Novel Optical Resolution Methods by Inclusion Crystallisation in Suspension Media and by Fractional Distillation

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Enantioselective inclusion crystallisation of a hydrophobic oily racemic guest and a crystalline optically active host compound is achieved efficiently by stirring a suspension of both components in hexane or water, allowing enantiomers to be separated by fractional distillation.

We have studied the optical resolution of various racemic guest compounds by inclusion crystallisation in optically active host compounds.[1] Recently, we found that efficient inclusion crystallisation can be achieved simply by mixing powdered crystalline host and a hydrophobic guest compound in hexane or water. This suspension method can be more efficient than recrystallisation. Furthermore, when combined with a distillation procedure, racemic compounds can be separated to enantiomers by fractional distillation.

For example, when a suspension of powdered optically active host, cyclopentane **1a**[2] (1.0 g, 2.14 mmol) in hexane (10 ml), was mixed with racemic-1-phenylethanol **2a** (0.262 g, 2.14 mmol) at room temp. for 6 h, a 2 : 1 inclusion crystal of **1a** and (−)-**2a** (1.12 g) was obtained. Heating the filtered inclusion crystal *in vacuo* gave (−)-**2a** (95% e.e.) (0.112 g, 85% yield). By a similar procedure, **2b–c**, **3a–b**, **4a–c**, and **5a–d** were resolved efficiently (Table 1). In some cases, the host **1b**[2] **1c**[2] or optically active **6**[3] are more effective than **1a**, as shown in Table 1.

Hosts **1** and **6** are insoluble in hexane but guest compounds

Table 1 Results of optical resolution using the inclusion crystallisation by suspension method

Host	Guest	Medium	Product	Yield (%)	Optical purity (% e.e.)	$[\alpha]_D$ (*c*, solvent)
1a	**2a**	Hexane	(−)-**2a**	85	95[b]	−42.0 (0.55, MeOH)
1a	**2a**	H_2O	(−)-**2a**	85	98[b]	−42.1 (0.98, MeOH)
1a	**2b**	Hexane	(−)-**2b**	75	100[c]	−40.8 (0.26, MeOH)
1a	**2b**	H_2O	(−)-**2b**	75	98[c]	−38.0 (0.25, MeOH)
1a	**2c**	Hexane	(+)-**2c**	89	92[b]	+18.3 (0.35, MeOH)
1a	**2c**	H_2O	(+)-**2c**	76	100[b]	+18.4 (0.70, MeOH)
1b	**3a**[a]	Hexane	(+)-**3a**	80	80[d]	+42.1 (0.83, $CHCl_3$)
1b	**3b**[a]	Hexane	(+)-**3b**	93	78[d]	+33.8 (0.83, $CHCl_3$)
1b	**4a**	Hexane	(−)-**4a**	82	100[e]	−127.3 (0.75, MeOH)
1a	**4a**	H_2O	(−)-**4a**	73	100[e]	−122.6 (0.51, MeOH)
1b	**4b**[a]	Hexane	(+)-**4b**	78	75[e]	+90.5 (0.60, MeOH)
6	**4c**	Hexane	(+)-**4c**	57	98[e]	+14.7 (0.73, MeOH)
6	**4c**	H_2O	(+)-**4c**	85	97[e]	+13.3 (0.82, MeOH)
1b	**5a**	Hexane	(+)-**5a**	75	100[d]	+38.7 (0.47, $CHCl_3$)
1b	**5a**	H_2O	(+)-**5a**	89	100[d]	+37.8 (0.65, $CHCl_3$)
1c	**5b**	Hexane	(+)-**5b**	78	100[d]	+27.3 (0.44, $CHCl_3$)
1c	**5b**	H_2O	(+)-**5b**	80	100[d]	+26.5 (0.22, $CHCl_3$)
1b	**5c**	Hexane	(+)-**5c**	59	70[d]	+24.8 (0.76, $CHCl_3$)
1b	**5c**	H_2O	(+)-**5c**	52	86[d]	+38.3 (0.12, $CHCl_3$)
1c	**5d**	Hexane	(+)-**5d**	76	75[f]	−32.3 (1.00, benzene)
1c	**5d**	H_2O	(+)-**5d**	74	47[f]	−21.0 (1.55, benzene)

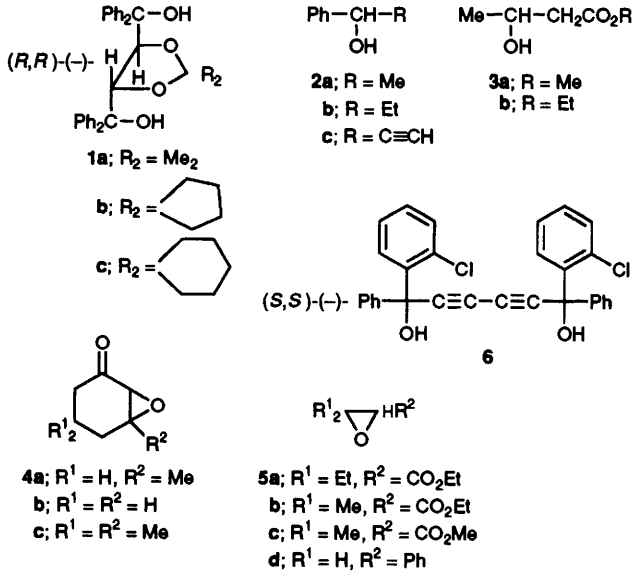
[a] No inclusion crystallisation occurred in water suspension. [b,c] Determined by HPLC using a column containing optically active solid phases, Chiralcel OJ and OB,† respectively. [d] Determined by measurement of ^1H NMR in the presence of chiral shift reagent, Eu(hfc)$_3$. [e] Determined by HPLC using the column containing optically active solid phase, Chiralpak As.† [f] Determined by comparison of the $[\alpha]_D$ value with that reported.[5]

2–5 are soluble in hexane, the inclusion crystallisation in hexane may proceed in the solid state. The enantioselective inclusion crystallisation was also found to proceed efficiently in aqueous suspension. For example, when a suspension of powdered **1a** (1.0 g, 2.14 mmol) and racemic **2a** (0.26 g, 2.14 mmol) in water (10 ml) containing *N*-hexadecyltrimethylammonium bromide (0.1 g) as a surfactant was stirred at room temp. for 24 h, a 2 : 1 inclusion crystal of **1a** and (−)-**2a** was obtained. Again, heating the filtered inclusion crystal *in vacuo* gave (−)-**2a** (98% e.e.) (0.11 g, 85% yield). This result clearly shows that the enantioselective inclusion crystallisation occurs efficiently in the solid state. This is probable because the solid-state inclusion complexation has been proved to occur by simple shaking of a mixture of powdered host and guest compounds.[4] In the water suspension experiment, however, surfactant is necessary to prevent coagulation of powdered host and hydrophobic guest compounds. By a similar procedure, **2b–c**, **3a–b**, **4a–c**, and **5a–d** were also resolved efficiently (Table 1). In the case of **3a**, **3b** and **4b**, however, no inclusion crystallisation occurred in water suspension (Table 1).

Efficiency of the resolution by the suspension method is sometimes higher than that by the recrystallisation method. For example, **4c** has been resolved by inclusion crystallisation with **6** in diethyl ether solution followed by two recrystallisations of the inclusion crystal, and (−)-**4c** of 100% e.e. has been obtained in 35% yield from the purified inclusion crystal by distillation.[6]

By using both **1c**- and (+)-**1c** host compounds in the suspension method, both enantiomers of guest compound can be obtained easily in optically pure state. For example, keeping a suspension of **1c** (1.0 g, 1.97 mmol) and racemic **4a** (0.5 g, 3.96 mmol) in hexane (10 ml) for 12 h gave an inclusion crystal (1.1 g) which upon distillation *in vacuo* gave (−)-**4a** of 100% e.e. (0.16 g, 65% yield). From the filtrate left after separation of the inclusion crystal, (+)-**4a** of 48% e.e. (0.29 g, 114% yield) was obtained by distillation. The crude (+)-**4a** was treated with (+)-**1c** in hexane (8.5 ml) as above to give finally (+)-**4a** of 100% e.e. (0.16 g, 62% yield).

† Chiralcel OJ and OB and Chiralpak AS are available from Daicel Chemical Industries, Ltd., Himeji, Japan.



When the resolution by the suspension method is combined with distillation, both enantiomers can be separated easily by fractional distillation. For example, after a suspension of **1a** (1.0 g, 2.14 mmol) and **2a** (0.26 g, 2.14 mmol) in hexane (1 ml) was kept at room temp. for 1 h, the mixture was distilled *in vacuo* to give initially uncomplexed (+)-**2a** of 59% e.e. (0.16 g, 125% yield) at lower boiling temperature. The residue was then distilled at elevated temperature and (−)-**2a** of 97% e.e. (0.09 g, 69% yield) was obtained at higher boiling temperature. By the same combination method, racemic **4c** was separated into enantiomers by fractional distillation in the presence of **6**, and (−)-**4c** of 68% e.e. (121% yield) and (+)-**4c** of 95% e.e. (63% yield) were obtained at lower and higher boiling temperatures, respectively. When the resolution by the combination method is repeated for the partially resolved samples, optically pure enantiomers can be obtained easily. Since the combination method is very simple and effective, this might be useful for large scale resolutions in industries.

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