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Resolution of hydrocarbons by inclusion complexation with a chiral host compound

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Abstract

Some racemic unsaturated hydrocarbons, 3- and 4-methyl and 4-vinylcyclohexene, bicyclo[4.3]nonane-2,5-diene, and 3-chloro- and 3,4-dichloro-1-butene were resolved as inclusion complex crystals with a chiral host compound derived from tartaric acid. The inclusion complexation, purified by repeating recrystallization from ether twice and decomposed by heating in vacuo, gave optically active hydrocarbons of 28–75% ee by distillation. The optical resolution by inclusion complexation in a water suspension medium and by fractional distillation in the presence of a chiral host was also applied to these hydrocarbons. © 2000 Elsevier Science Ltd. All rights reserved.

Preparation of optically active hydrocarbons is not easy and only a few examples of the preparation of optically active hydrocarbons have been reported. For example, optically active 3-phenylcyclohexene has been derived from tataric acid through eight steps.[1] Although one-step synthesis of optically active 3-methylcyclohexene from 2-cyclohexenol by the Grignard reaction using chiral nickel complex as a catalyst has been reported, the enantiomeric purity of the product has low, 15.9%, ee.[2] Some attempts at separation of the enantiomers of chiral hydrocarbons by chromatography have also been reported. For example, capillary gas chromatographic separation of the enantiomers of halogen-substituted butanes and butenes using a 2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl cyclodextrin liquid stationary phase has been reported.[3] Separation of the enantiomers of 3-[4,5] and 4-methylcyclohexenes[6] by similar chromatography has also been reported. These methods are, however, not very practical for the preparation of optically active hydrocarbons in bulk, even if the efficiency of separation is good. We report a simple resolution method of racemic hydrocarbons **2**–**4** by inclusion complexation with the optically active host compound, (*R,R*)-(–)-*trans*-4,5-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane **1**.[7]

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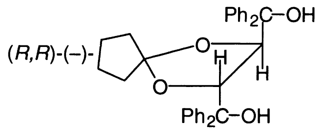
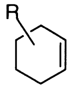
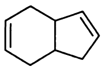


1

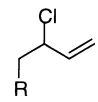


2

a: R=3-Me
b: R=4-Me
c: R=4-CH=CH$_2$



3



4

a: R=H
b: R=Cl

For example, when a solution of *rac*-3-methylcyclohexene **2a** (0.58 g, 6.1 mmol) and **1** (3 g, 6.1 mmol) in ether (15 ml) was kept at room temperature for 12 h, a 2:1 inclusion complex[8] of **1** and (–)-**2a** (2.5 g, 75% yield) was obtained as colorless prisms. The crystals were purified by two recrystallizations from ether to give the inclusion complex (2.4 g, 71% yield), which upon heating in vacuo afforded (–)-**2a** of 75% ee by distillation (0.19 g, 66% yield, $[\alpha]_D$ –66 (*c* 1.0, $CHCl_3$)). The enantiomeric excess of (–)-**2a** was determined by comparison of its $[\alpha]_D$ value with that reported.[2] It is valuable to be able to separate enantiomers of hydrocarbon by inclusion complexation with simple chiral host compound such as **1**. By inclusion complexation with (–)-**2a**, νOH of **1** (3590 and 3400 cm^{-1}) were shifted to lower frequencies (3400 and 3230 cm^{-1}). Since cyclohexane does not form an inclusion complex with **1**, hydrogen bonding between π-orbital of **2a** and the OH group of **1** would be important for the inclusion complex formation. Dissociation energies of 2:1 of **1** and (–)-**2a** were determined by DSC measurement to be 45 kJ mol^{-1}. This data show that the stabilization energy of the complex is quite high. By the same inclusion complexation in solvent followed by two recrystallizations of the inclusion complex, 4-methyl **2b** and 4-vinylcyclohexene **2c**, bicyclo[4.3]nonane-2,5-diene **3**, and 3-chloro-**4a** and 3,4-dichloro-1-butene **4b** were also resolved (Table 1). The optical purity of **2b**,[9] **2c**,[10] and **4a**[11] was determined by the

Table 1
Resolution of **2**–**4** by complexation with **1** through recrystallization from ether and water suspension methods

		Recrystllization method			Water suspension method		
Guest	Product	Yield (%)	$[\alpha]_D$[a]	ee(%)	Yield (%)	$[\alpha]_D$[a]	ee(%)
2a	(–)-**2a**	66	–66	75	86	–11	13
2b	(+)-**2b**	55	+31	33	82	+3	3
2c	(–)-**2c**	73	–12	28	64	–3	8
3	(–)-**3**	90	–16	c	53	–2	c
4a	(–)-**4a**	48	–28	56	65	–2	4
4b	(+)-**4b**	42	+15	c	71	+11	c

[a] All $[\alpha]_D$ values of **2a** were measured in $CHCl_3$ at *c* 1.0, and those of **2b-c**, **3**, and **4a-b** were measured in MeOH at *c* 1.0.

[b] Enantiomeric excess of the enantiomer obtained by the inclusion complexation followed by two recrystallizations of the inclusion complex was shown.

[c] Enantiomeric excess was not determined.

comparison of their $[\alpha]_D$ values with those reported. However, the enantiomeric excess of **3** and **4b** was not determined.

The resolution by inclusion complexation in a water suspension medium[12] is also applicable to hydrocarbons. For example, a suspension of powdered **1** (3 g, 6.1 mmol) and *rac*-**2a** (0.58 g, 6.1 mmol) in water (20 ml) containing hexadecyltrimethylammonium bromide as a surfactant was stirred for 48 h at room temperature. The inclusion complex formed was filtered and dried to give complex crystal (2.87 g, 87% yield), which upon heating in vacuo gave (–)-**2a** of 13% ee (0.25 g, 86% yield). By the same procedure, **2b**–**c**, **3** and **4a**–**b** were also resolved (Table 1).

The resolution method by fractional distillation in the presence of a chiral host[13] was also found to be applicable to these hydrocarbons. For example, when a mixture of powdered **1** (12 g, 24 mmol) and *rac*-**2a** (2.32 g, 24 mmol) was distilled at 40°C/20 mmHg, (+)-**2a** of 9% ee was obtained by volatilization (1.16 g, 100% yield). Further heating of the residue at 120°C/20 mmHg gave (–)-**2a** of 9% ee (1.16 g, 100% yield) by distillation. By mixing **1** and *rac*-**2a**, inclusion complexation of **1** and (–)-**2a** occurs, and the uncomplexed (+)-**2a** volatilizes at 40°C in vacuo and the complex of (–)-**2a** with **1** decomposes by heating at 120°C and (–)-**2a** comes out by distillation. By the same distillation method, **2b** and **4a**–**b** were also resolved (Table 2). However, this method was not applicable to **2c** and **3**.

By repeating the resolution through distillation, the enantiomeric excess of the product can be improved. Distillation of a mixture of **1** (5.4 g, 11 mmol) and (–)-**2a** of 9% ee (1.05 g, 11 mmol) at 40°C/20 mmHg and 120°C/20 mmHg gave *rac*-**2a** (0.5 g, 95% yield) and (–)-**2a** of 20% ee (0.5 g, 95% yield), respectively. Further distillation of a mixture of the (–)-**2a** of 20% ee (0.41 g, 4.3 mmol) and **1** (2.1 g, 4.3 mmol) at 40°C/20 mmHg and 120°C/20 mmHg gave (–)-**2a** of 9% ee (0.1 g, 49% yield) and (–)-**2a** of 28% ee (0.2 g, 97% yield), respectively. Similar purification of (+)-**4b** obtained by one distillation procedure (Table 2) can be accomplished by repeating the distillation. Distillation of a mixture of the (+)-**4b** of $[\alpha]_D$ +9 (1.39 g, 11 mmol) and **1** (5.49 g, 11 mmol) at 40°C/20 mmHg and 130°C/20 mmHg gave (–)-**4b** (0.7 g, 101% yield, $[\alpha]_D$ –3) and (+)-**4b** (0.51 g,

Table 2
Resolution of **2**–**4** by fractional distillation in the presence of **1**

	uncomplexed enantiomer				complexed enantiomer			
Guest	Product	$[\alpha]_D$[a]	Yield (%)	ee(%)	Product	$[\alpha]_D$[a]	Yield (%)	ee(%)
2a	(+)-**2a**	+8	100	9	(–)-**2a**	–8	100	9
2b	(–)-**2b**	–3	100	3	(+)-**2b**	+3	100	3
2c	*rac*-**2c**	0	127	0	*rac*-**2c**	0	82	0
3	*rac*-**3**	0	5	0	*rac*-**3**	0	27	0
4a	(+)-**4a**	+2	105	4	(–)-**4a**	–2	73	4
4b	(–)-**4b**	–9	85	b	(+)-**4b**	+9	86	b

[a] All $[\alpha]_D$ values of **2a** were measured in $CHCl_3$ in *c* 1.6, and those of **2b**-**c**, **3**, and **4a**-**b** were measured in MeOH in *c* 1.0.

[b] Enantiomeric excess was not determined.

74% yield, $[\alpha]_D$ +13), respectively. Further distillation of a mixture of (+)-**4b** of $[\alpha]_D$ +13.7 (0.41 g, 3.3 mmol) and **1** (1.61 g, 3.3 mmol) at 40°C/20 mmHg and 130°C/20 mmHg gave (+)-**4b** (0.17 g, 83% yield, $[\alpha]_D$ +6) and (+)-**4b** (0.2 g, 98% yield, $[\alpha]_D$ +20), respectively.

In conclusion, some racemic hydrocarbons **2**–**4** were resolved by inclusion complexation with a chiral host (compound **1**). When the resolution experiment was repeated, the enantiomeric excess of partially resolved hydrocarbon was improved.

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