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# Efficient resolution of 2,2′-dihydroxy-1,1′-binaphthyl by inclusion complexation with chiral *N*-(3-chloro-2-hydroxypropyl)-*N*,*N*,*N*-trimethylammonium chloride †

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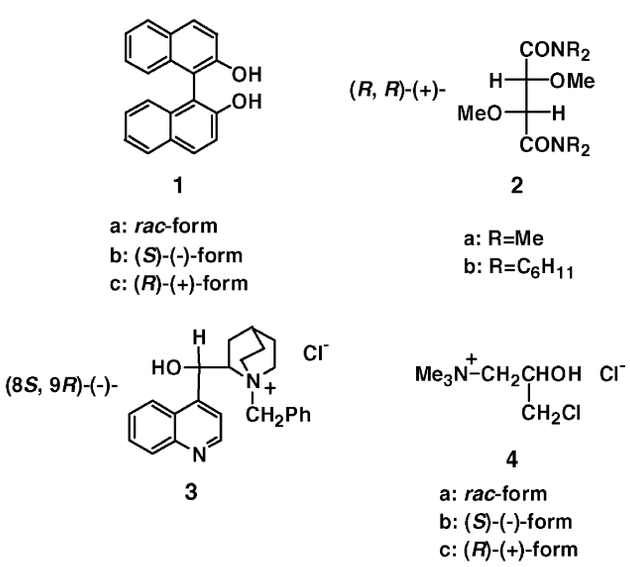
**The complete resolution of 2,2′-dihydroxy-1,1′-binaphthyl into its enantiomers by inclusion complexation with a commercially available derivative of choline, is reported. The two enantiomers are recovered in >99% ee from the inclusion complexes by simple dissolution in a diethyl ether–water medium and the resolving agent can be recycled.**

## Introduction

The enantiomers of 2,2′-dihydroxy-1,1′-binaphthyl (**1**) (Scheme 1) are important dissymmetric compounds possessing a $C_2$ axis which are used in asymmetric synthesis,[1] the separation of racemates by the formation of inclusion complexes[2] and as chiral shift reagents.[3]




**Scheme 1** Structures of the compounds.

Resolution of **1** is achieved commercially,[4] but other methods for the separation of the enantiomers of racemic 2,2′-dihydroxy-1,1′-binaphthyl (**1a**) have also been reported.[5–7] One quite effective method is by formation of inclusion complexes with the derivatives of tartaric acid (*R*,*R*)-(+)-2,3-dimethoxy-*N*,*N*,*N*′,*N*′-tetramethylsuccinamide (**2a**)[5] and (*R*,*R*)-(+)-2,3-dimethoxy-*N*,*N*,*N*′,*N*′-tetracyclohexylsuccinamide (**2b**)[5] as host compounds. However, since the above compounds are not commercially available and they must be synthesized from tartaric acid prior to the resolution experiment,[1] the method is very tedious. The most convenient resolution method reported so far is by formation of an inclusion complex with the commercially available chiral *N*-benzylcinchonidium chloride (**3**).[6] However, this method has also some disadvantages, because **3** is expensive and moreover, the process gives only the one (*R*)-(+)-enantiomer (**1c**) in 99% enantiomeric purity.

In the present communication, we report a very efficient resolution of **1a** by the commercially available salt (*S*)-(−)-*N*-(3-chloro-2-hydroxypropyl)-*N*,*N*,*N*-trimethylammonium chloride (**4b**), a derivative of choline. The method has several advantages: a) both antipodes **1b** and **1c** can be obtained in a common procedure; b) **4b** is four times cheaper than **3**; c) the crystalline inclusion complex of **4b** with **1b** formed can be separated easily into its components by dissolving it in an ether–water mixture.

## Result and discussion

Resolution of **1** with chiral **4** was investigated. When a solution of **1a** (100 g, 0.35 mol) and **4b** (39.5 g, 0.21 mol) in EtOH (800 ml) is kept at room temperature overnight, a 1 : 1 inclusion complex (**5b**) of **1b** with **4b** precipitates (60.3 g, 73% yield) as colorless crystals.[8] Treatment of the crystals of **5b** with a 1 : 1 diethyl ether–water mixture (1 L) results in dissociation into **1b** and **4b**, which dissolve in ether and water, respectively. From the ether solution, **1b** of 99.5% ee (34.5 g, 69% yield) is obtained, whereas from the aqueous solution **4b** (22.7 g, 57%) is recovered unchanged. The ethanolic solution left after separation of **5b** by filtration is subsequently dried. The remaining residue after treatment by a 1 : 1 diethyl ether–water mixture (1 L) gives an ether solution rich in **1c**. The aqueous solution contains **4b**, which is easily recovered by evaporation of water (15.8 g, 40% yield). When the ether solution is allowed to stand at room temperature overnight, **1a** crystallizes out as a 1 : 2 complex (**6**) with diethyl ether, whereas **1c** of 99% ee (31.5 g, 63% yield) is obtained from the remaining ether solution. The enantiomeric purities of **1b** and **1c** were determined by HPLC using the Chiralcel AD column containing chiral phase. The above experimental procedure is shown in Scheme 2. It is interesting to point out that the fact that only racemic **1**, and not its enantiomers, forms an insoluble complex with diethyl ether plays an important role in obtaining pure the second enantiomer.

The yields of the almost optically pure **1b** and **1c** obtained by the resolution experiment are 69 and 63% based on **1a** initially used, respectively. However, since 26% of **1a** was recovered as

† This paper is dedicated to Professor Thomas C. W. Mak on the occasion of his retirement from the Chinese University of Hong Kong.

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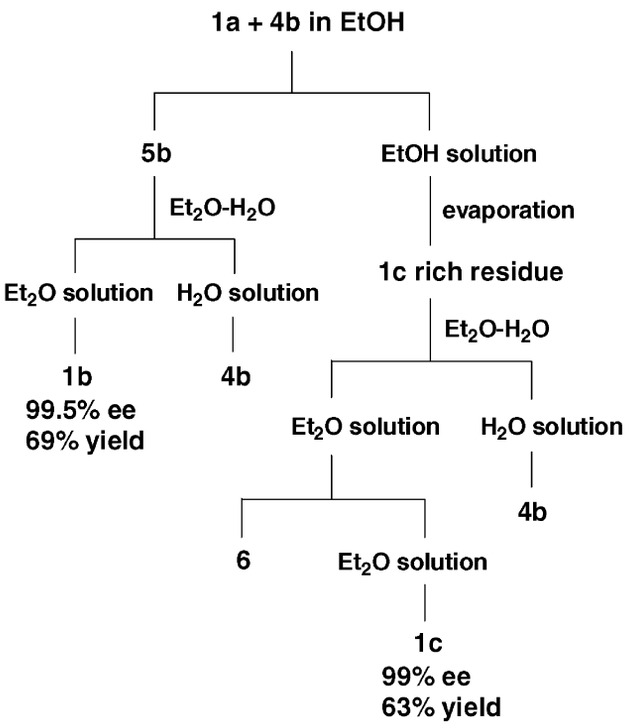


**Scheme 2** Experimental procedure of the resolution of **1a**.

its ether complex (**6**), real yields of **1b** and **1c** calculated based on the amount of **1a** which is consumed in the resolution are 93 and 85% respectively. On the other hand, 97.5% of **4b** initially used was recovered unchanged.

Resolution of **1a** was achieved also by using **4c**, instead of **4b**. When **4c** is used as the host instead of **4b** for the resolution of **1a**, a 1 : 1 inclusion complex (**5c**) of **1c** with **4c** is obtained. From the **4c** isolated, **1c** of 99.5% ee was obtained in 69% yield. From the filtrate left after separation of **5c**, **1b** of 99% ee was obtained in 63% yield.

Crystal structure analysis can illuminate some aspects of the resolution procedures. X-ray analysis of the inclusion complex of **1b** with **2b** has shown that a strong hydrogen bond between the hydroxyl group of **1b** and the amide carbonyl oxygen of **2b** plays an important role for the construction of the complex and their mutual chiral recognition.[7] Since the hydrogen bonding between **1b** and **2b** is very strong, a rather drastic process such as chromatography on silica gel or treatment with aqueous sodium hydrazine is necessary in order to dissociate the complex into its components.[5] In the case of the complex of **1c** with **3**, the hydroxyl groups of both **1c** and **3** bind to $Cl^-$ and extended hydrogen bond networks are constructed.[9] The inclusion complex of **1c** and **3** must be treated with HCl in order to dissociate it into its components.[5] In contrast, the present inclusion complex, **5c**, easily dissociates into **1c** and **4c** by mixing it with a diethyl ether–water medium.

Therefore, the crystal structure of **5c** has been determined[10] in order to see the exact intermolecular interactions of the species involved. There are three crystallographically independent host (**1c**) and guest (**4c**) molecules A, B and C in the asymmetric unit that have similar molecular geometries *i.e.* the binaphthyl moieties of the host are almost perpendicular to each other, their dihedral angles being 80.65°, 89.03° and 76.93° for A, B and C respectively and the bond distances and angles are very similar. Fig. 1 shows the common atom labeling and conformations of all hosts and guests. Fig. 2 displays the crystal packing of the inclusion complex in a view perpendicular to the *c*-axis. It consists of double layers of the host molecules parallel to the *ac* plane intercalated by layers of the ionic guest molecules, (*R*)-(+)-*N*-(3-chloro-2-hydroxypropyl)-*N*,*N*,*N*-trimethylammonium chloride. The crystallographically independent guest molecules within the guest layers are segregated in channels running along the *c*-axis (Fig. 2). The non-polar parts of the hosts are in the interior of the host-bilayers. No π–π stacking between the aromatic groups is exhibited. Instead, mutual T-shaped interactions take place between two adjacent naphthyl moieties that align head-to-head to form the host bilayer. The shortest C–H ··· C distance is 2.94 Å. On their exterior, the host bilayers are lined with the hydroxy groups that interact with the guest. The main contribution to the enantioselectivity of (*R*)-(+)-*N*-(3-chloro-2-hydroxypropyl)-*N*,*N*,*N*-trimethylammonium chloride is the H-bonding scheme involving each chloride anion of the guest to hydroxyls of two host molecules in adjacent bilayers and to the hydroxyl of the corresponding guest, as shown in Table 1 and Fig. 1. Both hydroxy groups of the hosts are H-bonded, each to a different chloride ion. The geometry of the ligands around the chloride ions is shown in Table 2. The chloride ion is 0.15 Å above the plane of the three oxygen atoms. Finally, T-shaped interactions between the substituted chlorine atom on the guest molecule and the naphthyl rings (Cl ··· C distances close to 3.6 Å), observed systematically in the three species A, B and C, contribute possibly to the enantioselectivity and the strength of the diastereoisomer.

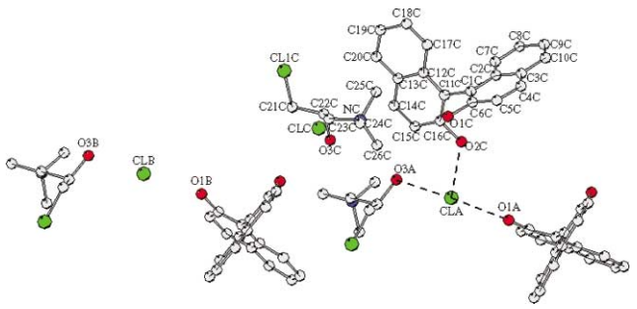


**Fig. 1** Host and guest molecules A, B and C in the crystal with atom labeling (drawn by program MOLSCRIPT[12]). Dotted lines indicate H-bonding (chloride ions are green and O atoms, red).

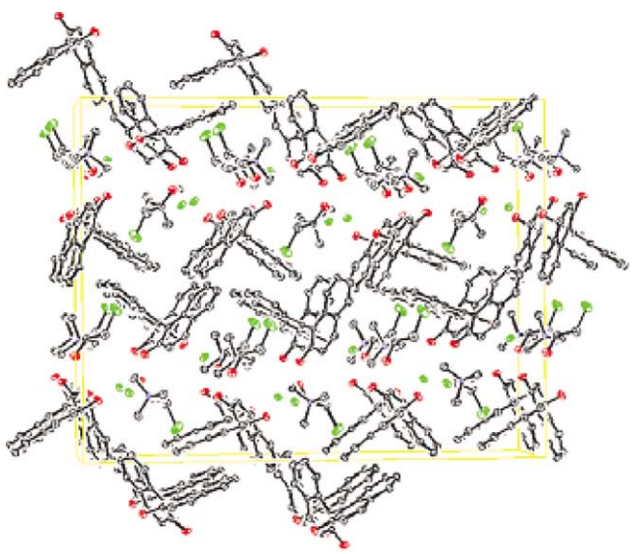

**Fig. 2** ORTEP diagram[13] showing the separate layers of the host and guest molecules of complex **5c**. Horizontal axis *a*, vertical *b* (ellipsoid probability 15%).

The overall structure resembles that of the inclusion complex between **1c** and **3**[9] in that the latter structure consists also of bilayers intercalated by chloride ions. In this case also the chloride anion H-bonds to three hydroxyls two of host and one of guest molecules with very similar $Cl^-$ ··· HO distances as in **5c**. However, there is a significant difference between the two complexes. The **1c/3** complex's bilayers consist of intermingled host and guest molecules, aligned in an alternating manner

**Table 1** H-bond distances and angles between chloride anions and hydroxy groups

| $Cl^- \cdots H–O$ | Distance (Å) $Cl^- \cdots H$ | Distance (Å) $Cl^- \cdots O$ | Angle (°) $Cl^- \cdots H–O$ |
|---|---|---|---|
| $Cl^-_A \cdots H–O_{1A}$ | 2.13(5) | 3.062(7) | 172 |
| $Cl^-_A \cdots H–O_{3A}$ | 2.23(2) | 3.163(8) | 174 |
| $Cl^-_A \cdots H–O_{2C}$ | 2.21(6) | 3.105(7) | 166 |
| $Cl^-_B \cdots H–O_{1B}$ [a] | 2.12(2) | 3.051(7) | 172 |
| $Cl^-_B \cdots H–O_{3B}$ [b] | 2.21(7) | 3.177(8) | 177 |
| $Cl^-_B \cdots H–O_{2A}$ [c] | 2.16(6) | 3.056(7) | 166 |
| $Cl^-_C \cdots H–O_{1C}$ [d] | 2.21(7) | 3.075(7) | 175 |
| $Cl^-_C \cdots H–O_{3C}$ [e] | 2.18(9) | 3.156(9) | 175 |
| $Cl^-_C \cdots H–O_{2B}$ | 2.20(2) | 3.085(7) | 159 |

[a] $0.5 + x, 0.5 - y, 1 - z$. [b] $2 - x, 0.5 + y, 0.5 - z$. [c] $2 - x, 0.5 + y, 1.5 - z$. [d] $2 - x, -0.5 + y, 1.5 - z$. [e] $2 - x, -0.5 + y, 0.5 - z$.

**Table 2** Geometry of ligands around the chloride ions

| $H \cdots Cl^- \cdots H$ | Angle (°) $H \cdots Cl^- \cdots H$ |
|---|---|
| $H–O_{2A} \cdots Cl^-_A \cdots H–O_{2C}$ | 93 |
| $H–O_{2A} \cdots Cl^-_A \cdots H–O_{3A}$ | 164 |
| $H–O_{2C} \cdots Cl^-_A \cdots H–O_{3A}$ | 99 |
| $H–O_{1B} \cdots Cl^-_B \cdots H–O_{1A}$ | 95 |
| $H–O_{1B} \cdots Cl^-_B \cdots H–O_{3B}$ | 167 |
| $H–O_{1A} \cdots Cl^-_B \cdots H–O_{3B}$ | 93 |
| $H–O_{1C} \cdots Cl^-_C \cdots H–O_{2B}$ | 96 |
| $H–O_{1C} \cdots Cl^-_C \cdots H–O_{3C}$ | 164 |
| $H–O_{2B} \cdots Cl^-_C \cdots H–O_{3C}$ | 95 |

along an axis. Thus the guest is mixed with the host, being part of the bilayers in the lattice and exhibits numerous close contacts with it. In contrast, in the present structure the host and guest molecules are found in separate layers and are interacting mainly *via* the chloride ions. Therefore, the fact that the components of complex **5c** dissociate in a mixture of diethyl ether–water, whereas **1c** and **3** are recovered from the corresponding complex by treatment with HCl, can be attributed to the closer association between host and guest molecules in the latter complex.

## Conclusion

In conclusion, the reported very efficient method to resolve racemic **1** into its enantiomers in 100% ee has the additional advantages that the two enantiomers are recovered by simple dissolution in a diethyl ether–water medium and the resolving agent is a cheap commercially available compound that can be recycled. The crystal structure of the inclusion complex (**5c**) between **1c** and **4c** explains its easy dissociation into the components. Furthermore, both racemic **1** and **4** were resolved simultaneously just by seeding with a single crystal of their chiral inclusion complex. This could be an important resolution technique in the future.

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8 60.3 g, 73% yield, mp 224–225 °C. Found: C, 65.97%; H, 6.24%; N, 3.01%. Calcd for $C_{26}H_{29}O_3NCl_2$: C, 65.82%; H, 6.16%; N, 2.95%.

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10 Crystal data for $(C_{20}H_{14}O_2)_3 \cdot (C_6H_{15}OClN^+Cl^-)_3$: $M_r$ = 1423.20, orthorhombic, space group $P2_12_12_1$ $a$ = 30.94(1), $b$ = 23.839(7), $c$ = 10.252(4) Å, $V$ = 7562(4) Å$^3$, $Z$ = 4, $\rho_{calc}$ = 1.250 g cm$^{-3}$, $2\theta_{max}$ = 117°, $\mu$(CuK$\alpha$) = 2.527 mm$^{-1}$, $T$ = 293 K, crystal dimensions 0.2 × 0.3 × 0.7 mm, $R1$ = 0.0446 for 4436 reflections with $F_o > 4s(F_o)$, $wR2$ = 0.1202, goodness-of-fit=1.059, Flack $x$ parameter = −0.049(2) for all 5968 independent reflections. Structure determination by direct methods (SHELXS) and refinement by SHELXL 97[11] based on $F^2$. All non-H atoms were treated anisotropically. H atoms determined by difference Fourier maps and were refined isotropically. The final difference Fourier map showed $\rho_{max}$ = 0.22 e Å$^{-3}$, and $\rho_{min}$ = −0.20 e Å$^{-3}$. CCDC reference number 202870. See http://www.rsc.org/suppdata/ob/b3/b314040g/ for crystallographic data in.cif or other electronic format.

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