Enantioselective Distribution Behavior of (±)-Pindolol in a Liquid–Liquid Two-Phase System Containing Optically Active Diol and Boric Acid

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Received October 16, 1995; accepted February 19, 1996

Enantioselective distribution of (±)-pindolol was observed in a chloroform–boric acid two-phase system in the presence of (1*R*,2*R*)-(+)-hydrobenzoin, 1,4-di-*O*-dodecyl L-threitol, (*R*)-(+)- or (*S*)-(−)-1,1′-2-binaphthol in the organic phase.

Key words boric acid; hydrobenzoin; binaphthol; enantioseparation; liquid–liquid extraction

We reported the enantioselective distribution behavior of β-aminoalcohols in a liquid–liquid two-phase system composed of dialkyl L-tartrate chloroform solution and boric acid aqueous solution.[1] It is postulated that a borate complex of tartrate and β-aminoalcohol (Fig. 1) is formed in the organic phase, where the 1,2-diol group of the tartrate is considered to be essential to chiral discrimination, and the ester group of the tartrate strengthens the stability of the complex with hydrogen bonding. To confirm these, chiral diols which have no carbonyl groups were subjected to the enantioselective extraction of (±)-pindolol in the liquid–liquid two-phase system.

Prelog *et al.*[2] reported the enantioselective distribution of β-aminoalcohols in the two-phase system of 1,2-dichloroethane solution of di-5-nonyl L-tartrate and the aqueous solution of sodium hexafluorophosphate. They described that the hydrogen bonding between the carbonyl groups of the tartrate and aminoalcohol was considered to be important in the chiral recognition.

In this study, we report that the enantioselective distribution of (±)-pindolol was observed in the chloroform–boric acid two-phase system in the presence of such chiral diols as (1*R*,2*R*)-(+)-hydrobenzoin, 1,4-di-*O*-dodecyl-L-threitol, (*R*)-(+)- or (*S*)-(−)-1,1′-2-binaphthol in the organic phase. It was proved that a 1,2-diol group, not ester groups, in the tartrate was essential in the chiral recognition of pindolol in the presence of boric acid. The importance of hydrogen bonding in the diastereomeric complex formation was also found.

Experimental

Chiral (1*R*,2*R*)-(+)-hydrobenzoin, 2,3-di-*O*-isopropylidene-L-threitol and dimethyl L-tartrate were purchased from Aldrich Chemical Co. (U.S.A.). (*R*)-(+)- and (*S*)-(−)-1,1′-2-Binaphthol were obtained from Tokyo Kasei Kogyo (Tokyo) and recrystallized from toluene before use. (±)-Pindolol was purchased from Wako Pure Chemical Ind. (Osaka).

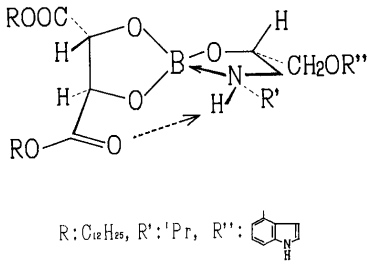

Fig. 1. Postulated Structure of the Borate Complex of Didodecyl L-Tartrate and Pindolol in the Organic Phase

(2*R*,3*R*)-(+)-Didodecyl L-tartrate (L-DDT) was prepared from L-tartaric acid according to the reported method.[1] 1,4-Di-*O*-dodecyl L-threitol was also prepared from 2,3-di-*O*-isopropylidene L-threitol by didodecylation with dodecylbromide in tetrahydrofurane in the presence of potassium *tert*-butoxide, and successive acid deprotection of the isopropylidene group.[3]

HPLC analysis was performed with an HPLC system 980 (JASCO, Tokyo) equipped with a chiral column of Chiral-Cel OD-R (4.6 i.d. × 25 cm, Daicel, Tokyo), Rheodyne sampling valve (20 μl) and data processor C-R6A (Shimadzu, Kyoto). The eluting solvent was a mixture of 0.1 M potassium hexafluorophosphate aqueous solution and acetonitrile (60 : 40), and it was monitored at 288 nm.

The extraction experiments of (±)-pindolol were performed as described earlier.[1]

Results and Discussion

The enantioselective distribution of pindolol enantiomers was observed in the liquid–liquid two-phase system in the presence of chiral diols (Table 1).

The selectivity with (+)-binaphthol was relatively low (α = 1.08 at 100 mM, and 1.12 at 200 mM) compared to the α values of 2.19 with 100 mM L-DDT, 1.36 with 100 mM 1,4-di-*O*-dodecyl L-threitol or 1.59 with 300 mM of hydrobenzoin. This indicated that the distance between the two oxygen atoms in the diol group might be important in the formation of a borate complex. A borate complex with a seven-membered ring is to be formed in the case

Table 1. The Enantioselective Distribution of (±)-Pindolol in a Two-Phase System Containing Chiral Diol in the Organic Phase and Boric Acid in the Aqueous Phase

Chiral diol	Distribution ratio		
	D_1	D_2	α
(2*R*,3*R*)-(+)-Didodecyl tartrate	0.790	1.730	2.19
(−)-1,4-Di-*O*-dodecyl L-threitol	0.096	0.131	1.36
(1*R*,2*R*)-(+)-Hydrobenzoin (300 mM)	1.419	2.251	1.59
(*R*,*R*)-(+)-1,1′-Bi-2-naphthol	0.235	0.253	1.08
(*R*,*R*)-(+)-1,1′-Bi-2-naphthol (200 mM)	0.413	0.464	1.12
(*S*,*S*)-(−)-1,1′-Bi-2-naphthol (200 mM)	0.402	0.349	0.87

Aqueous phase: 100 mM boric acid (pH 5.2), organic phase: 100 mM chiral diol in chloroform until otherwise stated, racemic sample: (±)-pindolol: 0.5 mM in the both of the phases, 25 °C, α (separation factor) = D_2/D_1.

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with binaphthol, while a five-membered ring is estimated to be formed with tartrate, threitol or hydrobenzoin.

L-DDT showed much better chiral recognition than the other diols used. The carbonyl groups of tartrates may have some assisting role in the stability of the borate complex, because 1,4-di-*O*-dodecyl L-threitol, which has the same stereochemical backbone as L-tartrate but has no carbonyl group, showed a much smaller separation factor than L-DDT. With a ball-and-stick molecular model of the borate complex, as shown in Fig. 1, one of the carbonyl groups of L-DDT comes close to the hydrogen atom of the amino group in pindolol.

The relationship between the enantioselectivity and the stereochemistry of 1,4-di-*O*-dodecyl L-threitol, (+)- and (−)-binaphthol agreed with the result obtained with L-tartrate. However, (1*R*,2*R*)-(+)-hydrobenzoin, which has a similar absolute configulation to (2*S*,3*S*)-D-tartaric acid,[4] showed reversed selectivity (*cf.* Table 1). Thus, in this case, the CH/π interaction[5] or π/π interaction between one of the phenyl groups of hydrobenzoin and isopropyl or an indol group of pindolol might exist. Further investigation into the relationship between the enantioselectivity and the absolute configurations of both components of the borate complex must be carried out.

Now, the chiral 1,2-diols can easily be prepared by catalytic asymmetric hydroxylation of olefins,[6] and a variety of chiral selectors can be designed. It is known that 1,3-diols can form a boric acid ester much easier than 1,2-diols,[7] so we must survey whether similar chiral recognition occurs using chiral 1,3-diols and boric acid in the future.

In conclusion, it was demonstrated that in a two-phase system consisting of a chloroform solution of optically active diols such as dialkyl tartrates, 1,4-dialkyl threitol, hydrobenzoin and binaphthol, and in boric acid aqueous solution, a racemic β-aminoalcohol, pindolol, showed enantioselective distribution behaviors. The postulated structure of the borate complex is supported by using chiral diols which have no carbonyl groups. It was also found that the preferential chiral discrimination of the L-tartrate to the other 1,2-diols arises from the presence the hydrogen bonding between the tartrate and one of the enantiomers of (±)-pindolol.

References and Notes

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3) 1,4-Di-*O*-dodecyl L-threitol obtained showed mp 54—55 °C, (recrystalized from *n*-hexane), $[\alpha]_D^{21}$ −2.2° (c=1.0, $CHCl_3$), IR (KBr) cm^{-1}; 3354, 2918, 2849, 1464, 1377, 1128, 1070, 727, NMR (500 MHz, in $CDCl_3$, ppm from TMS); 3.83 (br s, 2H), 3.52—3.6 (m, 4H), 3.41—3.51 (m, 4H), 2.86 (br s, 2H), 1.52—1.64 (m, 4H), 1.2—1.35 (m, 40H), 0.88 (t, J=8.5 Hz, 6H).
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