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OPTICAL RESOLUTION OF *ANTI* HEAD-TO-HEAD COUMARIN DIMER AND DETERMINATION OF ITS ABSOLUTE CONFIGURATION BASED ON CD SPECTRAL DATA

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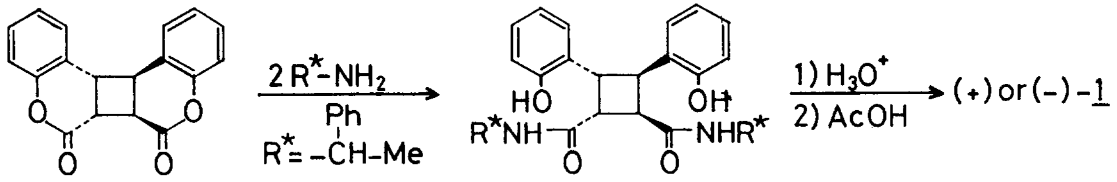
Abstract: *(±)-anti Head-to-head coumarin dimer was successfully resolved into a pair of optically active forms in high yields, of which the absolute configuration was determined on the basis of CD and ^{1}H-NMR spectral data.*

In the previous papers, we reported the lactone opening reaction of *anti* head-to-head coumarin dimer.$^{1)}$ As the lactone rings in the dimer are readily opened by nucleophiles under mild conditions, the optically active dimer is expected to be useful both as an optically active reagent with high reactivity in organic synthesis and as an optically active diacid component in polymer synthesis. But, there is no attempt for the optical resolution of the dimer, and its absolute configuration is unknown. In this paper, we wish to report the efficient optical resolution of *anti* head-to-head coumarin dimer by simple operation and its absolute configuration assumed on the basis of CD and ^{1}H-NMR spectral data.

The reaction of (±)-*anti* head-to-head coumarin dimer ((±)-1) with (*S*)-(-)-1-phenylethylamine proceeded easily to give the corresponding diastereomeric diamides (2 and 3), which had extremely large difference in solubility in dioxane or acetone / methanol. Consequently, both of 2 and 3 could be obtained in high chemical yields and high diastereomeric purities by crystallization from dioxane or acetone / methanol without any recrystallization. When (±)-1 (58.46 g, 0.20 mol) was allowed to react with (*S*)-(-)-1-phenylethylamine

(48.47 g, 0.40 mol) in dioxane (870 ml) at room temperature for 12 h, one of diastereomeric diamides (2) was deposited from the solution as white creamy precipitates. Washing the precipitates with dioxane (70 ml x 2) gave 2[2] (42.29 g, 79.1%) in a high diastereomeric purity.[3] The filtrate was evaporated to dryness, and the residue remained was crystallized from acetone / methanol (1,500 ml / 150 ml), giving the other diamide (3)[4] (35.54 g, 66.5%) in a high diastereomeric purity.[3] The evaporation of the filtrate followed by crystallization from acetone / methanol (10 : 1) gave 3 (7.66 g, 14.3%) as second crop. The total yield of 3 was 43.20 g (80.8%). After hydrolysis of each diamide (5.35 g, 0.01 mol) in 99% ethanol / concd. hydrochloric acid (100 ml / 50 ml) under reflux for 20 h, followed by lactonization of the crude hydrolyzed products in refluxing acetic acid (150 ml, overnight), recrystallization from ethyl acetate / hexane (2 : 3) gave (+)-1[5] (1.86 g, 63.6%) and (-)-1[6] (1.92 g, 65.7%) from 2 and 3, respectively. Small quantities of the optically active dimers were again converted into 2 and 3 by the reaction with (*S*)-(-)-phenylethylamine in order to determine the optical purities of (+)- and (-)-1, and they were found to be almost pure by HPLC analysis,[3] which indicating that no epimerization nor racemization took place during hydrolysis and lactonization.



(±)-1

2 or 3

The UV spectrum of (+)-1 in acetonitrile showed the absorption maximum at 215 nm (ε 25,000) due to acyloxyphenyl chromopheres, and its CD spectrum showed strong positive first Cotton effect ($\Delta\varepsilon_{228}$ +18) and negative second one ($\Delta\varepsilon_{215}$ -16) of the similar amplitude as shown in Fig. 1. Since the 215-nm $^1L_a \leftarrow {}^1A$ transition of acyloxyphenyls is mainly directed along the long axis,[7] the electron transition moments are considered to be parallel to phenolic C-O bonds and to be in the sense of a right-handed screw.

^{1}H-NMR spectrum of (+)-1 in DMSO-d_6 showed a singlet of four protons (Ha, Hb, Hc, and Hd in Fig.2) on the cyclobutane ring at δ 3.86 ppm. On the other hand, in ^{1}H-NMR of the lactone-opened derivatives of (+)-1, the signal of the protons on the cyclobutane ring split into pseudo double doublet at δ 3.5-3.6 ppm (Ha' and Hb') and δ 4.6-4.7 ppm (Hc' and Hd'), respectively (See Fig. 2). Since the signal of a methyne proton adjacent to an aryl group is known to appear at lower region in a magnetic field than that of a methyne proton adjacent to a carboxylic acid group, the methyne protons (Hc and Hd) in (+)-1 are considered to be largely shifted to up field. These observations indicate that each methyne proton (Hc and Hd) is strongly shielded by the other aryl group and that the methyne protons (HC' and Hd') in the lactone-opened derivatives are out of shielding zone. Based on the CD and ^{1}H-NMR spectral data and on the qualitative conformational examination using CPK and HGS models, it can be concluded that the absolute configuration of (+)-1 is (1*R*, 2*R*, 3*R*, 4*R*) as shown in Fig. 2.

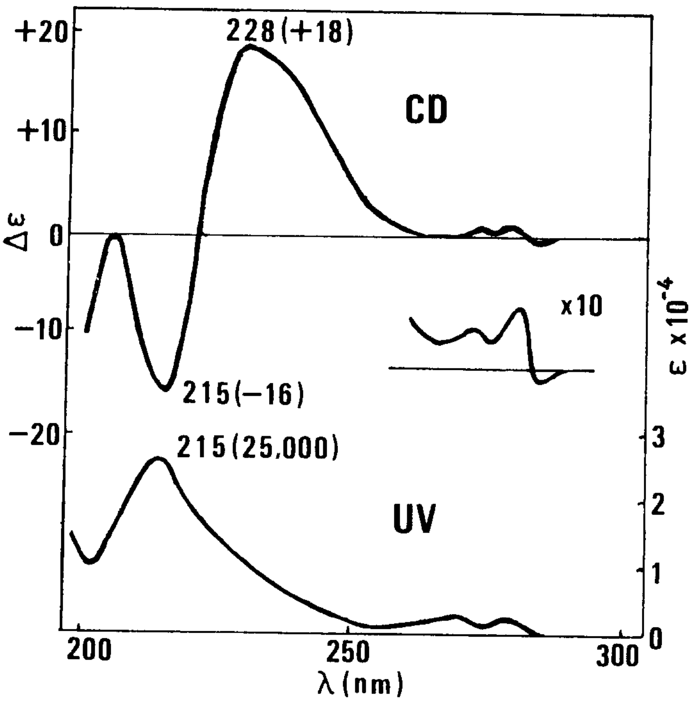


Fig. 1 CD and UV spectra of (+)-1

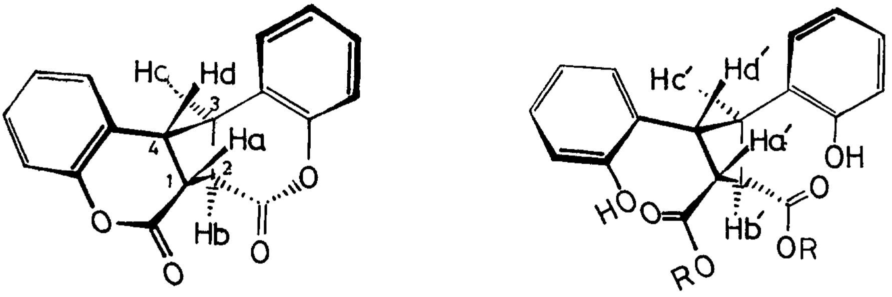


Fig. 2 The Assumed Conformation of (+)-1 and Its Lactone-opened Derivatives

References and Notes

1) M. Hasegawa, N. Yonezawa, T. Kanoe, and T. Ikebe, *J. Polym. Sci., Polym. Lett.,* 20, 309 (1982). N. Yonezawa and M. Hasegawa, *Bull. Chem. Soc. Jpn.,* 56, 367 (1983). M. Hasegawa, K. Saigo, H. Kastuki, N. Yonezawa, and T. Kanoe, *J. Polym. Sci., Polym. Chem. Ed.,* in press.

2) mp 237-238°C; $[\alpha]_D^{21}$ -19.0° (*c* 0.50, 99% MeOH). Found: C, 76.54%; H, 6.27%; N, 5.17%. Calcd for $C_{34}H_{34}N_2O_4$: C, 76.38%; H, 6.40%; N, 5.23%.

3) By HPLC analysis (LiChrosorb SI-60 4 mmϕ x 250 mm, C_6H_6 / AcOEt (1 : 1), 30 kg / cm^2, 0.4 ml / min), the contamination of the other diastereomeric diamide was less than 0.1%.

4) mp 246-247°C; $[\alpha]_D^{21}$ -177.3° (*c* 0.51, 99% MeOH). Found: C, 76.66%; H, 6.16%, N, 5.19%. Calcd for $C_{34}H_{34}N_2O_4$: C, 76.38%; H, 6.40%; N, 5.23%.

5) mp 168-169°C;[8] $[\alpha]_D^{21}$ +9.0°, $[\alpha]_{435}^{21}$ +66.0° (*c* 1.00, C_6H_6).

6) mp 168.5-169°C;[8] $[\alpha]_D^{21}$ -9.0°, $[\alpha]_{435}^{21}$ -65.8° (*c* 1.00, C_6H_6).

7) H. H. Jaffé, and M. Orchin, "*Theory and Applications of Ultraviolet Spectroscopy*," John Wiley and Sons, Inc., New York (1962), Chap. 12. N. Harada and K. Nakanishi, "*Circular Dichroic Spectroscopy —Exciton Coupling in Organic Stereochemistry —*," University Science Books, California (1982), Chap. 2.

8) The optically active dimer melting at 193-193.5°C was sometimes obtained, while its ^{1}H-NMR spectrum, HPLC retention time, and $[\alpha]_D$ were identical with those of the optically active dimer melting at 168-169°C. Their crystal systems were apparently quite different each other.

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