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Chiral Discrimination towards Racemic Alcohols through Host/Guest Clathrate Inclusion with Axially Chiral 1,1′-Binaphthyl-2,2′-dicarboxylic Acid

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Axially chiral 1,1′-binaphthyl-2,2′-dicarboxylic acid (**1**) was successfully utilised as a new type of chiral host molecule soluble in aqueous alkaline solution; 1-phenylalkan-1-ols were optically resolved by means of chiral host/guest clathrate inclusion giving optical purities ranging from 18 to 90% enantiomeric excess (e.e.), depending on the alkyl group.

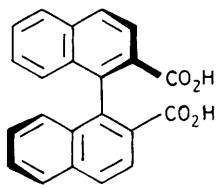
Recently, increasing attention has been paid to chiral clathrate inclusion, since this phenomenon is applicable to a useful method for optical resolution, especially of uncharged chiral organic compounds on a preparative scale.[1—4] From a practical viewpoint, Toda and co-workers have developed artificial host molecules with high chirality-discriminating abilities: *e.g.* acetylenic alcohols[2,4] and 1,1′-binaphthyl-2,2′-diol.[3] A common principle of constructing these chiral host molecules is based on the ability to form hydrogen bonds between host and guest, and the formation of host molecules with rigidly twisted skeletones, which are chiral.†

It has long been known that 1,1′-binaphthyl-2,2′-dicarboxylic acid (**1**) forms clathrate compounds with organic compounds.[5] Weber *et al.*[6] have shown recently that the co-ordination-assisted lattice inclusion with racemic (**1**) exhibits a high level of 'constitoselectivity' towards various guest molecules. Therefore, axially chiral (**1**) would be expected to be suitable as an artificial host molecule with asymmetric selectivity.

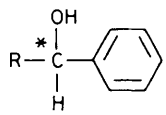
We report here the first example of chiral clathrates of (**1**), and their application to the direct optical resolution of racemic 1-phenylalkan-1-ols (**2a—f**). These alcohols have been resolved conventionally by fractional recrystallisations of the derivatising diastereoisomeric salts,[7] or kinetically by asymmetric-selective polymerisations.[8,9] These procedures, however, are tedious, involving esterification and saponification reactions.

Optically pure (**1**) was easily prepared in sufficient quantities to use freely as a host. (*RS*)-(**1**) (87.6 mmol) and anhydrous brucine (87.7 mmol) were dissolved in boiling acetone (1.5 l), the solution was cooled, and the precipitated salt collected by filtration. Recrystallisation from methanol–acetone gave the pure (+)-brucine salt in 41% yield {m.p. 211—214 °C; $[\alpha]_D^{25}$ +200° (*c* 0.5, $CHCl_3$)}. Treatment of the salt with HCl (6 M) and extraction with diethyl ether gave (*R*)-(**1**) in quantitative yield {m.p. 197—199 °C (decomp.); $[\alpha]_{546}^{25}$ +127° (*c* 1.0, 0.1 M NaOH)}. The mother liquor from the initial salt formation was decomposed similarly. The ether extract was evaporated to dryness, and the residual solids were digested with ether on heating. The insoluble residue was removed by filtration. Evaporation of the filtrate gave (*S*)-(**1**) in 45% yield {m.p. 199—200 °C (decomp.); $[\alpha]_{546}^{25}$ −127° (*c* 1.0, 0.1 M NaOH), $[\alpha]_D^{25}$ −41.6° (*c* 1.0, MeOH)}. The detailed procedure will be published elsewhere.[10]

Typically, for the optical resolution of racemic 1-phenylpropanol (**2c**), a solution of (*S*)-(**1**) (1.9 mmol) and (*RS*)-(**2c**) (3.7 mmol) in benzene (40 ml)‡ was concentrated to a half of the volume and allowed to stand at room temperature overnight; colourless crystals were deposited, collected, and



(*R*) - (**1**)



(**2**)

a; R = Me
b; R = Et
c; R = Pr^n
d; R = Pr^i
e; R = Bu^n
f; R = Bu^t

† The type of host/guest aggregate that is assisted by co-ordination has been termed 'co-ordinatoclathrate' by Weber *et al.* (ref. 6).

‡ At a 1 : 1 mole ratio of (**1**) : (**2**), the crystallisation of a benzene clathrate of (**1**) was predominant.

Table 1. Optical resolution of (*RS*)-(**2**) through chiral host/guest clathrate inclusion with (*S*)-(**1**).[a]

		Host/guest clathrate		Included (**2**)[d]		
Guest	Solvent	(**2**)/(**1**)[b] (mole/mole)	Yield[c] (%)	$[\alpha]_D^{25}$/°	Configuration	E.e./%
(**2a**)	C_6H_6	1/1	26	−8.2	*S*	18[e]
(**2b**)	C_6H_6	1/2	25	+33.1	*R*	70[f]
(**2c**)	C_6H_6	1/2	24	+40.9	*R*	90[g]
(**2c**)	C_6H_6	1/2[h]	24	−39.9	*S*	88[g]
(**2d**)	Et_2O	1/2	14	+37.9	*R*	79[i]
(**2e**)[j]	Et_2O	1/2	41	+13.3	*R*	35[k]
(**2f**)	Et_2O	0/[l]	—			

[a] (**2**)/(**1**) = 2/1 (mole/mole). [b] Determined from ^1H n.m.r. (in $CDCl_3$). [c] Isolated yield of the first crop based on (*RS*)-(**2**) used. [d] The decomposition of clathrates gave (**2**), the e.e.s and configurations of which were determined from the maximum rotations reported. [e] Based on $[\alpha]_D^{23}$ 45.5° (MeOH) (ref. 12). [f] Based on $[\alpha]_D^{21}$ 47.03° (C_6H_6) (ref. 13). [g] Based on $[\alpha]_D^{26}$ 45.2° (C_6H_6) (ref. 11). [h] (*R*)-(**1**) was used. [i] Based on $[\alpha]_D^{20}$ 47.7° (Et_2O) (ref. 14). [j] (**2**)/(**1**) = 1/1 (mole/mole). [k] Based on $[\alpha]_D^{25}$ 37.9° (C_6H_6) (ref. 15). [l] The benzene clathrate of (**1**) was obtained.

washed with benzene. The yield of the crystals (0.74 g) based on (*RS*)-(**2c**) used was estimated to be 24% as the clathrate was composed of (**1**) and (**2c**) in a 2 : 1 mole ratio, determined by ^1H n.m.r. spectroscopy {m.p. 156.2—158.6 °C: $[\alpha]_D^{25}$ −28.2° (*c* 1.0, MeOH)}. The clathrate was decomposed with aqueous NaOH,§ and extracted with diethyl ether. Bulb-to-bulb distillation of the organic extract *in vacuo* gave 0.11 g (20%) of (*R*)-enriched (**2c**) {$[\alpha]_D^{25}$ +40.9° (*c* 1.0, C_6H_6), 90% enantiomeric excess (e.e.)[11]}. A similar treatment of the benzene filtrate gave (*S*)-enriched (**2c**){0.43 g; 76% yield; $[\alpha]_D^{25}$ −11.1° (25% e.e.[11])}.

Table 1 shows the preliminary results of optical resolutions of racemic (**2a—f**). When a 1 : 2 mixture of (*S*)-(**1**) and (*RS*)-(**2a**) was crystallised from benzene, a 1 : 1 host/guest clathrate was obtained. The clathrate preferentially included (*S*)-(**2a**) over (*R*)-(**2a**) on crystallisation. However, the enantioselectivity was found to be not high from the %e.e. of (**2a**) included in the clathrate.

Under the same conditions, (**2b**) and (**2c**) were found to form 2 : 1 clathrates of (*S*)-(**1**) and alcohol. These clathrates preferentially included (*R*)-alcohols to give high e.e.s of 70 and 90%, respectively. Enantiomeric (*R*)-(**1**) matched the opposite (*S*)-alcohol in clathrate formation, as expected. When the above (*R*)-enriched (**2c**) was once more treated with (*S*)-(**1**), the included alcohol was found to be 100% optically pure {$[\alpha]_D^{25}$ +47.1° (*c* 2.3, C_6H_6)}. Interestingly, the sense of the stereoselection towards the two alcohol components was reversed from that observed for the 1 : 1 clathrate of (**2a**).

In the cases of (**2d**) and (**2e**), having more bulky alkyl substitutents, crystallisation from benzene was assumed to give a benzene clathrate of (**1**). ^1H N.m.r. analysis suggested that the clathrate was labile and that its composition varied with the time after isolation due to rather rapid release of benzene. Clathrates of these alcohols were crystallisable from Et_2O at high concentrations. The included (**2d**) was similarly enriched in the (*S*)-enantiomer of high e.e., while a moderate stereoselection was observed for the clathrate of (**2e**). For the most bulky of the alcohols screened, (**2f**), attempts to prepare the clathrate failed in benzene and Et_2O.

§ The chiral host was recovered from the aqueous layer without any noticeable loss in yield and optical purity.

The optical material balance was established with regard to the yield of the clathrate and the e.e.s of the two alcohols, obtained from the crystalline clathrate and from the filtrate within experimental error. The results indicate that discrimination of chirality for alcohols occurs through the clathrate inclusion with (**1**), not involving another asymmetric conversion. It is probable that the chiral lattice formed by the axially chiral host includes preferentially the better-fitting enantiomer of the guest alcohols. Therefore, the enantioselectivity in the inclusion as well as the composition of the clathrates may depend strongly upon the structure of the alkyl groups in the guest alcohols. Axially chiral (**1**) will be developed as an efficient chiral host for optical resolution methods through the chiral host/guest clathrate inclusion.

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