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Separation of *m*- and *p*-Ethylphenols, and of 2,4- and 2,5-Dimethylphenols by Inclusion Complexation with 1,1-Bis(*p*-hydroxyphenyl)cyclohexane as Host Compound

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Separation of isomers with the same or similar boiling points is very difficult, since fractional distillation cannot be used. For example, separation of *m*- (bp 214°C) and *p*-ethylphenol (bp 219°C) and of 2,4- (bp 212°C) and 2,5-dimethylphenol (bp 212°C) by fractional distillation is almost impossible. However, when an inclusion complexation process with 1,1-bis(*p*-hydroxyphenyl)-cyclohexane is applied, these isomers were easily separated. *m*- and *p*-Ethylphenols were separated on a ton scale by the inclusion complexation technique.

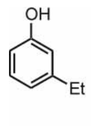
Keywords: Separation of isomers; Selective inclusion; Inclusion complexation; Ethylphenol; Dimethylphenol; Host compound

INTRODUCTION

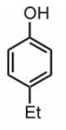
Since molecular recognition between host and guest compounds occurs very precisely in their inclusion crystal, one guest is included selectively from its mixture with other guests by a host compound. We have been studying the separation of isomers by using the inclusion technique [1–4]. When an optically active host compound is used for the inclusion complexation with racemic guests, enantiomers can easily be separated [3–6]. These separation methods are particularly important for separation of isomers with the same or similar boiling points, because fractional distillation cannot be used for the separation. In this paper, we report the separation of *m*- (bp 214°C) and *p*-ethylphenol (bp 219°C) and of 2,4- (bp 212°C) and 2,5-dimethylphenol (bp 212°C) by inclusion complexation with 1,1-bis(*p*-hydroxyphenyl)cyclohexane host compound.

RESULTS

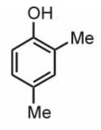
Separation of *m*- (**1a**, bp 214°C) and *p*-ethylphenol (**1b**, bp 219°C) and of 2,4- (**2a**, bp 212°C) and 2,5-dimethylphenol (**2b**, bp 212°C) by fractional distillation is almost impossible owing to their possessing very similar boiling points in the former case and the same boiling points in the latter case. However, these isomers can easily be separated by selective inclusion complexation with the commercially available host compound 1,1-bis(*p*-hydroxyphenyl)cyclohexane (**3**) [3,4]. In the separation of **1a** and **1b**, the experiment was carried out on a semi-industrial ton scale. In the separation experiment of **1a** and **1b**, compound **1a** (which is more valuable as a starting material for the synthesis of various chemicals) was isolated in a pure state. In the separation of **2a** and **2b**, inclusion selectivity for **2a** and **2b** changed dramatically depending on the ratio of these isomers.



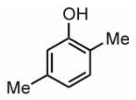
1a



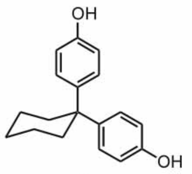
1b



2a



2b



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Separation of 1a and 1b

Before the separation experiment of **1a** and **1b** by inclusion complexation with **3** was carried out, authentic samples of the inclusion complexes of **1a** and **1b** with **3** were prepared. By recrystallization of **3** and **1a** from mesitylene, a 2:1 inclusion complex of **3** and **1a** was obtained as colorless crystals. By the same procedure, a 2:1 inclusion complex of **3** with **1b** was prepared also as colorless crystals. These complexes did not exhibit clear melting points. The 2:1 host–guest ratios were determined by elemental analysis. Unfortunately, however, crystals of these inclusion complexes were not appropriate for X-ray analysis, and their X-ray crystal structures could not be determined. Nevertheless, it is reasonable to consider that hydrogen bonding between the hydroxyl groups of **3** and **1a** or **1b** plays an important role in the formation of their supramolecular systems, since such hydrogen bonding has been observed in supramolecular systems composed of **3** and various guests [1–4].

When a mixed ethylphenol, which contains 70.1% **1a**, 26.3% **1b** and 3.6% impurities (300 kg), was treated with **3** (350 kg) in decane (1000 l)–acetone (400 l), a 2:1 inclusion complex of **3** and **1a** was formed as a slurry. The slurry was collected by using a centrifugal separator and was washed with decane (1400 l) to give the pure inclusion complex as crystals. Heating of the complex under reduced pressure gave **1a** by distillation, which upon redistillation gave 99.8% pure **1a** (142 kg, 67.6% yield). From the residue left after separation of **1a** from its inclusion complex by heating, **3** (350 kg, quantitative yield) was recovered. The procedure was repeated three times and in total 99.8% pure **1a** (426 kg, 67.6% yield) was obtained from the mixed ethylphenol (900 kg). From the residue left after separation of the inclusion complex of **1a** with **3**, **1b** was not separated in a pure form, since **1b** is not commercially very valuable in comparison to **1a**.

When the same separation experiment was carried out for the mixed ethylphenol (470 kg) in decane (800 l) by using **3** (550 kg), 99.4% pure **1a** (219 kg, 65.5% yield) was obtained and **3** (531 kg, 96.5% yield) was recovered.

Separation of 2a and 2b

Before the separation experiment of **2a** and **2b** by inclusion complexation with **3** was carried out, authentic samples of the inclusion complexes of **2a** and **2b** with **3** were prepared. Recrystallization of **3** and **2a** from mesitylene gave a 2:1 inclusion complex of **3** and **2a** as colorless crystals. By the same procedure, a 2:1 inclusion complex of **3** with **2b** was prepared also as colorless crystals. Neither inclusion complex showed a clear melting point, nor did they form appropriate crystals for X-ray analysis.

TABLE I Separation of **2a** and **2b** from their mixture (5 g) by inclusion complexation with **3** (1 g) in mesitylene (2 ml)*

Mixture composition (5 g)		Inclusion complex formed (g)	Proportion in the inclusion complex	
2a (g)	**2b** (g)		**2a** (%)[†]	**2b** (%)[†]
4.5	0.5	1.39	99	1
4.0	1.0	1.19	95	5
3.5	1.5	1.12	6	94
3.0	2.0	1.29	2	98
2.5	2.5	1.33	3	97
2.0	3.0	1.35	1	99
1.5	3.5	1.38	2	98
1.0	4.0	1.36	1	99
0.5	4.5	1.41	0	100

[*] Although the theoretical amount of the inclusion complex formed from **3** (1 g) is 1.23 g, complexes of more than 1.23 g were formed in most cases probably because of a coating of impurity on the complex crystal surface.
[†] Proportions of **2a** and **2b** in the inclusion complex were determined by gas chromatography.

When the inclusion complexation of various mixtures of **2a** and **2b** (5 g) with **3** (1 g) was carried out in mesitylene (2 ml), inclusion crystals were obtained in the amounts indicated in Table I. The quantities of **2a** and **2b** in the isolated inclusion complex were determined by gas chromatography (Table I). It is clear that **3** has a higher inclusion selectivity for **2b** rather than for **2a**. When the quantity of **2a** is higher than 80%, **2a** is included predominantly. However, when the quantity of **2a** is lower than 80%, **2b** is included predominantly (Table I). These selectivities are clearly shown in Fig. 1.

DISCUSSION

The host compound **3** showed higher inclusion selectivity for **1a** and **2b** rather than for **1b** and **2a**, respectively. Since inclusion crystals of these complexes were not suitable for X-ray analysis, the mechanism of selectivity could not be clarified on the basis of X-ray crystal structural data. However, a plausible reason for the selectivity is as follows.

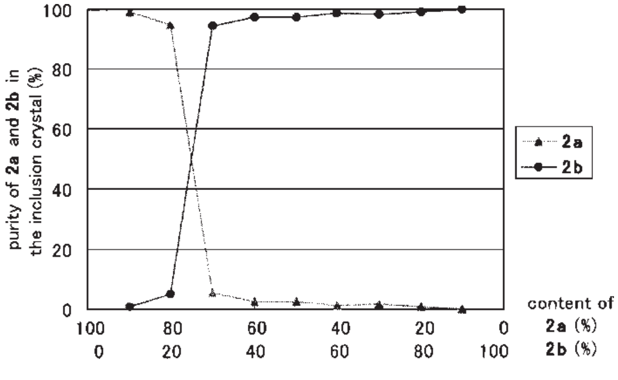

FIGURE 1 Relationship between the proportions of **2a** and **2b** in the mixture and the purity of the isomer separated by inclusion complexation with **3**.

The guest molecules of **1b** and **2a** which have a substituent at the *p*-position to the hydroxyl group cannot form a stable inclusion complex with **3**, because the *p*-substituent makes the inclusion crystalline lattice unstable for steric reasons. There are several examples that show that *p*-isomeric guests form inclusion complexes with a host less readily than do *m*-isomeric ones owing to steric reasons [5,6].

EXPERIMENTAL

Materials

Commercially available **3** and a mixed ethylphenol, which contains 70.1% **1a**, 26.3% **1b** and 3.6% impurities, were used for the experiment.

Preparation of 2:1 Inclusion Complexes of 3 with 1a and 1b

When a solution of **3** (1 g, 3.73 mmol) and **1a** (0.5 g, 4.09 mmol) in mesitylene (2 ml) was kept overnight at room temperature, a 2:1 inclusion complex of **3** with **1a** (1.20 g, 98% yield) was formed as colorless crystals that did not show a clear melting point. Calc. for $C_{44}H_{50}O_5$: C, 80.21; H, 7.65; O, 12.14%. Found: C, 80.22; H, 7.61; O, 12.30%. When a solution of **3** (1 g, 3.73 mmol) and **1b** (0.5 g, 4.09 mmol) in mesitylene (2 ml) was kept overnight at room temperature, a 2:1 inclusion complex of **3** with **1b** (1.21 g, 99% yield) was formed as colorless crystals that did not show a clear melting point. Calc. for $C_{44}H_{50}O_5$: C, 80.21; H, 7.65; O, 12.14%. Found: C, 80.10; H, 7.82; O, 12.40%.

Separation of 1a from the Mixed Ethylphenol by Inclusion Complexation with 3 in Decane–Acetone

The mixed ethylphenol (300 kg), **3** (350 kg), decane (1000 l) and acetone (400 l) were placed in a stainless steel vessel of 2 m^3 volume equipped with heater, and were heated under stirring until the mixture turned into a solution. Acetone was removed from the solution by distillation and decane (400 l) was added, and the resulting solution was kept overnight at room temperature. The slurry formed was collected by using a centrifugal separator. The wet slurry cake was suspended in decane (1400 l) and the inclusion crystals that precipitated were collected by using the centrifugal separator. This process was repeated again to give pure inclusion crystals. Dried inclusion crystals were placed in a stainless steel vessel equipped with a steam heater. The vessel containing the inclusion crystals was heated by a steam pressure of 4.5 kg cm^{-2} under 20 Torr to give **1a** by distillation, which upon redistillation gave finally 99.8% pure **1a** (142 kg, 67.6% yield). From the residue, **3** (350 kg, quantitative yield) was recovered.

The separation process was repeated three times, and finally 99.8% pure **1a** (426 kg, 67.6% yield) and recovered **3** (1050 kg, quantitative yield) were obtained by treatment of the mixed ethylphenol (900 kg) with **3** (1050 kg). When the separation experiment was carried out in decane, 99.4% pure **1a** (65.5% yield) was obtained. For example, upon treatment of the mixed ethylphenol (470 kg) with **3** (550 kg) in decane (800 l), 99.4% pure **1a** (219 kg, 65.5% yield) was obtained. In this case, **3** (531 kg, 96.5% yield) was recovered.

Preparation of 2:1 Inclusion Complexes of 3 with 2a and 2b

When a solution of **3** (1 g, 3.73 mmol) and **2a** (0.5 g, 4.09 mmol) in mesitylene (2 ml) was kept overnight at room temperature, a 2:1 inclusion complex of **3** with **2a** (1.20 g, 98% yield) was obtained as colorless crystals that did not show a clear melting point. Calc. for $C_{44}H_{50}O_5$: C, 80.21; H, 7.65; O, 12.14%. Found: C, 80.36; H, 7.87; O, 12.30%. When a solution of **3** (1 g, 3.73 mmol) and **2b** (0.5 g, 4.09 mmol) in mesitylene (2 ml) was kept overnight at room temperature, a 2:1 inclusion complex of **3** with **2b** (1.20 g, 98% yield) was formed as colorless crystals that did not show a clear melting point. Calc. for $C_{44}H_{50}O_6$: C, 80.21; H, 7.65; O, 12.14%. Found: C, 79.98; H, 7.97; O, 12.50%.

Separation of 2a and 2b by Inclusion Complexation with 3 in Mesitylene

When a solution of **3** (1 g, 3.73 mmol) and a mixture of **2a** and **2b** (5 g, 41.9 mmol) in the ratio indicated in Table I in mesitylene (2 ml) was kept overnight at room temperature, a 2:1 inclusion complex of **3** with a mixture of **2a** and **2b** was formed. The inclusion complex was filtered, washed with hexane and dried. The content of **2a** and **2b** in the inclusion complex was analysed by gas chromatography (Table I).

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