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Optical Resolution of Tertiary Acetylenic Alcohols and Secondary Alcohols by Complexation with Achiral Amines

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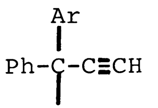
Partially resolved tertiary acetylenic alcohols and secondary alcohols were easily resolved completely by complexation with achiral amines such as 1,4-diazabicyclo[3.3.3]octane (DABCO), N,N'-dialkylpiperazine, N,N,N',N'-tetramethylethylenediamine, and pyrazine, to give optically pure enantiomers. Interestingly, DABCO formed more stable complex with optically pure enantiomers but the other amines formed more stable complex with racemic compounds.

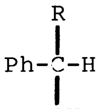
Previously, we have reported a novel optical resolution method of tertiary acetylenic alcohols (**1**) by complexation with alkaloids such as brucine and sparteine.1-3) It was also found that the method can be applied to secondary alcohols (**2**).4) In both cases, however, partially resolved other enantiomers are obtained from the filtrate left after the separation of complex of the optically pure enantiomers with alkaloid. Recently, we found that the partially resolved such alcohols can easily be purified by complexation with simple achiral diamines such as 1,4-diazabicyclo[3.3.3]octane (DABCO) (**3**), N,N'-dialkylpiperazine (**4**), N,N,N'N'-tetramethylethylenediamine (**5b**), and pyrazine (**6**), to give optically pure alcohols. Very interestingly, **3** forms a 1:2 complex with optically pure **1** and **2**, selectively, and **4**, **5b**, and **6** form a 1:2 complex with racemic **1** and **2**, selectively. In the latter case, therefore, optically pure **1** and **2** were obtained from the filtrate left after the separation of the complex of racemic compound. However, achiral monoamine such as quinuclidine (**7**) forms unstable 1:1 complex only with optically pure **1**.

For example, when a solution of **3** (0.56 g, 5.05 mmol) and 72.5% ee (+)-**1a** (1.22 g, 5.03 mmol) in MeOH (5 ml) was kept at room temperature for 12 h, a 1:2


$Ph-C(Ar)(OH)-C\equiv CH$

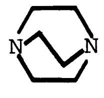
1

a: Ar=2-Cl-C_6H_4-
b: Ar=2-Br-C_6H_4-
c: Ar=2-F-C_6H_4-
d: Ar=2,4-dimethyl-C_6H_4-


$Ph-CH(R)(OH)$

2

a: R=CCl_3
b: R=tBu



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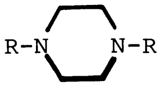

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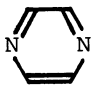
a: R=Me
b: R=iPr

$Me_2N-(CH_2)_n-NMe_2$

5

a: n=1
b: n=2
c: n=3



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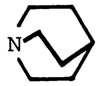

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complex of **3** and 100% ee (+)-**1a** (0.55 g, 37%) was obtained as colorless prisms (mp 139-141 °C, $[\alpha]_D$ +117°)5), which upon distillation gave 100% ee (+)-**1a** (0.44 g, 36%, $[\alpha]_D$+138°). From the filtrate, 55.9% ee (+)-**1a** (0.76 g, 62%, $[\alpha]_D$ +77.2°) was obtained. Optical purity of **1** was determined by comparing its $[\alpha]_D$ value with reported one.3) By the same method, **1b**, **1c**,and **2a** were also easily resolved (Table 1). Of course, when partially resolved (-)-enantiomers were used, optically pure (-)-enantiomers were obtained. In the case of **1c**, however, racemic **1c** formed complex with **3**, and 99.4% ee (+)-**1c** was obtained from the filtrate left after the separation of the complex (Table 1). The 99.4% ee (+)-**1c** gave 100% ee enantiomer by repeating the complexation with **3** once more. Although **3** does not form complex with **1d**, **4a** forms a 1:2 complex with **1d**. Complexation of 43.8% ee **1d** with **4a** gave a 1:2 complex of **4a** and racemic **1d**. From the filtrate, 60.2% ee (+)-**1d** was obtained. When two more complexations were repeated for the 60.2% ee (+)-**1d**, 100% ee (+)-**1d** ($[\alpha]_D$ +59.1°) were obtained in 17.5% yield (Table 1). It is interesting that the purification method is very effective for the simple secondary alcohol such as **2a** (Table 1).

Table 1. Purification of partially resolved alcohols by complexation with amines

Partially resolved alcohols			Amines	Alcohols obtained from					
				Complex			Filtrate		
	$[\alpha]_D$/°	Opt. purity/% ee		Yield/%	$[\alpha]_D$/°	Opt. purity/% ee	Yield/%	$[\alpha]_D$/°	Opt. purity/% ee
1a	+100	72.5	**3**	36	+138	100	62	+77.2	55.9
1b	+109	78.4	**3**	37	+139	100	62	+43.1	31.0
1c	+26.9	51.8	**3**	51	+2.9	5.6	48	+51.6	99.4
1d	+25.9	43.8	**4a**	46	0	0	43	+35.6	60.2
2a	+13.3	36.0	**3**	32	+36.9	100	68	+2.2	6.0
2b	+10.4	32.3	**4b**	42	0	0	56	+14.9	46.3

Table 2. Purification of 72.5% ee (+)-1a by complexation with amines

Amines	Alcohols obtained from					
	Complex			Filtrate		
	Yield/%	$[\alpha]_D$/°	Opt. purity/% ee	Yield/%	$[\alpha]_D$/°	Opt. purity/% ee
3	36	+138	100	62	+77.2	55.9
4a	35	+30.4	22	65	+137	99.4
5b	26	+20.8	15	67	+126	91
6	41	+61.0	44	58	+123	89

Neither 3 nor 4a was effective for purification of 2b. However, 4b was effective for the purification to give 46.3% ee 2b (Table 1), which finally gave 100% ee 2b ($[\alpha]_D$ +20.7°) in 22% yield by repeating the complexation three more times.

In order to know what kind of amine is the most effective for the purification, five other amines, 5a-c, 6, and 7 were tested together with 4a for the purification of 72.5% ee (+)-1a and these results were compared with that by 3 (Table 2). 3 was the most effective for the purification. Although 4a, 5b, and 6 were also quite effective, 5a, 5c, and 7 did not form complex with 1a. The result suggests that the alicyclic diamine having a rigid structure is the most effective.

It is interesting that 3 forms complex with optically pure alcohols except the case of 1c, more easily, and all other amines form complex with racemic alcohols, more easily. However, all the amines form complex with racemic alcohols exclusively when racemic alcohols are used for the complexation instead of partially resolved ones. The selectivity was studied in detail by comparing the dissociation energy of complexes (Table 3). The complex of 3 with (+)-1a is more stable than that with racemic 1a. However, the complex of 4a with racemic 1a is much more stable than that with (+)-1a. In the case of 5b and 6, only the racemic 1a formed the complex with these amines. 7 forms a 1:1 complex only with optically pure 1a, but its stability is very low (Table 3).

Table 3. Mp and ΔH6) of a 1:2 complex of amines with racemic and (+)-1a

Amines	Complex with			
	Racemic 1a		(+)-1a	
	mp(Θ_m/°C)	ΔH(kJ·mol^{-1})	mp(Θ_m/°C)	ΔH(kJ·mol^{-1})
3	126-129	51	139-141	65
4a	121-125	110	115-118	71
5b	112-114	100	---	---
6	84-89	61	---	---
7a)	---	---	70-78	11

a) 1:1 complex.

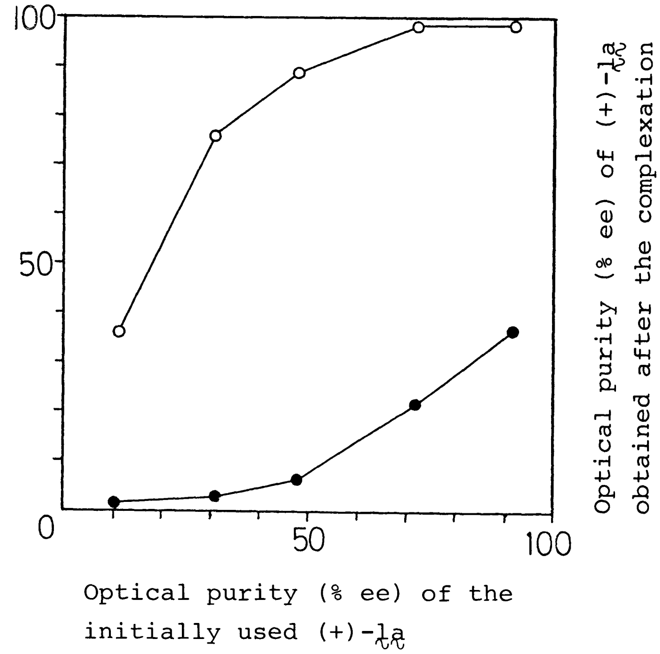

Fig. 1. Relation between the optical purity of the initially used (+)-**1a** and of the (+)-**1a** obtained after the complexation with **4a**.

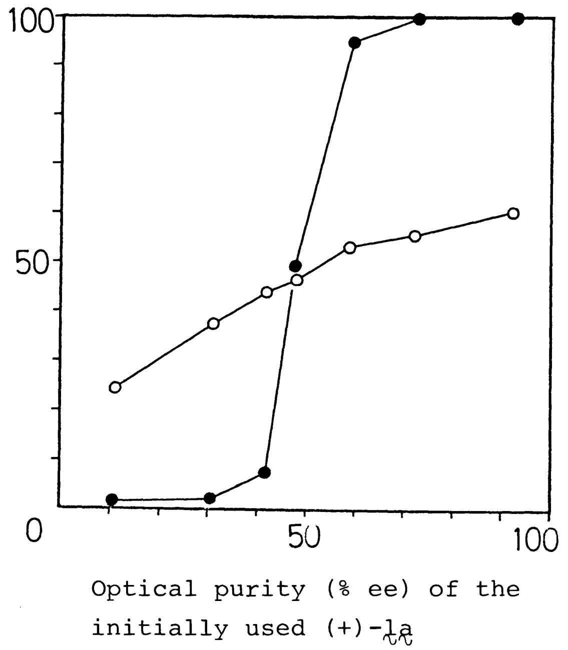

Fig. 2. Relation between the optical purity of the initially used (+)-**1a** and of the (+)-**1a** obtained after the complexation with **3**.

(-●- % ee of (+)-**1a** obtained from complex
-○- % ee of (+)-**1a** obtained from filtrate)

The relation between optical purity of the initially used (+)-**1a** and of the (+)-**1a** obtained after the complexation with **4a** and **3** is shown in Figs. 1 and 2, respectively. In the both cases, efficiency of the resolution is quite high when the optical purity of the initially used (+)-**1a** is higher than 60% ee. Nevertheless, partially resolved (+)-**1a** of much lower optical purity can also be purified by repeating the complexation. For example, 30% ee (+)-**1a** gives 74.6% ee enantiomer by the first complexation with **4a**, which then gives 99.4% ee enantiomer by the second complexation with **4a** (Fig. 1).

References

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2) F. Toda, K. Tanaka, H. Ueda, and T. Ōshima, J. Chem. Soc., Chem. Commun., 1983, 1513.

3) F. Toda, K. Tanaka, H. Ueda, and T. Ōshima, Israel J. Chem., 25, 338 (1985).

4) unpublished data.

5) All the $[\alpha]_D$ values were measured in MeOH at the concentration of *c* 1.0.

6) The dissociation energy (ΔH) was obtained from DSC data (Rigaku DSC-8230).

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