Optical Resolution of Binaphthyl and Biphenanthryl Diols by Inclusion Crystallization with *N*-Alkylcinchonidium Halides. Structural Characterization of the Resolved Materials

Fumio Toda* and Koichi Tanaka

Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790, Japan

Zafra Stein and Israel Goldberg*

School of Chemistry, Sackler Faculty of Exact Sciences, Tel-Aviv University, 69978 Ramat-Aviv, Israel

Received April 11, 1994[⊗]

Racemic 2,2′-dihydroxy-1,1′-binaphthyl and 10,10′-dihydroxy-9,9′-biphenanthryl have been resolved effectively by crystalline complexation with commercially available *N*-alkylcinchonidium halides. The resolved complexes were studied by X-ray diffraction methods in order to characterize the intermolecular interaction and recognition schemes. The results indicate the significance of directional hydrogen bonding and aryl–aryl interaction modes in the molecular recognition process.

Introduction

Inclusion crystallization has proven to be an effective method for the separation of structural isomers and resolution of optically active organic materials.[1,2] Many chiral organic compounds have been resolved by formation of solid, diastereoisomeric complexes with naturally-occurring resolving agents (e.g., tartaric acid, brucine, and related alkaloids). The molecular recognition between these complexing partners is directed by specific intermolecular forces (e.g., hydrogen bonding and $\pi-\pi$ interactions), as well as by steric complementarity. The presence of an optically pure host generates a chiral lattice and provides an asymmetric environment for enantioselective cocrystallization with the guest component and for effective separation of the latter from a racemic mixture. Chiral resolutions of neutral organic substrates by the inclusion crystallization method are very simple, often yielding 100% optically pure cocrystals in good yield.[3] The host and guest components can easily be recovered from the solid material in their pure forms by chromatographic methods. We have previously reported effective preparations of optically pure enantiomers of various organics by inclusion complexation with optically active binaphthyl and biphenanthryl diol derivatives.[4,5] The latter are also useful in asymmetric synthesis[6] and as chiral shift reagents.[7] Optically active crown ethers that incorporate the 2,2′-dihydroxybinaphthyl spacer were found to enantioselectively bind amino acids and esters.[8] Various methods have been used in the past to synthesize optically active isomers of these convenient hosts. Among them, enantioselective complexations with reagents derived from natural tartaric acid were quite effective.[9] In order to extend and simplify the resolution procedure, an effort has been made to find alternative and more readily available resolving reagents for the biaryl diols. Chiral amines such as cinchona alkaloids have previously been used as optically active catalysts in homogeneous media.[10] Their interaction with suitably functionalized 1,1′-binaphthyl derivatives was found to be characterized by a high degree of chiral recognition.[11] In a previous publication, we demonstrated that an effective resolution of the enantiomers of 2,2′-dihydroxy-1,1′-binaphthyl (**1**) and 10,10′-dihyroxy-9,9′-biphenanthryl (**2**) can be achieved by inclusion complexation with *N*-alkylcinchonidium halides.[12] A comprehensive evaluation of the structures of resolved complexes and of the intermolecular interaction modes within these cocrystals is presented below. The crystal and molecular structures of the 1:1 complexes of **1** with *N*-benzylcinchonidium chloride (**3**) [structure **I**] and of **2** with *N*-butylcinchonidium bromide (**4**) [structure **II**] are described in detail in this report.

Experimental Section

Optically active *N*-alkylcinchonidium halides were obtained commercially from Aldrich Chemical Co., Inc.

Determination of Optical Purity. The enantiomeric purity of the resolved materials was determined by HPLC, using a column containing an optically active solid phase, Chiralpak AS or Chiralpak OC.[13] Solvent mixtures of hexane/EtOH (95/5) and hexane/*i*PrOH (90/10) were used as eluents.

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1994.

[1] *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic Press: London, 1984; Vols. I–III; Oxford University Press: Oxford, 1991, Vols. IV, V.

[2] *Molecular Inclusion and Molecular Recognition–Clathrates I and II*; Weber, E., Ed.; Topics in Current Chemistry; Springer: Berlin, 1987, 1988; Vols. 140, 149.

[3] Toda, F. *Top. Curr. Chem.* **1987**, *140*, 43.

[4] Toda, F.; Mori, K.; Stein, Z.; Goldberg, I. *Tetrahedron Lett.* **1989**, *30*, 1841. Mori, K.; Toda, F. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2127. Toda, F.; Mori, K.; Stein, Z.; Goldberg, I. *J. Org. Chem.* **1988**, *53*, 308.

[5] Toda, F.; Tanaka, K. *Tetrahedron Lett.* **1988**, *29*, 1807. Toda, F.; Tanaka, K. *J. Org. Chem.* **1991**, *56*, 7332. Toda, F.; Tanaka, K.; Yagi, M.; Stein, Z.; Goldberg, I. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1215. Toda, F.; Soda, S.; Goldberg, I. *Ibid.* **1993**, 2357.

[6] Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709. Seebach, D.; Beck, A. K.; Roggo, S.; Wonnacott, A. *Chem. Ber.* **1985**, *118*, 3673. Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143. Wang, J.-T.; Fan, X.; Feng, X.; Qian, Y.-M. *Synthesis* **1989**, 291.

[7] Toda, F.; Mori, K.; Okada, J. *Chem. Lett.* **1988**, 131.

[8] Knobler, C. B.; Gaeta, F. C. A.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1988**, 330. Peacock, S. C.; Walba, D. M.; Gaeta, F. C. A.; Helgeson, R. C.; Cram, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 2043. Peacock, S. C.; Domeier, L. A.; Gaeta, F. C. A.; Helgeson, R. C.; Timko, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 8190. Goldberg, I. *J. Am. Chem. Soc.* **1977**, *99*, 6049.

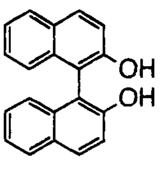
[9] Toda, F.; Tanaka, K. *J. Org. Chem.* **1988**, *53*, 3607. Toda, F.; Tanaka, K.; Nassimbeni, L. R.; Niven, M. *Chem. Lett.* **1988**, 1371.

[10] Colonna, S.; Re, A.; Wynberg, H. *J. Chem. Soc. Perkin Trans. 1* 1981, 547. Julia, S.; Ginebreda, A.; Guixer, J.; Masana, J.; Tomas, A.; Colonna, S. *Ibid.* **1981**, 574.

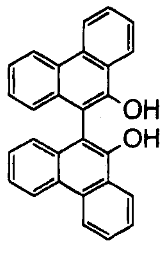
[11] Castro, P. P.; Georgiadis, T. M.; Diederich, F. *J. Org. Chem.* **1989**, *54*, 5835.

[12] Tanaka, K.; Okada, T.; Toda, F. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1147.

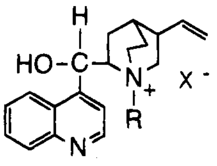
0022-3263/94/1959-5748$04.50/0



1



2



3 : $R=PhCH_2$, X=Cl

4 : R=n-Bu, X=Br

Optical Resolution of 2,2′-Dihydroxy-1,1′-binaphthyl. A solution of *N*-benzylcinchonidium chloride (**3**) (0.74 g, 1.76 mmol) and *rac*-**1** (1 g, 3.5 mmol) in 20 mL of MeOH was kept at room temperature for 6 h, yielding a 1:1 complex of **3** and (*R*)-(+)-**1** which precipitated as colorless prisms (0.89 g, 72% yield, mp 277−279 °C). Decomposition of the filtered complex with dilute HCl, followed by extraction with ethyl acetate and evaporation of the solvent gave (*R*)-(+)-**1** {95% *ee*; 0.35 g, 70% yield, $[\alpha]_D = +31.5$ (*c* = 1.0, THF)}. Recrystallization of the crude product from MeOH gave pure (*R*)-(+)-**1** {100% *ee*; 0.3 g, 60% yield, $[\alpha]_D = +33.2$ (*c* = 1.0, THF)}. Treatment of the filtrate left with dilute HCl yielded (*S*)-(−)-**1** {42% *ee*; 0.62 g, 124% yield, $[\alpha]_D = -13.9$ (*c* = 1.0, THF)}.

Optical Resolution of 10,10′-Dihydroxy-9,9′-biphenanthryl. A solution of *N*-butylcinchonidium bromide (**4**) (0.14 g, 0.33 mmol) and *rac*-**2** (0.25 g, 0.65 mmol) in 10 mL of acetonitrile was kept at room temperature for 24 h, yielding a 1:1:1 complex of **4**, (*R*)-(+)-**2**, and MeCN which precipitated as colorless prisms (0.22 g, 83% yield, mp 168−169 °C). Decomposition of the filtered complex with dilute HCl gave pure (*R*)-(+)-**2** {100% *ee*; 0.1 g, 80% yield, $[\alpha]_D = +58$ (*c* = 1.0, $CHCl_3$)}. Treatment of the filtrate left with dilute HCl yielded (*S*)-(−)-**2** {58% *ee*; 0.15 g, 80% yield, $[\alpha]_D = -35$ (*c* = 1.5, $CHCl_3$)}.

Crystal Structure Analyses. Suitable crystals for X-ray diffraction were prepared by slow evaporation of the corresponding methanol and acetonitrile solutions. The X-ray diffraction measurements were carried out at room temperature (ca. 298 K) on an automated CAD4 diffractometer equipped with a graphite monochromator, using Mo Kα ($\lambda = 0.7107$ A) radiation. Intenisty data were collected by the $\omega-2\theta$ scan mode with a constant scan speed of 4 deg/min. Possible deterioration of the analyzed crystal was tested by detecting periodically the intensities of three standard reflections from different zones of the reciprocal space and was found negligible during the experiment. No corrections for secondary extinction effects were applied. The two structures were solved by direct methods (SHELXS-86)[14] aided by Fourier techniques, and refined by full-matrix least-squares (SHELX-76)[15], including the positional and anisotropic thermal parameters of the non-hydrogen atoms. All hydrogen atoms attached to carbon were introduced in calculated positions, the methyls being treated as rigid groups. Hydrogens of the hydroxyl groups were located directly in difference-Fourier maps. The final refinements were based on experimental weights $w = 1/\sigma^2(F_0)$, minimizing $w(\Delta F)^2$.

For structure **I** data were collected out to $2\theta_{max} = 54°$. Crystal data are $C_{46}H_{43}N_2O_3Cl$, formula weight 707.31, orthorhombic, space group $P2_12_12_1$, $a = 10.513(1)$, $b = 13.573(3)$, $c = 26.569(3)$ A, $V = 3791.2$ A^3, $Z = 4$, $D_{calc} = 1.239$ g cm^{-3}, $F(000) = 1496$, μ(Mo Kα) = 1.40 cm^{-1}.

A total of 4061 unique reflections with positive intensities were measured. Data were not corrected for absorption. The refinement calculations converged at $R = 0.065$ and $wR = 0.066$ for 2268 observations having $F_0 \geq 6\sigma(F_0)$. The CH=CH$_2$ residue was found to be disordered in the crystal with two alternative positions, at almost equal occupancies, for the terminal carbon. This disordered fragment was included in the crystallographic refinement with a restrained geometry and isotropic thermal parameters only. At convergence, the highest peaks and deepest troughs of the difference density map were 0.62 (near the disordered group) and −0.23 e Å^{-3}, respectively, confirming the correctness of the structure.

For structure **II**, data were collected out to $2\theta_{max} = 50°$. Crystal data are $C_{53}H_{52}N_3O_3Br$, formula weight 858.92, orthorhombic, space group $P2_12_12_1$, $a = 8.189(1)$, $b = 12.534(3)$, $c = 43.042(5)$ A, $V = 4417.9$ Å^3, $Z = 4$, $D_{calc} = 1.291$ g cm^{-3}, $F(000) = 1800$, μ(Mo Kα) = 9.65 cm^{-1}.

A total of 3475 unique reflections with positive intensities were recorded. An empirical method was applied to correct the data for absorption.[16] The final refinement converged at $R = 0.066$ and $wR = 0.064$ for 1598 reflections above the threshold of $6\sigma(F_0)$. At convergence the peaks and troughs of the difference-Fourier density maps didn't exceed 0.39 and −0.42 Å^{-3}, respectively. Presence of a heavy atom and the relatively low data-to-parameters ratio affected the precision of the crystallographic determination, resulting in relatively large esd's of the positional and thermal parameters.

Results and Discussion

Optical Resolution. Details of the resolution procedure are outlined in the Experimental Section. Typically, the racemic biaryl diol and a suitable cinchonidium halide derivative, in a molar ratio of 2:1, were dissolved in a standard solvent (e.g., methanol or acetonitrile), and the solution was left overnight at room temperature to allow crystallization of the preferred complex. The crude form of the latter was then purified, if necessary, by further recrystallization from the same solvent. From the filtrate left after separation of the crystalline phase, the second enantiomer of the diol compound was isolated. Finally, the resolved enantiomers of the biaryl diol were recovered from the pure crystalline complex by treatment with a dilute acid and chromatography. The parent cinchonidine alkaloid does not form inclusion complexes with either with **1** or **2** and is therefore ineffective in separation of the biaryl diol compounds in question.

Structural Analysis. Final atomic coordinates of **I** and **II**, along with lists of anisotropic thermal parameters, H-atom coordinates, bond lengths and bond angles, have been deposited with the Cambridge Crystallographic Data Centre. They can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. Molecular dimensions obtained for the various molecules in the two structures are in good agreement with standard values and exhibit no extraordinary features (some deviations observed in **II** can be attributed to the low precision caused by the limited amount of significant diffraction data). In the biaryl diols, the two naphthyl fragments in **I** and the two phenylanthryl groups in **II** are nearly at right angles to each other; the dihedral angles between the mean planes of those aryl residues are 101.5° in **I** and 90.0° in **II**. The intermolecular organization and association in the two crystal structures are illustrated in Figures 1 and 2.

Structure **I** can be best described as consisting of continuous chains of interlinked species that are aligned in an alternating manner parallel to the (0,1,1) lattice plane of the crystal (Figure 1). The chloride anion provides the bridging link between two diol molecules and the cinchonoid cation located in between, by accepting three hydrogen bonds from the surrounding moieties at

---

(13) Chiralpak AS and Chiralpak OC are available from Daicel Chemical Industries, Ltd., Himeji, Japan.

(14) Sheldrick, G. M. SHELXS-86. In *Crystallographic Computing 3*; Sheldrick, G. M., Kruger, C., Goddard, R., Eds.; Oxford University Press; Oxford, 1985; pp 175−189.

(15) Sheldrick, G. M. SHELX-76. Program for Crystal Structure Determination, University of Cambridge, England, 1976.

(16) Walker, N.; Stuart, D. *Acta Crystallogr.* **1983**, *A39*, 158.

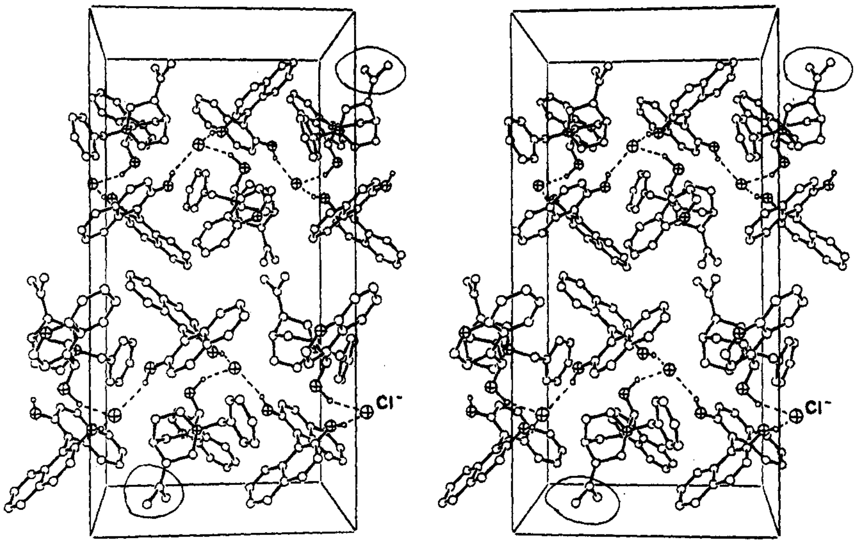


Figure 1. Stereoview of the crystal structure **I**, approximately down the *a* axis (*b* is horizontal). The heteroatoms are marked by crossed circles and the hydrogen bonding interactions by dashed lines. The encircled Y-shaped fragment represents the 2-fold disordered orientation of the terminal C=CH$_2$ residue. Contents of one and one-half unit cell are shown to illustrate better the intermolecular interaction scheme.

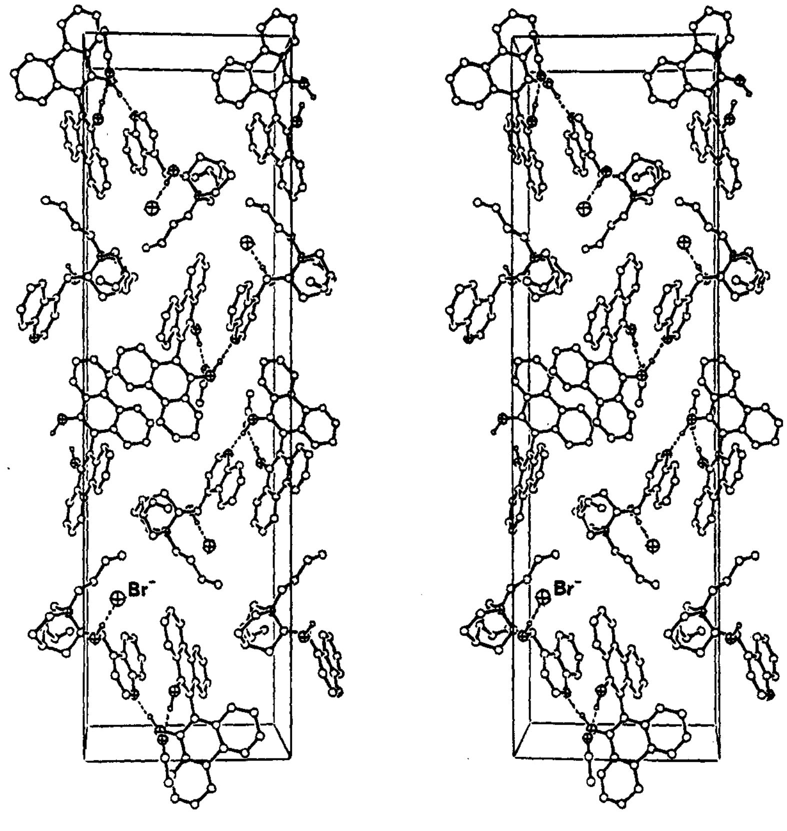


Figure 2. Stereoview of the crystal structure **II**, approximately down the *a* axis (*b* is horizontal). The heteroatoms are marked by crossed circles and the hydrogen bonding interactions by dashed lines. Contents of one and one-half unit cell are shown to illustrate better the intermolecular interaction scheme.

OH⋯Cl distances of 3.1–3.2 Å. The bifunctional diol entity is associated with two different Cl$^-$ ions along the chain, thus yielding the repeating pattern of intermolecular O–H⋯Cl bonds. The relatively large dihedral angle of the binaphthyl unit (101.5°) reflects a strained arrangement caused by optimization of these interactions. Characteristic aromatic–aromatic interactions between the two components, which involve the benzyl substituent, are an additional stabilizing feature of the chain structure of this more stable diastereoisomer. They involve a T-shaped interaction between the benzene ring of the cinchonidium derivative and two naphthyl rings of neighboring diols, in which C–H bond dipoles of the former are oriented toward the negatively charged carbon atoms of the latter.[17] The shortest relevant nonbonding H⋯C distances in **I** are within the range of 2.7–2.9 Å. Such interactions are known to dominate the structural organization in many aromatic materials and are now considered important in the design of new host receptors.[17,18] Side packing of the hydrogen bonded chains is also stabilized by similar T-shaped contacts between the naphthyl residues, as well as by other weak dispersive interactions. The disorder of the ethylenic fragments, which are located in the interchain zone, indicates, however, a less than perfect steric fit between neighboring chain arrays.

In the solid state, the halide anion is distant from the sterically hindered quaternary nitrogen site of the cinchonidium cation. Rather, it lies near to and forms a hydrogen bond with, the polarized hydroxyl group. This occurs also in structure **II**, as is illustrated in Figure 2 [at OH(cation)···Br = 3.12 Å]. Here, however, the larger phenanthryl spacer groups prevent a simultaneous close approach of three moieties around the halide anion, and a different intermolecular arrangement is evident. This structure consists of locally hydrogen-bonded 1:1 entities of host-to-guest, the H-bond involving one OH group of the biphenanthrol framework as a proton donor and the nitrogen site of the quinoline ring as a proton acceptor (at OH···:N of 2.77 Å). The host–guest association is complemented by an effective $\pi-\pi$ stacking interaction between nearly parallel phenanthryl and quinoline rings, lying at an average distance of 3.4 Å from each other. The large, "soft" Br^- ion is rather surrounded by a lipophilic CH environment. The second hydroxyl group of the biphenanthrol moiety is effectively solvated, *via* a weak hydrogen bond (at OH···:N of 2.92 Å), by an acetonitrile solvent molecule incorporated into the crystal lattice. Inclusion of the solvent component appears to be essential, in this case, to optimize the H-bonding potential of the constituent species, as well as to fill the empty space around the biaryl diol, but it has no effect on the selective recognition features of the interacting host and guest components. The less extensive intermolecular linkage in this structure is reflected in a more pronounced thermal motion of the individual entities at room temperature. Moreover, in the unconstrained environment, the observed dihedral angle between the two phenanthryl rings is ideally 90°.

In some respects, the structural properties of **II** are similar to those exhibited by other naturally occurring alkaloids (e.g., brucine and strychnine).[19] Crystal structures of the complexes of these hosts with chiral guests are also characterized by localized H-bond associations. Yet, the particular molecular shape of those optically active alkaloid compounds limits the possible packing motifs, which lends the alkaloids their effectiveness as resolving agents of optically active organics by crystalline inclusion.

The results described above illustrate the nature of the nonbonded interactions in the cocrystals of cinchonidium salts with the biaryl diols, which, in turn, determines the molecular recognition between the interacting partners. The intermolecular binding involves directional hydrogen-bonding and aryl–aryl $\pi-\pi$ stacking and "edge-to-face" interaction modes, while the enantioselectivity is induced by steric fit between the complexing constituents, as well as by the chirality features of the tight crystalline environment. It has already been shown that racemic-**1** could not be resolved by complexation with **4** and racemic-**2** did not form complexes with **3**.[12] This observation, along with the above results, suggest that fine-tuning of the cinchonidium resolving agent, by choosing a suitable alkyl or aryl substituent and selecting an appropriate counterion, is required for each particular application.

---

(17) Klebe, G.; Diederich, F. *Phil. Trans. R. Soc. Lond. A.* **1993**, *345*, 37, and references cited therein.

(18) Burley, S. K.; Petsko, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 7995.

(19) Gould, R. O.; Walkinshaw, M. D. *J. Am. Chem. Soc.* **1984**, *106*, 7840.