CHEMISTRY LETTERS, pp. 1149 - 1152, 1984. © The Chemical Society of Japan 1984

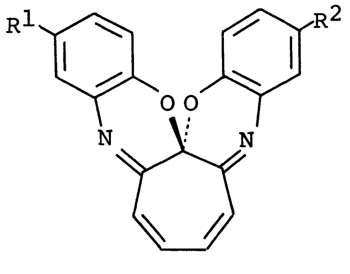
RESOLUTION, ABSOLUTE CONFIGURATION, AND PHOTORACEMIZATION OF CHIRAL TROPONOID ACETALS, CYCLOHEPTA[2,1-b:2,3-b']DI[1,4]BENZOXAZINES

Yoshio OKAMOTO,* Shiro HONDA, Heimei YUKI,
Hikaru NAKAMURA,† Yoichi IITAKA,*† and Tetsuo NOZOE*††
Department of Chemistry, Faculty of Engineering Science,
Osaka University, Toyonaka, Osaka 560
†*Faculty of Pharmaceutical Sciences, The University of Tokyo,*
Hongo, Bunkyo-ku, Tokyo 113
††*Tokyo Research Laboratories, Kao Corporation,*
Bunka, Sumida-ku, Tokyo 131

The title chiral troponoid compounds were resolved in optically pure forms by high-performance liquid chromatography on a chiral poly(triphenylmethyl methacrylate) column. The compounds showed large optical rotations. The absolute configuration of (-)-3,12-dichloro derivative was found to be *R* by X-ray analysis. Resolved enantiomers were racemized upon UV irradiation in solution.

Nozoe and co-workers reported on an unusual tropoquinonoid title compound (**1a**),[1] together with a more efficient synthetic way of **1a** and its derivatives (**1b**-**d**).[2] These spiro compounds possess C_2 symmetry and are axially dissymmetric. Although the resolution of these compounds by conventional methods would not be routine because of the lack of functionality and stability, it was effectively achieved by high-performance liquid chromatography (HPLC) on a chiral poly(triphenylmethyl methacrylate) (PTrMA) column.[3,4] In this letter we describe the resolution, absolute configuration, and photoracemization of the troponoids.

(+)-PTrMA was prepared by asymmetric anionic polymerization[5] and was used as packing material for HPLC after coating on macroporous silica gel.[3] Chromatography was accomplished on a JASCO TRIROTAR-II equipped with UV detector employing methanol as eluent at 15 °C. Optical rotation was measured on a JASCO DIP-181 polarimeter at 25 °C and circular dichroism (CD) spectra were taken on a JASCO J40 CD apparatus at room temperature. The concentration of samples was estimated with extinction coefficients, 7860 for (±)-**1a**, 7890 for (±)-**1b**, 8610 for (±)-**1c**, and 6470 for (±)-**1d** at 376 nm in methanol. Photoracemization was conducted in a 5-cm quartz optical cell by using a 15-W fluorescent lamp (daylight type) as an irradiation source. A sample was irradiated at a distance of 30 cm from the source. No racemization took place during the measurement of optical rotation in the polarimeter.



1a ($R^1 = R^2 = H$)
1b ($R^1 = R^2 = CH_3$)
1c ($R^1 = R^2 = Cl$)
1d ($R^1 = H$, $R^2 = CH_3$)

Figure 1 is the chromatogram for the resolution of **1a** on a (+)-PTrMA column. Complete base line separation was attained for all the compounds. In all cases, (-) isomers eluted first and separation factors α[6] were about 13. A similar pronounced chiral recognition by PTrMA has been observed in the resolution of hexahelicene.[7] Recrystallization of the earlier eluting fractions of (-)-**1a** and (-)-**1c** afforded yellow crystals with mp 184-185 °C and 234-235 °C, respectively.

The resolved enantiomers exhibited large rotation values comparable to that of hexahelicene which is one of the compounds noted for its high polarizability.[8] The $[\alpha]^{25}_{589}$ of the first-eluted antipodes were -4700° ($\underline{c}$ 0.0018) for (-)-**1a**,[9] -4900° ($\underline{c}$ 0.0009) for (-)-**1b**, -4100° ($\underline{c}$ 0.0015) for (-)-**1c**, and -3700° ($\underline{c}$ 0.0010) for (-)-**1d** in methanol.[10]

The UV and CD spectra of **1a** are illustrated in Fig. 2. The CD spectra of the enantiomers exhibited a clear mirror image relation. The spectral patterns of **1b**, **1c**, and **1d** were very similar to those in Fig. 2; the UV and molar circular dichroism ($\Delta\varepsilon$) data are summarized in Table 1.

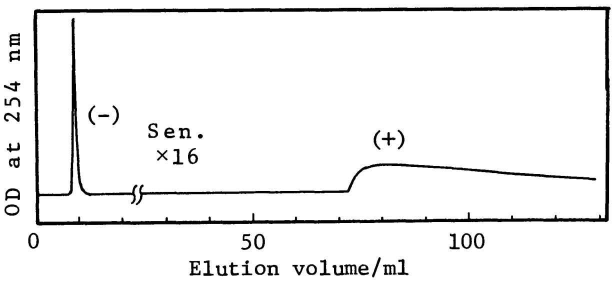


Fig. 1. Chromatographic resolution of **1a** on a (+)-PTrMA column (25 × 0.46 cm). Flow rate of methanol = 0.5 ml min^{-1}.

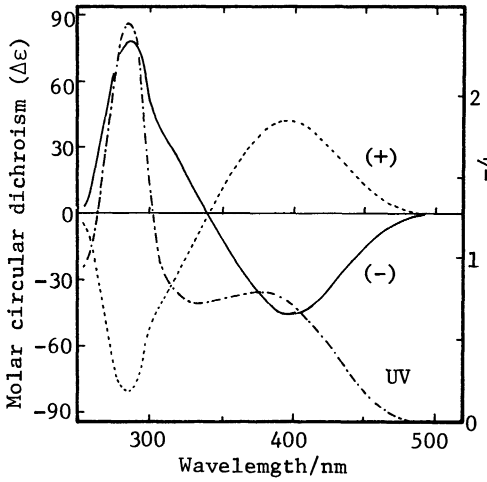


Fig. 2. UV and CD spectra of (+)- and (-)-**1a** in methanol.

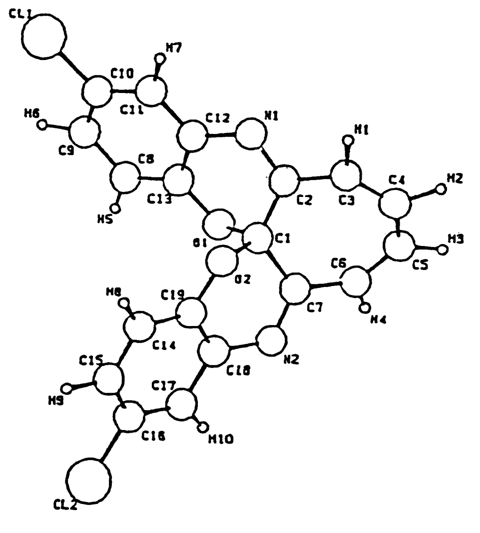


Fig. 3. Molecular structure of (-)-**1c** representing absolute configuration drawn by PLUTO program.[12]

Table 1. UV and CD data in methanol

Compound	λ_{max}/nm (ε)	λ/nm ($\Delta\varepsilon$)
(-)-**1a**	378(7930) 285(23500)	398(-45.3) 340(0) 287(+80.4)
(-)-**1b**	380(7920) 287(21800)	408(-48.2) 344(0) 289(+74.4)
(-)-**1c**	380(8610) 280(23800)	402(-48.6) 342(0) 280(+80.1)
(-)-**1d**	380(6500) 287(17800)	404(-38.6) 342(0) 287(+64.0)

It has been demonstrated that (+)-PTrMA interacts more strongly with optical isomers such as P-(+)-hexahelicene and (-)-Tröger base which possess a $\underline{C}_2$ axis and P-helicity with respect to their aromatic groups.[7] If this is true for the present system, the (-) isomers which interacted more weakly with (+)-PTrMA possess the $\underline{R}$ absolute configuration (M-helicity). This was confirmed by X-ray analysis of the earlier eluting fraction of (-)-1c (Fig. 3).[11,12] The molecule has a pseudo diad axis (not crystallographic) through C1 and the midpoint of C4-C5 bond. The bond lengths and angles are very close to each other between the two halves of the molecule and the values agree well with those expected from the chemical structure. The seven-membered ring is twisted about the diad and the oxazine ring takes a deformed boat form with the flag-pole atom C1 which deviates more than 0.5 Å from the least-squares plane formed by the four atoms.

The optically active isomers in solution were optically stable in the dark, but slowly racemized upon irradiation with UV light; the irradiation, however, induced no UV spectral change. Figure 4 shows the results of the photoracemization of (-)-1a at 1, 25, and 40 °C in methanol. The racemization must be a first-order reaction with respect to the substrate in view of the good linearity of the first-order plots shown in Fig. 4. The rate constants (k) are summarized in Table 2 together with the data obtained in dioxane. The Arrhenius plots exhibited good straight lines and activation energies were estimated to be 17.6 kJ mol^{-1} in methanol and 15.5 kJ mol^{-1} in dioxane.

In the photochromism of a spiropyran 2 and related compounds, which are structurally similar to 1a, the formation of colored species has been identified spectrophotometrically.[13] Although the mechanism of the photoracemization of 1a might be explained in the same way, we could not detect any new UV peaks and ESR signals upon UV irradiation of 1a at -50 and 25 °C. The photoracemization of 1a and its derivatives may provide a useful probe for investigating the molecular motion of polymeric materials in the solid state[14] because of their large optical rotation and lack of racemization in a rigid matrix encountered in crystals.

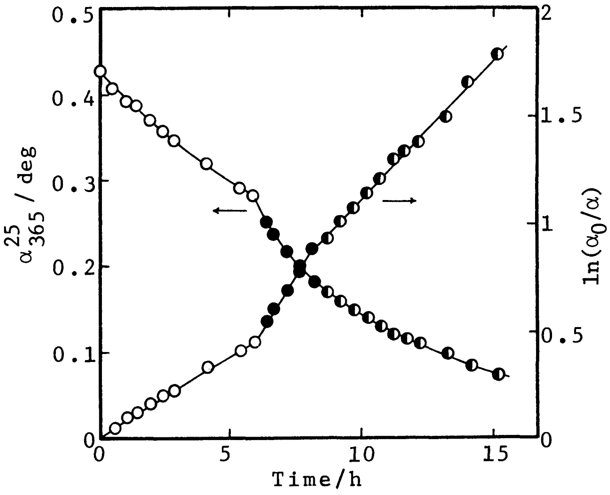
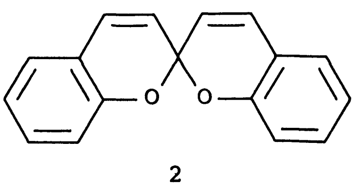


Fig. 4. Photoracemization of (-)-1a at 1 (○), 25 (◐), and 40 °C (●) in methanol. $[\mathbf{1a}]_0 = 3.9 \times 10^{-5}$ mol l^{-1}.



2

Table 2. Rate constants (k) in the photoinduced racemization of (-)-1a in methanol and dioxane

Solvent	k/h^{-1}			
	1 °C	15 °C	25 °C	40 °C
Methanol	0.073	—	0.13	0.19
Dioxane	—	0.18	0.21	0.30

The authors wish to express their thanks to Prof. Sumio Ishikawa and Mr. Hidetsugu Wakabayashi (Josai University) for the compounds **1**a-d. We thank Prof. Koji Nakanishi of Columbia University for his valuable advice and Dr. Mikiharu Kamachi of Osaka University for ESR measurements. We are also grateful to Prof. Hamao Umezawa, President of Institute of Microbial Chemistry, Tokyo, for generously allowing one of us (H.N.) to carry out X-ray analysis in the University of Tokyo.

References

1) T. Someya, H. Okai, H. Wakabayashi, and T. Nozoe, Bull. Chem. Soc. Jpn., 56, 2756 (1983).
2) T. Nozoe, H. Okai, H. Wakabayashi, and S. Ishikawa, Chem. Lett., preceding paper.
3) Y. Okamoto, S. Honda, I. Okamoto, S. Murata, R. Noyori, and H. Takaya, J. Am. Chem. Soc., 103, 6971 (1981).
4) R. Noyori, N. Sano, S. Murata, Y. Okamoto, H. Yuki, and T. Ito, Tetrahedron Lett., 23, 2969 (1982); Y. Kawada, H. Iwamura, Y. Okamoto, and H. Yuki, ibid., 24, 791 (1983); M. Nakazaki, K. Yamamoto, T. Ikeda, T. Kitsuki, and Y. Okamoto, J. Chem. Soc., Chem. Commun., 1983, 787; Y. Okamoto, S. Honda, E. Yashima, and H. Yuki, Chem. Lett., 1983, 1221; A. Tajiri, M. Fukuda, M. Hatano, T. Morita, and K. Takase, Angew. Chem. Suppl., 1983, 1283; Y. Okamoto, E. Yashima, K. Hatada, and K. Mislow, J. Org. Chem., 49, 557 (1984).
5) Y. Okamoto, H. Shohi, and H. Yuki, J. Polym. Sci. Polym. Lett. Ed., 21, 601 (1983).
6) See, for instance, Ref. 3.
7) Y. Okamoto, I. Okamoto, and H. Yuki, Chem. Lett., 1981, 835.
8) M. S. Newman and D. Lednicer, J. Am. Chem. Soc., 78, 4765 (1956).
9) $[\alpha]_{577}^{25}$ -5600°, $[\alpha]_{546}^{25}$ -7700°, $[\alpha]_{435}^{25}$ -29200°, $[\alpha]_{365}^{25}$ +68800°.
10) The resolved samples contained a small amounts of contaminants eluted from the column. These showed negligible rotation and absorption above 250 nm.
11) The crystals of (-)-**1**c were grown in an acetonitrile solution as a yellow small hexahedron. One of the crystals of approximate dimensions 0.2 × 0.14 × 0.12 mm was chosen for X-ray diffraction study. The lattice constants and intensity data were collected by a Philips PW1100 diffractometer using graphite monochromated CuK$_\alpha$ radiation. Crystal data: $C_{19}H_{10}N_2O_2Cl_2$, MW 369.2. Orthorhombic, space group $P2_12_12_1$, Z = 4, D_{cal} = 1.501 g cm^{-3}. Lattice constants; a = 12.716(6), b = 17.435(9), c = 7.373(4) Å, V = 1635 Å^3. μ for CuK$_\alpha$ = 37.6 cm^{-1}.
Intensities of 2212 reflections were measured as above the $I>2\sigma(I)$ level in the 2θ range of 6° through 156° of which 196 were symmetrically equivalent and 346 were the Friedel reflections. The R_F factors were calculated to be 4.16% for the former 196 reflections and 5.84% for the latter 346. A total of 1670 reflections were obtained by averaging the symmetry related reflections, which corresponds to 82% of the number of theoretically possible reflections within the same range of 2θ. The structure was solved by the direct method using MULTAN program (P. Main, M. M. Woolfson, and G. Germain, Acta Crystalogr., Sect. A, 27, 368 (1971)). The two prominent peaks in one of the E maps were accounted for the Patterson map and the 22 atoms located on this E map were subjected to the refinement process. Refinement by the difference-Fourier and the least-squares method established the whole structure and the final R value including 10 hydrogen atoms was 4.68%.
The absolute configuration was determined by taking into account the anomalous dispersion effect of the chlorine atom for CuK$_\alpha$ radiation (f' = 0.348, f" = 0.702) ("International Tables for X-Ray Crystallography", Vol. IV, p. 148, The Kynoch Press, Birmingham, England (1974)). Of 133 Friedel pairs for which the observed intensity difference between the Friedel reflections was greater than 3%, 111 pairs agree with the calculated intensity differences assuming the absolute configuration shown in Fig. 3. The final refinement of the structure by the block-diagonal least-squares method including dispersion corrections yielded the R value of 4.63% (The table of atomic coordinates may be obtained from the Cambridge Crystallographic Database and that of temperature factors and F_o-F_c from one of the authors (Y.I.)).
12) PLUTO "Cambridge Crystallographic Database," Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England (1983).
13) Y. Hirshberg and E. Fischer, J. Chem. Soc., 1954, 297, 3129.
14) G. Smets, Adv. Polym. Sci., 50, 18 (1983).

(Received April 26, 1984)