumarin dimer can be easily resolved into pure enantiomers by fractional crystallization of the lactone-ring-opened diastereomeric diamides with (*S*)-(−)-1-phenylethylamine followed by hydrolysis and relactonization. The optically active dimer reacts with two molar equivalents of (*S*)-(−)-1-phenylethylamine to give the corresponding diamides, which are diastereomeric and thus show different chemical shifts in the ^{1}H NMR spectra and retention time in HPLC. Accordingly, the optically active dimer was considered to be useful as a chiral derivatizing agent. We report here the use of the optically active dimer in the determination of the enantiomeric excess of a chiral amine or alcohol on the basis of ^{1}H NMR spectral and/or HPLC analysis.

Results and Discussion

The reaction of (*R*,*R*,*R*,*R*)-(−)$_{589}$-*anti* head-to-head coumarin dimer ((−)-**1**) with two molar equivalents of a racemic primary amine (**2**) at 60 °C for 3 h was effected smoothly to give a mixture of three diastereomeric diamides (**3**, **4**, and **5**) in high yield. For example, when 1-phenylethylamine (**2a**) was used as the racemic amine substrate, a mixture of diastereomeric diamides (**3a**, **4a**, and **5a**) was obtained in 99% yield. The diastereomer distribution was based on the ^{1}H NMR spectral data. The methyl proton signals of the diastereomer mixture appeared at two isolated magnetic fields, δ 0.7—1.0 ppm (one doublet) and δ 1.1—1.4 ppm (two doublets), and the area ratio of these two distinct regions was 1:1 as shown in Fig. 1. On the basis of the chemical shifts of methyl protons of **3a** and the enantiomer of **5a** as reported in our previous paper,[5] it is concluded that the methyl proton signal of **3a** appeared at a higher magnetic field than that of **5a** by virtue of the shielding by the cis-oriented hydroxyphenyl group. The two methyl proton signals arising from (*S*)- and (*R*)-1-phenylethylamino moieties in **4a** might be observed in almost the same regions of the magnetic field as those in **3a** and **5a**, respectively. Similarly, methyl proton signals were observed in two regions with an area ratio of 1:1 when either 1-(4-isopropylphenyl)ethylamine (**2b**), 1-phenylpropylamine (**2c**), *s*-butylamine (**2d**), norephedrine (**2e**), or 2-amino-1-butanol (**2f**) were employed as the primary amine substrate. The results from the synthesis of diastereomer mixtures and the chemical shifts of their methyl proton signals are shown in Table 1.

For amino alcohols such as **2e** and **2f**, the preferred reaction of the amino functions with **1** was established



1
(*R*,*R*,*R*,*R*)

2

3: R^*-(*R*,*R*,*R*,*R*)-R^*
4: $\bar{\mathrm{R}}^*$-(*R*,*R*,*R*,*R*)-R^*
5: $\bar{\mathrm{R}}^*$-(*R*,*R*,*R*,*R*)-$\bar{\mathrm{R}}^*$

by the exclusive formation of diastereomeric diamides, and no ester formation was detected in their IR spectra. The low reactivity of the alcohol under these conditions was confirmed by the separate reactions of (−)-**1** with methanol and ethanol, which gave no esters and resulted in the quantitative recovery of (−)-**1**. The versatility of **1** as an optically active derivatizing agent is enhanced by the observation that the β-methyl protons in the amine having an α-asymmetric carbon such as **2c** and **2f** are also shielded by the cis-oriented hydroxyphenyl group, yielding methyl proton signals of the diastereomer mixtures in two distinct regions. Moreover, it is advantageous that the amide formation requires no condensing agent.

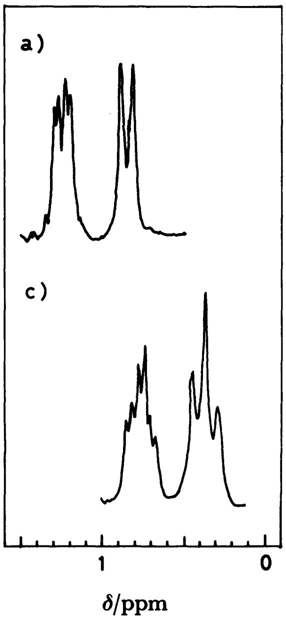


Fig. 1. ^{1}H NMR spectra of methyl protons of diastereomeric diamide mixtures: a) of **3a**, **4a**, and **5a**; c) **3c**, **4c**, and **5c**.

The HPLC of the diastereomer mixture (**3**, **4**, and **5**) showed three base-line separated peaks. Typical examples are shown in Fig. 2. The area ratio of **3a**, **4a**, and **5a** obtained from (−)-**1** and racemic **2a** was 25.4:49.7:24.9, giving the enantiomer ratio of 50.3:49.7. Moreover, the HPLC analysis of minus-enantiomer-enriched **2a** (49.4% optical purity based on its specific rotation) showed the area ratio of 56.7:40.4:2.9, representing 53.8% of enantiomeric excess. The ratios are in good agreement with those predicted. Similarly, the distribution of **3**, **4**, and **5**

Table 1. Yield and chemical shifts of diastereomeric diamide mixture (**3**, **4**, and **5**)

Amine	Yield/%	Methyl proton/δ, ppm (DMSO-d_6)	
2a	99	0.85	1.25 1.27
2b	97	0.83	1.15
2c	97	0.35	0.76
2d	95	0.42	0.90
2e	95	0.34	0.72
2f	96	0.32	0.75 0.78

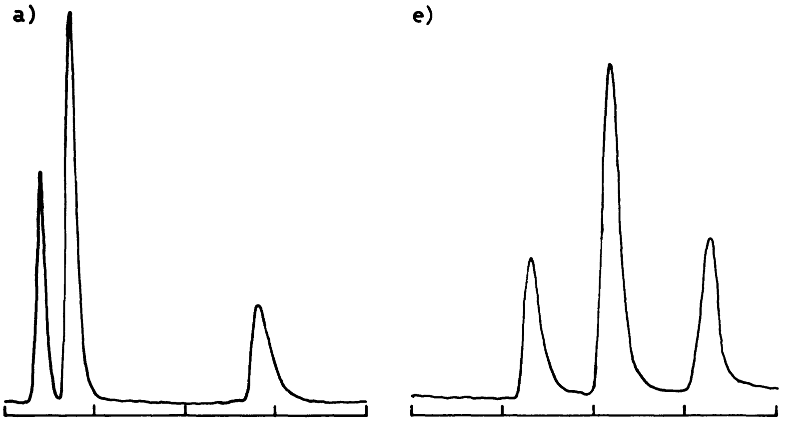


Fig. 2. HPLC of diastereomeric diamide mixtures: a) **3a**, **4a**, and **5a**; e) **3e**, **4e**, and **5e**.

Table 2. HPLC of diastereomeric diamide mixture (**3**, **4**, and **5**)

Diamide	Retention Time/min			Area ratio/%			Eluent
a	13.9	17.7	38.4	25.4	49.7	24.9	C_6H_6/AcOEt = 60/40
b	12.1	15.9	47.3	26.0	48.3	25.7	70/30
c	43.8	62.1	126.4	23.9	53.7	22.4	80/20
d	22.6	28.3	39.4	24.9	50.4	24.7	50/50
e	32.8	41.5	52.3	22.6	52.0	25.4	50/50
f	14.2	19.3	35.6	24.9	47.1	28.0	MeOH/AcOEt = 8/92

prepared from **2b**—**2f** was in nearly 1:2:1 area ratio as shown in Table 2. These results indicate that the HPLC analysis of the diastereomeric diamides prepared from optically active **1** and a given chiral amine is also useful for the determination of enantiomeric excess of the amine. No measurable kinetic resolution was considered to occur during the course of the ring-opening reaction since the reactions of racemic **1** with racemic amines (**2a**—**2f**) gave the corresponding diastereomer mixtures in high yields and in the area ratio of 1:2:1 as determined by HPLC.

The HPLC of the reaction mixture of (—)-**1** and **2a**, obtained without work-up, also showed three peaks of **3a**, **4a**, and **5a** in the area ratio of nearly 1:2:1. Small peaks due to impurities in different regions from the main peaks were also noted. The result indicates that the work-up is not always necessary for the HPLC analysis.

The reaction of **1** with an alcohol was reexamined to see if **1** can also be used as an optically active derivatizing agent for alcohols, since the reaction did not take place under the conditions of 60 °C for 3 h as mentioned above. After some elaboration, two equimolar amounts of lithium alcoholate were found to effect the reaction smoothly with (—)-**1** at room temperature to give a mixture of three diastereomeric esters (**7**, **8**, and **9**) in good yield. In the case of the diastereomeric diesters derived from alcohols having an α-asymmetric carbon and an α-methyl such as 1-phenylethanol (**6a**) and 2-butanol (**6b**), the methyl proton signals were also observed at two regions in the area ratio of 1:1 in their ^{1}H NMR spectra, respectively. However those of the diastereomer mixture obtained from 2-phenyl-1-propanol (**6c**) having a β-asymmetric carbon and a β-methyl were observed with difficulty in almost the same region. HPLC analysis of the diastereomer mixtures, obtained not only with **6a** and **6b** but also with **6c** gave satisfactory results. In all cases, three peaks were observed with base-line separation, and the area ratios of the peaks approximated to 1:2:1. The results are shown in Tables 3 and 4.

TABLE 3. YIELD AND CHEMICAL SHIFTS OF DIASTEREOMERIC DIESTER MIXTURE (**7**, **8**, AND **9**)

Alcohol	Yield/%	Methyl proton/δ, ppm (DMSO-d_6)		
6a	99	0.83	1.21	1.23
6b	99	0.52	0.97	
6c	99		1.01	

Experimental

The ^{1}H NMR and IR spectra were recorded on a Hitachi R-40 Spectrometer (90 MHz) and a JASCO IRA-1 Spectrophotometer, respectively. The HPLC analyses were carried out on a LiChrosorb SI-60 column (4×250 mm) under the conditions of 70 kg/cm^2 and 0.5 ml/min using a Shimadzu SPD-2A UV detector (280 or 285 nm).

Materials. Optically active coumarin dimer (**1**) was prepared by the method reported in the previous paper.[5] The racemic amines (**2a**—**2d** and **2f**) were dried overnight with NaOH pellets and distilled carefully under an argon atmosphere or under reduced pressure in the presence of NaOH pellets. Norephedrine (**2e**) was regenerated from its hydrochloric acid salt, dried overnight, and used without recrystallization. The alcohols (**6a**—**6c**) were predried with molecular sieves 3A for 1 d and distilled before use.

General Procedure for the Preparation of Diastereomeric Diamide Mixture. A mixture of (—)-**1** (1.0 mmol) and the racemic amine (2.0 mmol) in dry dioxane (4.5 ml) was warmed at 60 °C for 3 h under an argon atmosphere. The residue, left after evaporation of the solvent, was dissolved in chloroform or ethyl acetate (150—200 ml) and washed successively with 1 M HCl solution (50 ml×2, 1 M=1 mol dm^{-3}), 4% NaHCO$_3$ solution (50 ml), and sat. NaCl solution (50 ml). After drying over anhydrous Na$_2$SO$_4$, evaporation of the solvent followed by drying under reduced pressure at about 45 °C for 1 d gave a mixture of three diastereomeric diamides (**3**, **4**, and **5**).

General Procedure for the Preparation of Diastereomeric Diester Mixture. To a solution of the alcohol (2.0 mmol) in dry dioxane (4 ml) was added a hexane solution of butyllithium (2.1 mmol) on cooling, and the mixture was stirred at room temperature for 1 h. A solution of (—)-**1** (1.0 mmol) in dry dioxane (4 ml) was added at room temperature dropwise during a period of 20 min. After stirring at the temperature for 24 h, the solvent was removed under reduced pressure. The remaining residue was dissolved in ethyl acetate (100 ml), washed successively with 0.2 M HCl solution (15 ml) and water (50 ml), and dried over anhydrous Na$_2$SO$_4$. Evaporation of the solvent to dryness gave the corresponding mixture of diastereomeric diesters (**7**, **8**, and **9**).

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TABLE 4. HPLC OF DIASTEREOMERIC DIESTER MIXTURE (**7**, **8**, AND **9**)

Diester	Retention Time/min			Area ratio/%			Eluent
a	11.2	12.9	14.9	27.4	47.4	25.2	C$_6$H$_6$/AcOEt = 90/10
b	29.1	33.1	37.8	26.4	48.0	25.6	93/7
c	37.0	40.8	45.3	25.6	46.9	27.5	C$_6$H$_6$/CH$_3$CN = 96/4

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