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Determination of Enantiomeric Excesses of Chiral Amines by Using an Enantiomerically Pure *Anti* Head-to-Head Coumarin Dimer Derivative

Yutaka Adegawa, Takeshi Kashima, and Kazuhiko Saigo*

Department of Synthetic Chemistry, Faculty of Engineering, The University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113, Japan

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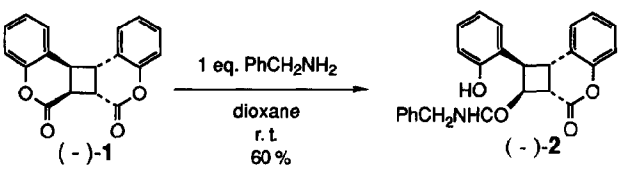
Abstract: Monolactone-monoamide **2**, prepared from enantiomerically pure (*S,S,S,S*)-(-)-*anti* head-to-head coumarin dimer (**1**) and an equimolar amount of benzylamine, was easily reacted with chiral amines to give mixtures of diastereomeric diamides without any condensing agent. The enantiomeric excesses of the chiral amines were successfully determined by ^{1}H NMR spectral and/or HPLC analysis of the mixtures of diastereomeric diamides.

Derivatization of a chiral compound with an enantiomerically pure (enantiopure) reagent is widely used for the assay of enantiomeric excess (ee) of the chiral compound by NMR and chromatographic techniques. A considerable number of studies have been made concerning the development of enantiopure derivatizing agents.[1] For example, it has been shown from our laboratory that enantiopure *anti* head-to-head coumarin dimer (**1**)[2] reacted with two molar amounts of chiral amines to give mixtures of diastereomeric diamides (diastereodiamides), which showed nonequivalent chemical shifts in their ^{1}H NMR spectra and different retention times in their high performance liquid chromatography (HPLC).[3] However, since **1** is a difunctional compound, the reaction of (*S,S,S,S*)-(-)-**1** with both enantiomers of a chiral amine gives a mixture of three kinds of diastereodiamides, resulting in the complication in the ^{1}H NMR and HPLC analyses.

Recently, we found that a monolactone-monoamide was easily prepared by the reaction of (-)-**1** with an equimolar amount of a certain achiral amine. Such an easy preparation of a monolactone-monoamide is attributable to: 1) The difference in reactivity between two lactone rings in **1**; when one of the lactone rings is opened by a nucleophile, the reactivity of the other lactone ring is lowered due to the release of the strain. 2) The difference in solubility between dilactone **1** and the monolactone-monoamide; the deposition of the monolactone-monoamide from the reaction solution prevents the second lactone ring-opening reaction. Moreover, in the reaction of a monolactone-monoamide with chiral amines, kinetic resolution of the amines did not occur.[4] These observations indicate that a monolactone-monoamide derived from **1** is potent as an enantiopure derivatizing reagent. In this paper, we describe the determination of the enantiomeric excesses of chiral amines by using an enantiopure monolactone-monoamide.

Benzylamine was used as an achiral amine for the synthesis of a monolactone-monoamide derivative



(-)-**1** (-)-**2**

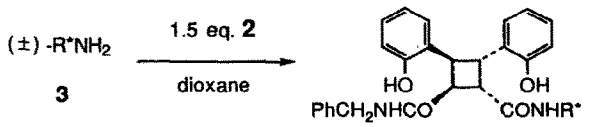


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Table 1. Ring-opening addition reaction of **2** with racemic amines **3**

amine	temp ℃	time h	yield[a] %
3a	30	5.5	86
3b	50	8.0	98
3c	50	5.5	78
3d	50	8.0	90
3e	30	5.5	78

a) Isolated by silica gel column chromatography.

from enantiopure **1**, taking into account its high nuleophilicity and the region in which its ^{1}H NMR signals appear. When (-)-**1** was allowed to react with an equimolar amount of benzylamine in 1,4-dioxane at room temperature, a white precipitate was deposited. The precipitate comprised only monolactone-monoamide (-)-**2**, which was confirmed on the basis of HPLC analysis as well as ^{1}H NMR and IR spectral analyses.[5]

Monolactone-monoamide (-)-**2** easily reacted with racemic amines, such as *sec*-butylamine (**3a**), 1-phenylethylamine (**3b**), 2-amino-1-butanol (**3c**), 1-amino-2-propanol (**3d**), and 2-methylbutylamine (**3e**), in 1,4-dioxane at 30 or 50 °C to give the corresponding pairs of diastereodiamides (Table 1).[6] In each Runs, after the complete consumption of the amine was checked by thin layer chromatography (TLC), the reaction mixture was concentrated to dryness and was directly analyzed by ^{1}H NMR without isolation of diamide **4**.[6] Since no signal arising from the skeleton of **2** was observed in a magnetic field higher than 3 ppm in the ^{1}H NMR spectrum of the concentrated reaction mixture, the methyl proton signals arising from the amine moiety of the mixture of diastereodiamides were clearly observed in the magnetic field. Moreover, the methyl proton signals appeared apart from each other (Table 2), and the area ratio for the methyl proton signals was almost 1:1, representative of the ee of the amine. A typical example is shown in Fig. 1.

It is noteworthy that non-equivalence in chemical shift of methyl proton signals was observed not only for an amine having a methyl moiety at the α-asymmetric carbon from the nitrogen but also for an amine having a methyl moiety at the β-asymmetric carbon from the nitrogen. In addition, diastereodiamides **4** exhibit larger

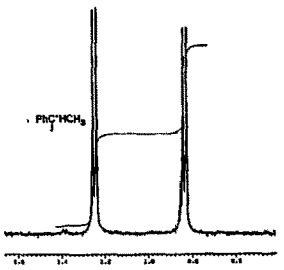

Fig. 1. ^{1}H NMR spectrum of **4b**.

Table 2. Non-equivalence in chemical shift of mixtures of diastereodiamides

diamide	methyl protons[a] δ, ppm			solvent
4a	0.35	0.74	(β-methyl triplet)	DMSO-d_6
4b	0.84	1.25	(α-methyl doublet)	DMSO-d_6
4c	0.29	0.75	(β-methyl triplet)	DMSO-d_6
4d	0.90	0.98	(α-methyl doublet)	$CDCl_3$
4e	0.66	0.69	(α-methyl doublet)	$CDCl_3$

a) By JEOL GX-400 spectrometer (400 MHz).

Δδ than the corresponding α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA)-derived diastereomeric amides. For example, the α-methyl doublets of diastereodiamides **4a** resonated 0.39 ppm (DMSO-d_6, 295K) apart from each other, while Δδ between the α-methyl doublets of the corresponding MTPA-derived diastereomeric amides was only 0.07 ppm under similar conditions ($CDCl_3$, 298K).[7] It can be said with fair certainty that such a large Δδ arises from the shielding effect by the *cis*-oriented hydroxyphenyl moiety in diamide **4a**.

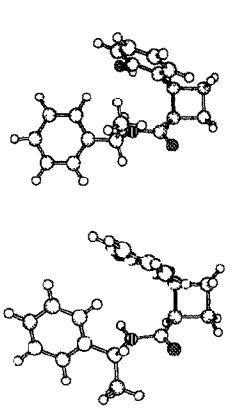

Fig. 2. The optimized structures of model compounds: a) (*S*,*S*)-(*S*)-**5**; b) (*S*,*S*)-(*R*)-**5**.

In order to apply the present method to the prediction of the absolute configurations of chiral amines, the correlation between absolute configuration and non-equivalence in ^1H NMR chemical shift was investigated. At first, semiempirical MO calculations with PM3 Hamiltonian were performed for the model compounds of both diastereomers of **4b**.[8] The optimized structures of model compounds (*S*,*S*)-(*S*)-**5** and (*S*,*S*)-(*R*)-**5** are shown in Fig. 2. As can be seen from Fig. 2, the α-methyl group of (*S*,*S*)-(*S*)-**5** is more effectively shielded by the hydroxyphenyl moiety than that of (*S*,*S*)-(*R*)-**5**. This result is in good agreement with the fact that the α-methyl signal arising from the amine moiety in (*S*,*S*,*S*,*S*)-(*S*)-**4b** is observed at higher magnetic field than that in the corresponding (*S*,*S*,*S*,*S*)-(*R*)-**4b**. From these results, the absolute configuration of an amine having a methyl moiety at the α-asymmetric carbon from the nitrogen is considered to be determinable on the basis of the non-equivalence in ^1H NMR chemical shift of **4**, derived from (*S*,*S*,*S*,*S*)-(-)-**2** and the amine. Validity of this method was examined for 1-(1-naphtyl)ethylamine (**3f**) and 2-amino-1-propanol (**3g**). Pairs of diastereodiamides **4f** and **4g** were prepared by the reaction of (*S*,*S*,*S*,*S*)-(-)-**2** with both enantiomers of **3f** and **3g**, and their ^1H NMR were measured. The α-methyl doublet in each (*S*,*S*,*S*,*S*)-(*S*)-form was observed in a magnetic field higher than that in the corresponding (*S*,*S*,*S*,*S*)-(*R*)-form, as was expected.

The enantiomeric excesses of chiral amines **4a-d** could be also determined by the HPLC analysis of the concentrated reaction mixtures. Each HPLC profile showed three base-line separated peaks, which were attributable to **2** and both diastereomers of **4**. Moreover, the area ratio for the two diastereomers, was almost 1:1, representative of the ee of the amine (Table 3).

Table 3. HPLC analysis of mixtures of diastereodiamides

diamide	retention time min		area ratio %		eluent
4a	8.60	11.78	48.2	51.8	EtOAc/$CHCl_3$=1/1[b]
4b	4.79	8.88	52.8	47.2	EtOAc/Hexane=1/1[b]
4c	3.84	5.76	47.7	52.3	$CHCl_3$/MeOH=11/1[c]
4d	11.80	13.66	49.4	50.6	$CHCl_3$/MeOH=20/1[c]
4e	44.80	46.11	———	[a]	$CHCl_3$/MeOH=75/1[d]

a) Partially resolved. b) LiChrosorb Si 60. Flow rate: 1.0 ml min^{-1}. c) LiChrospher Si 60. Flow rate: 1.0 ml min^{-1}. d) LiChrosorb Si 60. Flow rate: 0.5 ml min^{-1}.

The assay of the ee of a partially resolved chiral amine was performed in practice: (-)-**4** was allowed to react with 0.67 equimolar amount of (*S*)-(-)-enantiomer-enriched **3b** (87% optical purity on the basis of its specific rotation; 87% ee on the basis of the ^{1}H NMR analysis of its MTPA-derived amide), and then the concentrated reaction mixture was directly analyzed by ^{1}H NMR (500 MHz). The area ratio for the α-methyl doublets of the mixture of diastereodiamides **4b** was 93.6:6.4, representative of 87% ee. The value is in good agreement with that expected.

The ^{1}H NMR and HPLC analyses of a mixture of diastereodiamides, prepared from enantiopure **2** and a given chiral amine, are applicable for the determination of the ee of the amine. Moreover, the present amide formation requires no condensing agent, and no work-up is necessary. From these points of view, enantiopure monolactone-monoamide **2** is quite useful as a chiral derivatizing agent.

References and Notes

1) For a review; I. T. Horvath and J. M. Millar, *Chem. Rev.*, **91**, 1441 (1991).

2) K. Saigo, N. Yonezawa, K. Sekimoto, M. Hasegawa, K. Ueno, and H. Nakanishi, *Bull. Chem. Soc. Jpn.*, **58**, 1000 (1985). Correction for the absolute configuration of *anti* head-to-head coumarin dimer; *Bull. Chem. Soc. Jpn.* **60**, 2704 (1987).

3) K. Saigo, K. Sekimoto, N. Yonezawa, F. Ishii, and M. Hasegawa, *Bull. Chem. Soc. Jpn*, **58**, 1006 (1985).

4) For example, when (-)-**2** was allowed to react with four molar amounts of *sec*-butylamine (**3a**) at 30 °C for 4 h as shown in a typical procedure[6] (after the complete consumption of (-)-**2** was checked by TLC, the reaction mixture was concentrated to dryness), the diastereomeric ratio of the product was found to be almost 1:1 by ^{1}H NMR.

5) Yield 60%; mp 209.0~210.5 °C ($CHCl_3$); $[\alpha]_D$ -155 (*c* 0.5, acetone); ^{1}H NMR ($CDCl_3$) δ=3.81-3.87 (2H, m), 4.08 (1H, dd, *J*=5 and 15 Hz), 4.19 (1H, pseudo t, *J*=9 Hz), 4.25 (1H, dd, *J*=5 and 15 Hz), 4.42 (1H, pseudo t, *J*=9 Hz), 6.17 (1H, t, *J*=5 Hz), 6.42 (1H, s), 6.71-6.75 (3H, m), 7.00-7.28 (9H, m), and 7.39 (1H, d, *J*=7 Hz); ^{13}C NMR (DMSO-d_6) δ=35.91, 36.48, 41.97, 45.38, 50.12, 114.67, 116.88, 118.88, 123.33, 123.79, 124.65, 126.37, 126.69, 127.86, 128.06, 128.10, 128.66, 138.83, 151.44, 155.26, 169.58, and 169.69; IR (KBr) 3400, 1760, 1648, 1460, 1258, 1248, 1194, 1466, and 756 cm^{-1}. Found: C, 75.02; H, 5.39; N, 3.40%. Calcd for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.29; N, 3.51%.

6) A typical procedure is as follows: A mixture of (-)-**2** (104.9 mg, 0.26 mmol) and **3b** (21.2 mg, 0.175 mmol) in 1,4-dioxane (0.5 ml) was warmed at 50 °C under an argon atmosphere. After being stirred for 8 h at that temperature, the complete consumption of **3b** was checked by TLC, and then the reaction mixture was concentrated to dryness under reduced pressure. A part of the mixture was purified by silica gel column chromatography (eluent; ethyl acetate) to afford **4b** (98%).

7) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).

8) In order to simplify semiempirical MO calculations, (*S,S*)-(*S*)-**5** and (*S,S*)-(*R*)-**5** were selected as model compounds for **4b** with omitting a C_2 symmetric pair of hydroxyphenyl and amide groups. The model compounds were constructed by replacing a benzyl proton with a methyl group in (*S,S*)-*N*-benzyl-2-(2-hydroxyphenyl)cyclobutanecarboxamide, of which the structure was estimated on the basis of the crystal structure of *N,N'*-dibenzyldiamide derivative of (*S,S,S,S*)-(-)-**1** (recrystallized from ethyl acetate; R~15 %). For the constructed structures, semiemprical MO calculations were performed on a HITAC M-880 by using MOPAC Ver. 6.01 with complete geometry optimization; MOPAC Ver. 6.0, J. J. P. Stewart, QCPE #455; revised as Ver. 6.01 by T. Hirano, Ochanomizu University, for HITAC machine, *JCPE Newsletter*, **2**, 26 (1991).