Communications

Novel Chiral Recognition in Host−Guest Inclusion Complexes Depends on Their Molar Ratios: Efficient Resolution of 2,2′-Dihydroxy-1,1′-biphenyl Derivatives and CD Spectral Study of Inclusion Complex Crystals

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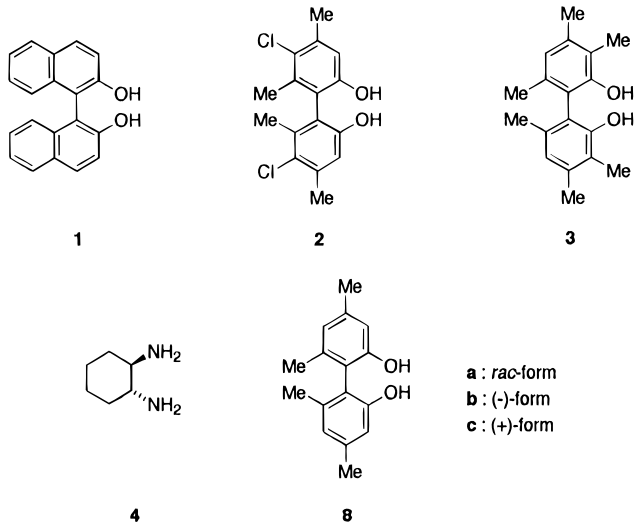
It is known that optically active 2,2′-dihydroxy-1,1′-binaphthyl (**1**) is useful not only as a key compound in the preparation of chiral catalysts for asymmetric synthesis[1] but also as a chiral shift reagent[2] and as a chiral host compound for the optical resolution of guest compounds.[3] The axially-chiral 2,2′-dihydroxy-1,1′-biphenyl derivatives **2** and **3** are also expected to behave in a similar fashion and, indeed, may have advantages as chiral ligands in catalysts for asymmetric synthesis because of their much simpler structures. Recently, chiral 5,5′-dichloro-2,2′-dihydroxy-4,4′,6,6′-tetramethylbiphenyl (**2**) was reported to be a good chiral ligand in highly efficient catalysts for asymmetric synthesis.[4,5] In the literature,[4] a diastereomeric mixture of the phosphite derivative of *rac*-**2** (**2a**) bearing (−)-**1** (**1b**) as a chiral ligand was resolved by column chromatography to give the chiral phosphite bearing the two chiral ligands **1** and **2**. Its Rh(I) complex was shown to be a highly efficient catalyst for asymmetric hydroformylations of a variety of olefinic substrates.[5] However, the preparation method of the chiral catalyst is rather complicated, and chiral **2** itself has not been prepared yet. In order to prepare the catalyst more easily and to prepare the chiral **2** itself, development of a direct resolution method of **2a** is required.

It was found that **2a** can easily be resolved by complexation with optically active *trans*-1,2-diaminocyclohexane (**4**). During the resolution study, we also found the very interesting result that the chiral recognition ability between **2** and **4** in the inclusion complex depends on their molar ratio. Hence, although **4b** formed a 1:1 complex with **2a**, **4b** formed a 2:1 complex with optically active **2c**. Resolution of **2a** was accomplished only in the latter case. When a solution of **4b** (0.76 g, 6.66 mmol) and **2a** (2 g, 6.68 mmol) in toluene (0.3 mL) was kept at room temperature for 2 h, a 1:1 complex of **4b** and **2a** (**5**) was formed as colorless needles (2.43 g, 88% yield, mp 140−141 °C). On the other hand, when a solution of **4b** (1.85 g, 16.2 mmol) and **2a** (2.5 g, 8.1 mmol) in toluene (3 mL) was kept for 1 h, a 2:1 complex of **4b** and **2c** (**6**) was formed as colorless needles, after recrystallization from toluene (1.45 g, 67% yield, mp 116−117 °C, $[\alpha]_D$ +17.3° (*c* 1.0, MeOH)). The crystals were dissolved in a mixture of AcOEt (20 mL)−dilute HCl (20 mL), and the AcOEt layer evaporated to give **2c** of 100% ee as colorless needles (0.78 g, 62% yield, mp 233−235 °C, $[\alpha]_D$ +67.2° (*c*, 1.0, MeOH)). The toluene solution left after separation of the crude complex (**6**) was dissolved in a mixture of AcOEt (20 mL)−dilute HCl (20 mL). From the AcOEt layer, **2b** of 100% ee was obtained as colorless needles, after three recrystallizations from toluene (0.52 g, 52% yield, mp 233−235 °C, $[\alpha]_D$ −67.2° (*c*, 1.0, MeOH)). The optical purities were determined by HPLC on the chiral stationary phase Chiralpak AS by using hexane−EtOH (95:5) as an eluent. From the aqueous HCl solution, **3b** was recovered by neutralization with NaOH.



This is the first finding that chiral recognition in an inclusion complex changes drastically depending on the host:guest molar ratio. Although the same resolution of **2a** by complexation with **4b** has already been attempted previously by Sayo, he has isolated only the 1:1 complex (**5**), but not **6**, and concluded that the resolution of **2a** by this method is impossible.[6] Very recently, we have also found that photoirradiation of 1:1 and 1:2 inclusion complexes of *N*-allylfuran-2-carboxanilide with the optically active host (*R*,*R*)-(−)-*trans*-2,2-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane in the solid state gives (−)- and (+)-photocyclization products, respectively.[7] In these 1:1 and 1:2 inclusion complexes, the achiral furan derivative would be arranged in chiral forms so as to produce (−)- and (+)-photocyclization products, respectively, by irradiation. Thus, our present and former findings strongly indicate that chemists who are studying inclusion complexation should check carefully the possibility of formation of more than one compound in complexation experiments.

Unfortunately, however, neither **5** nor **6** formed suitable crystals for X-ray analysis, and the mechanism of

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S0022-3263(96)02280-3 CCC: $14.00

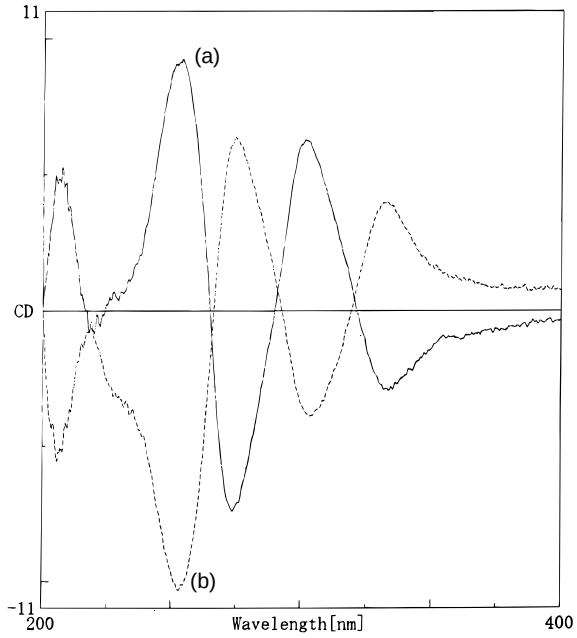

Figure 1. CD spectra of **6** (a) and **7** (b) in Nujol mulls at a concentration of 3 mg in 50 mg of liquid paraffin and employing 10 accumulations and 50 nm/min scanning speed.

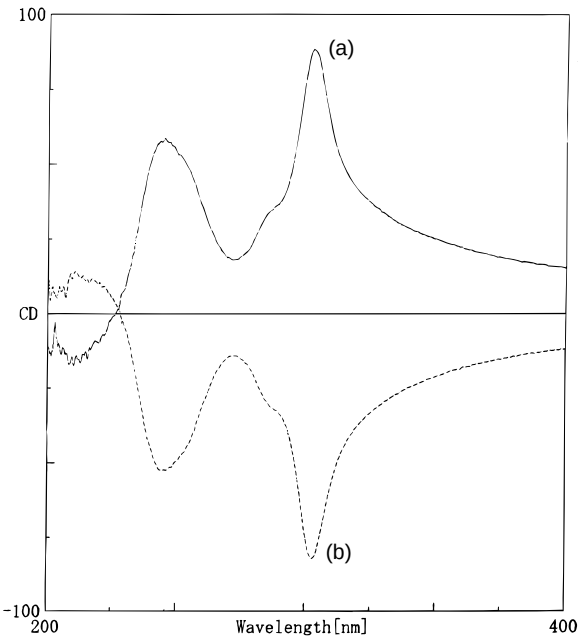

Figure 2. CD spectra of **2c** (a) and **2b** (b) as Nujol mulls at a concentration of 3 mg in 50 mg of liquid paraffin and employing five accumulations and 50 nm/min scanning speed.

the dependence of chiral recognition on the host:guest molar ratio could not be studied. Instead, CD spectra of these inclusion complexes in the solid state were studied. Although **5** did not show any clear CD spectrum, **6** showed a strong CD spectrum with a (+)-Cotton effect in a Nujol mull (Figure 1). The 2:1 inclusion complex of **4c** and **2b** (**7**) showed a CD spectrum with a nicely mirror-imaged relationship to that of **6** (Figure 1). **4b** and **4c** did not show any clear CD spectrum; however, **2b** and **2c** showed strong CD spectra with (−)- and (+)-Cotton effects, respectively, at about 250 and 300 nm (Figure 2). This is reasonable because **2** shows UV absorptions in the solid state at about 250 and 300 nm. Although **6** and **7** also showed CD spectra with (+)- and (−)-Cotton effects at about 250 and 300 nm, the intensity of these absorptions are about one tenth of those for **2b** and **2c**.

2,2′-Dihydroxy-3,3′,4,4′,6,6′-hexamethyl-1,1′-biphenyl (**3**) however, formed only a 1:1 inclusion complex with **4** in which precise chiral recognition is present. When a solution of **4b** (0.42 g, 3.68 mmol) and **3a** (2 g, 7.4 mmol) in toluene (0.3 mL) was kept for 2 h, a 1:1 complex of **4b** and **3c** was formed as colorless needles, after one recrystallization from toluene, (0.8 g, mp 117−125 °C, $[\alpha]_D$ +3.1° (*c* 1.0, MeOH)). Treatment of the complex by the procedure applied to **6** gave **3c** of 100% ee as colorless needles (0.39 g, 39% yield, mp 127 °C, $[\alpha]_D$ +23.7°, (*c* 1.0, MeOH)). Treatment with dilute HCl of the toluene solution left after separation of the crude complex of **4b** and **3c** gave **3c** of 87% ee (0.94 g, 94% yield), which upon recrystallization from toluene gave **3c** of 100% ee (0.5 g, 50% yield). The optical purities of **3b** and **3c** were determined by ^{1}H NMR spectral measurements in the presence of the chiral shift reagent (+)-phenylethylamine.

To our knowledge, two other resolution methods of 2,2′-dihydroxy-1,1′-biphenyl derivatives have been reported.[8] Although an effective resolution of 2,2′-dihydroxy-4,4′,6,6′-tetramethyl-1,1′-biphenyl (**8**) by complexation with *N*-benzylcinchonidium chloride has been reported, this method is not applicable to either **2** or **3**. Furthermore, chiral **8** does not form effective catalysts for asymmetric synthesis.[9] Resolution of some less substituted derivatives through acetal formation with menthone has been reported,[10] but it is uncertain whether or not this method is applicable to the resolution of the fully substituted **2** and **3**.

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