# Enantioselective Extraction of Di-*O*-benzoyltartrate Anion by Ion-Pair Extractant Having Binaphthyl-Unit

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A lipophilic diphosphonium salt **1** having binaphtyl-type axial chirality was developed as a novel ion-pair extractant. By use of (*R*)-**1**, (−)-di-*O*-benzoyltartrate ((−)-DBT) was extracted more effectively than (+)-DBT. The enantioselectivity ($\alpha = D_{(-)}/D_{(+)}$; $D$: distribution ratio) was 1.3—1.4. When monophosphonium-type extractants (**2** and **3**) having structures similar to that of **1** were used, the enantioselectivity was heavily lowered. Equilibrium studies revealed that the extraction occurs *via* formation of a 1 : 1 ion-pair complex between **1** and DBT at pH 7.5—8.0. The effects of pH, ionic strength, and temperature on the extractability and the enantioselectivity were investigated. The enantioselectivity decreased with lowering pH, and was higher at lower temperatures. The optical purity of DBT in the aqueous phase was gradually enhanced by multistage extraction. From an NMR analysis of the **1**·DBT complex, the resonances of methylene-protons adjacent to phosphonium in the more extractable complexes ((*R*)-**1**·(−)-DBT and (*S*)-**1**·(+)-DBT) shifted to a higher field compared to those of the less extractable complexes ((*R*)-**1**·(+)-DBT and (*S*)-**1**·(−)-DBT).

Resolution of enantiomers has been discussed mainly in crystallization systems and in chromatography systems. In the field of solvent extraction, optical resolution (chirality recognition) has so far been scarcely studied, except for the works with Cram's chiral crown ethers.[1-6]

Crown ethers interact only with cationic species such as amino acids and amines. To extract anionic species, the use of ion-pair extraction is essential. However, in the framework of ion-pair extraction there are few reports on the chirality recognition.[7,8] Ion-pair complexes are generally outer sphere complexes between cations and anions; these ions frequently combine with each other through mediation by several water molecules within the complexes. Therefore, it is generally believed that the specificity is not appreciably expected in ion-pair formation itself, whereas a selectivity could be attained via i) a difference in the solubility to aqueous phase, ii) that to organic phase, iii) acid-base reaction, and iv) complex formation in aqueous media. However, two enantiomers in ion-pair extraction systems would behave quite similarly regarding the factors i)—iv).

In order to separate enantiomers by ion-pair extraction, a specificity should exist in the ion-pair formation itself; a difference in the steric hindrance between the enantiomers can result in a specificity when they form ion-pair complexes with chiral ion-pair extractants. However, such a difference hardly reflects the difference in distribution ratios of each enantiomer. This may be a main reason for the scarcity of reports on the chirality recognition in ion-pair extractions.

Recently, we studied ion-pair extractions of organic anions from the viewpoint of molecular recognition.[9-16] In a previous communication,[17] we briefly reported a new type of ion-pair extractant having an axial chirality (binaphthyl unit), which exhibited the ability of chirality recognition in the ion-pair extraction of an organic dicarboxylate anion, di-*O*-benzoyltartrate (DBT). This demonstrates a possibility of chirality recognition by proper design of the extractant molecule. However, the extractant reported has a low lipophilicity and hence is not of practical use as an anion-exchange extractant.

In the present study, we synthesized a chiral extractant of high lipophilicity, (*R*)-(−)- or (*S*)-(+)-1,1′-binaphthyl-2,2′-diylbis[(*p*-octylbenzyl)diphenylphosphonium] dibromide (abbreviated as (*R*)-**1** or (*S*)-**1**; Fig. 1). By using this as an ion-pair extractant (anion-exchange extractant), we examined factors affecting the chirality recognition and extractability. Further, the ion-pair complexes of optical isomer were investigated by NMR. The potential of optical resolution by use of the chiral ion-pair extractant is discussed.

In the field of chromatography, it is known that optical resolution of ionic enantiomers in aqueous media is considerably difficult. Ion-pair extraction is the basis of ion-pair chromatography, and thus, the study of chiral ion-pair extraction is important from such a point of view, as well.

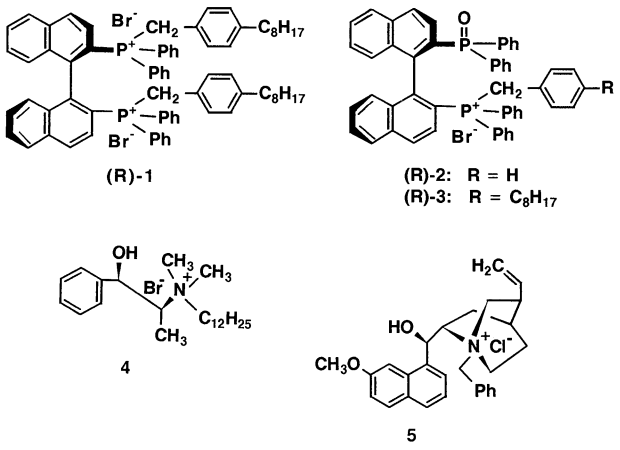



Fig. 1. Ion-pair extractants having chirality.

## Experimental

**Synthesis of (*R*)-1.** *p*-Octylbenzyl bromide was obtained from *p*-octylbenzonic acid via methylation, $LiAlH_4$-reduction, and bromination by phosphorus tribromide. The bromide (4.5 g, 16 mmol), (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl ((*R*)-BINAP; 2.0 g, 3.2 mmol), and *N*,*N*-dimethylformamide (DMF, 10 mL) were charged in a grass tube, which was then sealed along with a stirring magnet under vacuum after several freeze-pump-thaw cycles. The sealed tube was heated at 130 °C for 3 h with internal stirring. After removal of DMF and unreacted *p*-octylbenzyl bromide from the reaction mixture by evaporation with a rotary pump, white crude crystals were obtained. The crystals were purified by column chromatography on silica gel. The column with the crude product was washed with 1,2-dichloroethane and the product was eluted with ethanol. Colorless crystals were obtained. Yield (3.1 g, 81%), mp 214—216 °C. Found: C, 74.58; H, 6.50%. Calcd for $C_{74}H_{78}P_2Br_2$: C, 74.74; H, 6.61%. $[\alpha]_D^{25}$ −142°, $[\alpha]_{546}^{25}$ −186°, $[\alpha]_{435}^{25}$ −487° (*c* 1.0, ethanol). $^1H$ NMR ($CDCl_3$) $\delta$=0.87 (6H, t; $CH_3$), 1.15—1.5 (24H, br; $CCH_2C$), 2.42 (4H, t; $CH_2Ph$), 4.72 and 4.75 (2H, two d, $J_{PCH}\approx J_{HCH}\approx$12 Hz; $PhCH_2P$), 5.26 and 5.29 (2H, two d, $J_{PCH}\approx J_{HCH}\approx$12 Hz; $PhCH_2P$), and 6.6—8.3 (40H, m; aromatic). $^{31}P$ NMR ($CDCl_3$) $\delta^P$ (from $H_3PO_4$)=20.9 (s). (*S*)-**1** was similarly prepared from (*S*)-BINAP (Yield; 2.9 g, 76%). Its physicochemical properties were identical with those of the enantiomer except in the sign of rotation. Found: C, 74.48; H, 6.71%.

**Synthesis of (*R*)-2.** (*R*)-BINAP (2.0 g, 3.2 mmol), benzyl bromide (0.55 g, 3.2 mmol), and DMF (18 mL) were charged in a grass tube and treated in a manner similar to that for (*R*)-**1** synthesis (130 °C, 20 h). Then, 1.1 g of hydrogen peroxide solution (30%) was added to the reaction mixture, and this was heated at 100 °C for 3 h. Yield (1.4 g, 54%), mp 175—179 °C. Found: C, 75.53; H, 4.95%. Calcd for $C_{51}H_{39}OP_2Br$: C, 75.65; H, 4.85%. $[\alpha]_D^{25}$ −49° (*c* 1.0, ethanol). $^1H$ NMR ($CDCl_3$) $\delta$=3.81 and 3.84 (1H, two d, $J_{PCH}\approx J_{HCH}\approx$12 Hz; $PhCH_2P$), 5.52 and 5.57 (1H, two d, $J_{PCH}\approx J_{HCH}\approx$12 Hz; $PhCH_2P$), and 6.4—8.0 (36H, m; aromatic). (*R*)-**3** was similarly prepared from (*R*)-BINAP and *p*-octylbenzyl bromide. The product was identified by elemental analysis and $^1H$ NMR.

**Reagents.** (−)-*N*-Dodecyl-*N*-methylephedrinium bromide (**4**) and (−)-*N*-benzylquininium chloride (**5**) were purchased from Merck and used after recrystallization. Other chemicals were of reagent grade and used without further purification.

**Extraction Procedure.** An aqueous solution containing the chiral anion (DBT) was shaken with an organic solution containing an extractant in a stoppered centrifuge tube for 3 h in a thermostated bath (±0.1 °C). As extracting solvent, a mixture of 1,2-dichloroethane and carbon tetrachloride (1 : 1) was mainly used. After a phase-separation procedure was rapidly carried out, the concentration of the anion in the aqueous phase was determined by HPLC with a Shimadzu LC-6A liquid chromatograph equipped with a UV detector SPD-6A (275 nm). A column packed with octadecylsilyl (ODS) silica (150 mm×4.6 mm, Wakosil 5C18-200) was used. The eluent was a mixed solution (water–methanol 3 : 2) containing 2 mM (1 M=1 mol $dm^{-3}$) $Na_2HPO_4$–$KH_2PO_4$ buffer. Enantioselectivity ($\alpha$), the ratio between the distribution ratios of both enantiomers, was obtained as an average of more than three runs.

**Multistage Extraction.** An aqueous solution (10 mL) containing 5 mM racemic DBT, 15 mM NaBr, and 0.1 M $Na_2HPO_4$–$KH_2PO_4$ buffer (pH 7.5) was shaken with an organic solution (1,2-dichloroethane, 10 mL) containing 10 mM (*R*)-**1** for 3 h at 2 °C. After phase separation, the concentration of DBT in the aqueous phase was determined, and the optical rotation of the solution was measured by a polarimeter (JASCO DIP-370 with Hg lamp (435 nm); 10 cm cell) (first-step extraction).

A 9.6 mL aliquot of the aqueous phase after the extraction was taken up, in which 0.1 mL of 0.5 M NaBr solution was added. The resulting solution was shaken with 4 mL of the fresh organic solution containing 10 mM (*R*)-**1** in a similar manner. After phase separation, the concentration and the optical rotation were measured (second-step extraction). Then, 9.2 mL of the aqueous phase after the second-step extraction was taken up, and the solution was treated in a similar manner, except that 0.05 mL of 0.5 M NaBr solution was added (third-step extraction).

In the case of (*S*)-**1** extractant, the extraction procedure was similarly carried out except that 9.4 mL of the aqueous phase was used in the second-step extraction and 9.0 mL, the third-step extraction.

**NMR Analysis of Ion-Pair Complex.** An aqueous solution (20 mL) containing 50 mM (−)- or (+)-DBT and 0.5 M $Na_2HPO_4$–$KH_2PO_4$ buffer (pH 7.5) was shaken with a 1,2-dichloroethane solution (20 mL) containing 5 mM (*R*)- or (*S*)-**1** for 2 h at room temperature. The organic phase was separated. After removal of the solvent by evaporation, the ion-pair complex was obtained (yield: 93%). A portion of it was dissolved in $CDCl_3$ and analyzed by NMR with a JEOL JNM-GSX 400 instrument.

## Results and Discussion

**Extraction of Enantiomeric DBT.** Table 1 summarizes the extraction of enantiomeric DBT by use of various extractants having chirality. When (*R*)-**1** was used, which is a dicationic diphosphonium salt having an axially chiral unit (binaphtyl unit), (−)-DBT was more effectively extracted than (+)-DBT. In contrast, (+)-DBT was more efficiently extracted than (−)-DBT by use of (*S*)-**1** as extractant. Thus, "enantioselective" extraction took place by use of **1** as an ion-pair extractant. The enantioselectivity $\alpha$ was 1.36. When the extraction using (*R*)-**1** was performed at 20 °C, the enantioselectivity was lower than 1.36. When pure 1,2-dichloroethane was used as extracting solvent instead of the mixture solvent (1,2-dichloroethane+carbon tetrachloride) under otherwise identical conditions, the enantioselectivity somewhat decreased.

Compounds **2** and **3** have structures similar to that of **1** but are monocationic phosphonium salts (Fig. 1). When they were used as extractants, the enantioselectivity was considerably lower. Compounds **4** and **5** are commercial phase-transfer catalysts having asymmetric carbons. These did not exhibit chirality recognition as ion-pair extractants.

In the extraction of mandelate by (*R*)-**1**, the (−)-isomer was somewhat more extracted than the (+)-isomer

Table 1. Extraction of Enantiomeric DBT by Chiral Extractant[a)]

| Extractant | Buffer mM | pH | [NaBr] mM | Temp °C | (+) or (−)[b)] | Distribution ratio[c)] $D_A$ | $D_B$ | $\alpha=D_A/D_B$ |
|---|---|---|---|---|---|---|---|---|
| (*R*)-**1** | 5 | 7.5 | 0.4 | 2 | (−) | 0.400 | 0.294 | 1.36 |
| (*S*)-**1** | 5 | 7.5 | 0.4 | 2 | (+) | 0.392 | 0.290 | 1.35 |
| (*R*)-**1** | 2 | 7.0 | 0.3 | 2 | (−) | 1.10 | 0.818 | 1.34 |
| (*R*)-**1** | 2 | 7.0 | 0 | 20 | (−) | 1.08 | 0.911 | 1.18 |
| (*R*)-**2** | 2 | 7.0 | 0 | 20 | (−) | 1.93 | 1.84 | 1.05 |
| (*R*)-**3** | 2 | 7.0 | 0 | 20 | — | 3.68 | | d) |
| **4** | 2 | 7.0 | 0 | 20 | — | 1.58 | | d) |
| **5**[e)] | 2 | 6.1 | 0 | 20 | — | 0.74 | | d) |

a) The aqueous phase initially contained 0.1 mM DBT, NaBr, and $Na_2HPO_4$–$KH_2PO_4$ buffer, while the organic phase (1,2-dichloroethane+carbon tetrachloride, 1:1) contained 0.2 mM extractant. b) More extractable enantiomeric DBT. c) $D_A$ and $D_B$ denote the distribution ratios of more and less extractable enantiomeric DBTs, respectively. d) The $\alpha$ value could not be evaluated ($\alpha<1.02$). e) 5 mM of the extractant was added.

($\alpha$=1.1). However, in the extraction of dansyl-amino acids such as dansyl-phenylalanine and dansyl-serine by **1** and **3**, the enantioselective extraction was hardly attained under relevant conditions.

**Extraction Equilibrium.** The extraction of DBT by **1** was investigated in detail. We assume that extraction of the dianion (DBT) by the dicationic extractant (**1**) involves the formation of a 1:1 ion-pair complex between **1** and DBT. The reaction and the extraction constant ($K_{ex}$) are defined as follows:

$$(Q{\cdot}Br_2)_o + (A^{2-})_w \rightleftharpoons (Q{\cdot}A)_o + 2(Br^-)_w, \quad (1)$$

and

$$K_{ex} = [Q{\cdot}A]_o[Br^-]_w^2/[Q{\cdot}Br_2]_o[A^{2-}]_w, \quad (2)$$

where $Q^{2+}$ and $A^{2-}$ denote **1** and DBT, respectively, and subscripts w and o denote the aqueous and organic phases, respectively. Eq. 2 is converted into a logarithmic form:

$$\log [Q{\cdot}A]_o/[Q{\cdot}Br_2]_o[A^{2-}]_w = \log K_{ex} - 2\log [Br^-]_w. \quad (3)$$

The $Q{\cdot}Br_2$ and the complex, Q·A, are highly lipophilic and do not appreciably dissolve in the aqueous phase. The distribution ratio of $Q{\cdot}Br_2$ was larger than 100 in 1,2-dichloroethane/water system. Thus, the values of $\log [Q{\cdot}A]_o/[Q{\cdot}Br_2]_o[A^{2-}]_w$ and $\log [Br^-]_w$ in Eq. 3 can be easily obtained experimentally.

Figure 2 shows the plots of $\log [Q{\cdot}A]_o/[Q{\cdot}Br_2]_o[A^{2-}]_w$ against $\log [Br^-]_w$ in the extraction of DBT by (*R*)-**1** at pH 7.5 and 8.0. The plot is a straight line with a slope of 2. This indicates that the extraction reaction (1) occurs via the formation of a 1:1 ion-pair complex between **1** and DBT under the relevant pH conditions. The ratio, $K_{ex}$ ((−)-DBT)/$K_{ex}$((+)-DBT)=1.47, was obtained at pH 7.5.

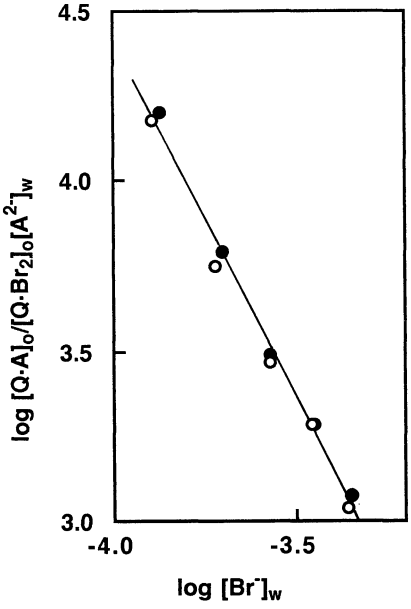



Fig. 2. Extraction of (−)-DBT by (*R*)-**1** at pH 7.5 (●) and at pH 8.0 (○). The aqueous phase initially contained 0.1 mM (−)-DBT, 0—0.4 mM NaBr, and 5 mM $Na_2HPO_4$–$KH_2PO_4$ buffer, while the organic phase (1,2-dichloroethane+carbon tetrachloride, 1:1) contained 0.2 mM (*R*)-**1** (2°C).

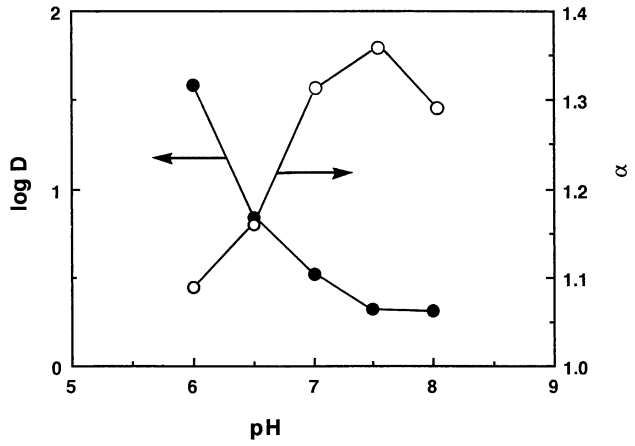



Fig. 3. Effect of pH on the extractability of (−)-DBT and the enantioselectivity ($\alpha$). Conditions were the same as those in Fig. 2 except that pH was varied (NaBr: 0 mM).

**Effect of pH and Ionic Strength.** Figure 3 shows the plot of log $D$ ($D$: distribution ratio of DBT) against pH in the aqueous phase. The extractability of DBT was decreased with increasing pH in the range 6.0—7.5, and is almost constant at pH above 7.5. This suggests that by lowering pH, the protonated DBT is involved to a higher degree in the extraction reaction ($Q^{2+}\cdot Br^-\cdot AH^-$ complex is extracted) and thus the extractability is raised. As mentioned above, the 1 : 1 ion-pair complex ($Q^{2+}\cdot A^{2-}$) is only extracted via Eq. 1 at pH above 7.5.

The enantioselectivity was enhanced with an increase in pH (Fig. 3). A two-point ion-pair formation within the complex between **1** and DBT may play an important role in the enantioselectivity, as will be discussed later.

Figure 4 depicts the effect of ionic strength in the aqueous phase. The extractability is nearly independent of the ionic strength, while the enantioselectivity decreases slightly, as the ionic strength increases.

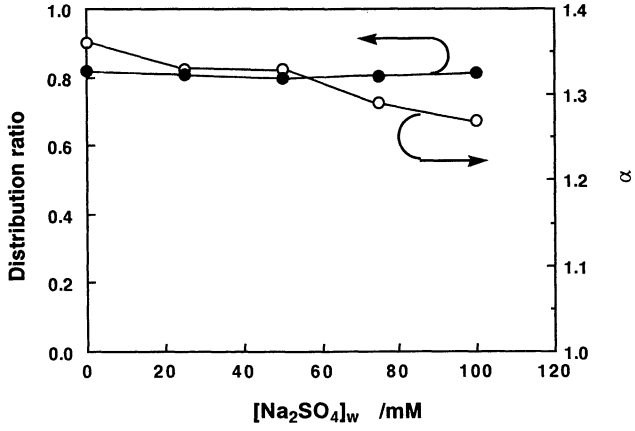



Fig. 4. Effect of ionic strength on the extractability of (−)-DBT and the enantioselectivity ($\alpha$). Conditions were the same as those in Fig. 2 except that a prescribed amount of $Na_2SO_4$ was added and 2 mM buffer was used (pH: 7.5; NaBr: 0.2 mM).

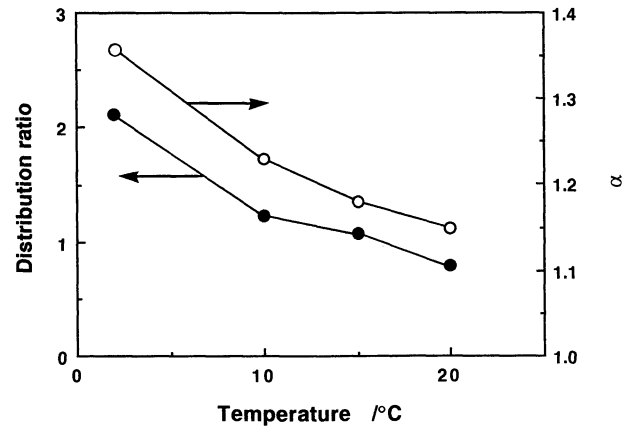



Fig. 5. Effect of temperature on the extractability of (−)-DBT and the enantioselectivity ($\alpha$). Conditions were the same as those in Fig. 2 except that the temperature was varied (NaBr: 0 mM; pH: 7.5).

**Effect of Temperature.** The effect of temperature is given in Fig. 5. Both the extractability and the enantioselectivity decrease with an increase in the temperature. The chirality recognition of **1** may come from a difference between the steric hindraces of binaphtyl unit for both enantiomers. As the temperature is lowered, the rigidity of binaphtyl unit increases, resulting in the enantioselectivity enhancement. A similar situation was reported in the studies of Cram's crown ether.[3]

**Multistage Extraction.** Table 2 summarizes the results of multistage extraction. In each extraction step, the conditions were adjusted to give the % extraction of roughly 50%. As the extraction step went up in the case of (*R*)-**1** extractant, the optical purity of (+)-DBT in the aqueous phase was gradually enhanced; however, the concentration of DBT in the aqueous phase was inevitably decreased. Conversely, when (*S*)-**1** was used, the optical purity of (−)-DBT was increased. The conditions of multistage extraction in the cases of (*R*)-**1** and (*S*)-**1** were somewhat different from each other. Therefore, as seen in Table 2, the optical purities obtained in both cases were a little different.

The enantioselectivity ($\alpha$) calculated from the optical purity in the first step was 1.42, which is comparable to the values obtained from the separate-mode extraction experiments ((+)- and (−)-DBTs were separately extracted) shown in Table 1 etc. Table 2 shows that the optical purity is improved as the extraction step is repeated. By designing a sophisticated device such as a counter-current extraction system, complete resolution of racemic DBT could be attained.

**NMR Analysis of Ion-Pair Complex.** Table 3 summarizes the chemical shifts of $^1H$ and $^{31}P$ within the ion-pair complex, **1**·DBT, in $CDCl_3$. The chemical shifts of the two methylene-protons adjacent to the phosphonium phosphorus atom in **1** ($H^a$ and $H^b$) are different from each other. Free rotation of the methylene-carbon is limited because of a steric hindrance around the phosphorus atom. A similar situation was observed in the case of the methylene-protons within **2**

Table 2. Multistage Extraction[a]

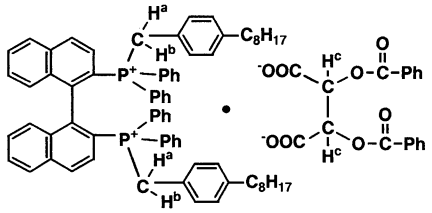
| Extractant **1** | Extraction step | $[DBT]_w$[b] | O.R.[c] | O.P.[d] |
|---|---|---|---|---|
| | | mM | ° | % |
| (*R*) | 1 | 2.42 | +0.027 | 9.2 |
| | 2 | 1.40 | +0.030 | 18 |
| | 3 | 0.555 | +0.024 | 36 |
| (*S*) | 1 | 2.39 | −0.027 | 9.3 |
| | 2 | 1.33 | −0.029 | 18 |
| | 3 | 0.522 | −0.022 | 34 |

a) Extraction conditions are described in text. b) The concentration of DBT remained in the aqueous phase after each extraction step. c) Optical rotation of the aqueous phase ($\lambda$=435 nm). d) Optical purity of DBT in the aqueous phase.

Table 3. Chemical Shifts of H and P within the Ion-Pair Complex **1**·DBT in $CDCl_3$[a]

| Complex[b] | **1**[c] | | | DBT |
|---|---|---|---|---|
| | $H^a$ | $H^b$ | P | $H^c$ |
| (*R*)·$Br_2$ | 5.27 | 4.73 | 20.9 | — |
| (*S*)·$Br_2$ | 5.29 | 4.75 | 20.9 | — |
| (*R*)·(−) | 5.05 | 4.41 | 21.1 | 5.87 |
| (*R*)·(+) | 5.15 | 4.56 | 21.1 | 5.89 |
| (*S*)·(−) | 5.14 | 4.58 | 21.1 | 5.88 |
| (*S*)·(+) | 5.07 | 4.40 | 21.1 | 5.88 |

a) $\delta(^1H)$ from tetramethylsilane; $\delta(^{31}P)$ from $H_3PO_4$. b) For example, (*R*)·(−) denotes the complex between (*R*)-**1** and (−)-DBT. c) For $H^a$ and $H^b$, the top of apparent triplet peak (two doublet peaks are overlapped) is indicated.



**1**-DBT ion-pair complex

and **3** (see experimental section).

The couple of the ion-pair complexes enantiomeric to each other, (*R*)·(−)-(*S*)·(+) couple and (*R*)·(+)-(*S*)·(−) couple, naturally exhibited almost the same chemical shifts for the methylene-protons ($H^a$ and $H^b$); e.g., (*R*)·(−) denotes the complex between (*R*)-**1** and (−)-DBT. However, the chemical shifts for the former couple ((*R*)·(−) and (*S*)·(+)) were shifted to higher field by 40—70 Hz compared to those in the latter couple ((*R*)·(+) and (*S*)·(−)).

As previously described, the extractabilities of (*R*)·(−) and (*S*)·(+) were higher than those of (*R*)·(+) and (*S*)·(−) (Table 1). It is considered that the extractability is enhanced when the ion-pair is more tightly formed. In this case, the electron-withdrawing property of phosphonium decreases, so that the methylene-protons ($H^a$ and $H^b$) are shifted to higher field.

The chemical shifts of phosphonium phosphorus atom itself and the methine-proton in DBT are nearly common among the four optical isomers (Table 3).

**Chirality Recognition in Ion-Pair Extraction.** It is found that the enantioselective extraction of DBT is possible by use of **1** as ion-pair extractant. To our knowledge, there has been only one report dealing with the chirality recognition of ionic species in ion-pair extraction system.[7] An enantioselective extraction of mandelate anion is studied, in which a chiral ammonium salt, a derivative of α-methylbenzylamine, is used as extractant. So far, ion-pair extractants having axial chirality have not been studied.

The concept of "three-point interaction" has often been used to explain the mechanism of chirality recognition in chromatographic studies.[18] This concept is applicable to the present system of ion-pair extraction. There is a three-point interaction between **1** and DBT, two ion-pair interactions and one steric interaction (or π–π interaction) of aromatic rings.

When the monocationic extractants **2** and ***3*** were used, the enantioselectivity was heavily decreased (Table 1). These extractants cannot perform such a three-point interaction. Moreover, as shown in Fig. 3, the enantioselectivity was decreased with lowering pH in the aqueous phase. As the pH is lowered, the involvement of protonated DBT to the extraction reaction rises. Thus, the three-point interaction hardly works between **1** and DBT. Consequently, the three-point interaction can be favorably at work, only when the extraction reaction involves both the dicationic **1** and dianionic DBT, leading to high chirality recognition.

The chiral ion-pair extractant **1** possesses a high chirality recognition ability and a high extraction ability resulting from its high lipophilicity. The chirality recognition by ion-pair extraction may open a new realm of optical resolution for ionic species in aqueous media.

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