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OPTICAL RESOLUTION OF AMINE *N*-OXIDE BY DIASTEREOISOMERIC COMPLEX FORMATION WITH OPTICALLY ACTIVE HOST COMPOUND

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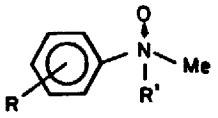
Abstract: *Optical stereoisomers of various amine N-oxides with one or two chiral centers can effectively be resolved by selective crystalline complexation with an optically active host. Intermolecular interaction schemes and absolute configurations of the N-oxide guests are revealed by crystallographic analyses of the diastereoisomeric complexes.*

In 1908 optically active *N*-ethyl-*N*-methylaniline *N*-oxide was prepared by fractional recrystallizations of its salt with α-bromocamphosulfuric acid.[1] This is the first known example of isolation of an optically active amine *N*-oxide. The second optical resolution of amine *N*-oxide in the form of a tartaric acid salt was achieved by the same procedure 18 years later.[2] In both cases, however, the optical purity of the resolved amine *N*-oxide (and thus the effectiveness of the proposed procedure) has not been determined.[1,2]

We now report on the optical resolution of various amine *N*-oxides by complexation with an optically active host compound. By this method we were able to resolve not only arylalkylmethylamine *N*-oxides (**1a-1e**) but also one of the diastereoisomers in each case of the piperidine *N*-oxides (**2,3**). Especially, the former compounds were resolved quite efficiently to give optically pure enantiomers. Optical purity of the *N*-oxide was easily determined by ^{1}H NMR measurements in the presence of the new chiral shift reagent (*R,R*)-(-)-1,6-di(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol (**4**).[3] Its absolute configuration can directly be established by crystal structure analysis of the corresponding diastereoisomeric inclusion complex.

1a: R=H; R'=Et
1b: R=*m*-Me; R'=Et
1c: R=*m*-Me; R'=*i*Pr
1d: R=*p*-Me; R'=Et
1e: R=*p*-Me; R'=*i*Pr
1f: R=*o*-Me; R'=Et



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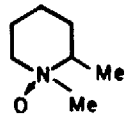

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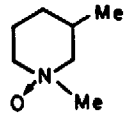
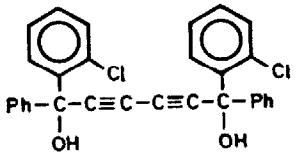
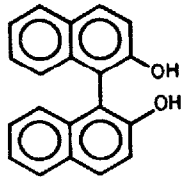


4: (*R,R*)-(-)-form



5a: (*R*)-(+)-form
5b: (*S*)-(-)-form



Compounds **1a-1f**, and **2-3** were prepared according to the procedures reported in refs. 4 and 5, respectively. Optical resolutions of the **1a-1f** *N*-oxides were carried out by complexation with the (*R*)-(+)-form of 2,2'-dihydroxy 1,1'-binaphthyl (**5a**) as described in the following example. When a solution of **1b** (1.2 g, 7.2 mmol) and **5a** (1.0 g,

3.6 mmol) in THF (20ml)-hexane (10 ml) mixture was kept at room temperature for 5 h, a 1:1 complex of (+)-**1b** and **5a** was obtained as colorless prisms. The latter were recrystallized from THF-hexane to give pure crystals of the complex (0.85 g, 53% yield, mp 167-169 °C). The complex was separated to its components by column chromatography on silica gel. Firstly, **5a** (0.5 g) was recovered from a fraction eluted by ethylacetate-benzene (1:4). Secondly, **1b** of 100% ee {0.29 g, 48%, $[\alpha]_D$ +11.9° (*c* 0.2, $CHCl_3$)} was obtained from a fraction eluted by MeOH. Evaporation of the filtrate left after separation of the complex between (+)-**1b** and **5a**, gave crude (-)-**1b**. Treatment of the latter with **5b** in a similar manner to that described above, followed by column chromatography, yielded finally (-)-**1b** of 100% ee {0.24 g, 40%, $[\alpha]_D$ -11.9° (*c* 0.2, $CHCl_3$)}. Compounds **1a** and **1c-1e** were resolved effectively by the same method (Table 1). Only **1f** could not be resolved as its both enantiomers were included in the crystals with **5a** at the same time.

Table 1. Data on optical resolution of the *N*-oxide compounds **1a-1f**.

Compound	mp (°C)[a]	yield (%)	$[\alpha]_D$ (deg)	optical purity (%ee)
1a	175-177	21	+16.4	100
1b	167-169	48	+11.9	100
1c	127-130	39	+24.6	73
1d	149-153	30	+13.0	100
1e	131-132	68	+29.5	100
1f[b]	155-156	-	-	-

[a]Data for the 1:1 complexes between (+)-**1** and **5a**; [b]No resolution occurred

The optical purity of the resolved material was determined by monitoring the *N*-Me signal in ^1H NMR spectra of solutions containing the chiral shift reagent **4** (measurements were carried out in $CDCl_3$ using JEOL JNM-PMX 60 spectrometer). In the presence of **4** the *N*-Me signal of racemic **1** is split into two peaks as shown in Table 2. The signal of **1a** and **1c-1e** is split enough to determine the optical purity in the presence of an equimolar amount of **4**. Two molar amounts of **4** are necessary, however, in order to obtain a sufficient splitting of the *N*-Me signal of **1b** and **1f**, and to determine the optical purity of these derivatives (Table 2).

Table 2. The effect of reagent **4** on the chemical shifts (δ, ppm) of the *N*-Me protons in **1**.

	Molar ratio of **4** to **1**		
Compound	0:1	1:1	2:1
1a	3.503	3.232, 3.278	
1b	3.480	3.230, 3.250	3.136, 3,164
1c	3.400	3.200, 3.253	
1d	3.487	3.184, 3.220	
1e	3.403	3.188, 3.232	
1f	3.623	3.334, 3.366	3.208, 3.262

It has recently been demonstrated that optical resolution of phosphine oxides by complexation with **5a** or **5b** is strongly related to spatial relationships between the corresponding constituents in the crystal phase.[6] In order to examine whether similar correlations can be made in the *N*-oxide case, we have undertaken crystallographic study of the diastereomeric complexes between **1** and **5**. The more stable 1:1 complex of (+)-**1b** with **5a** crystallized in the monoclinic space group $P2_1$ with two entities of the complex in the unit cell [**I:** a=10.327(3), b=10.576(2), c=11.836(4) Å, β =107.32(3)°]. The less stable 1:1 complex between (-)-**1b** and **5a** crystallized in the triclinic space group P1 with one entity of the complex in the unit cell [**II:** a=7.755(4), b=9.027(4), c=9.456(3) Å, α =107.60(3), β =97.66(4), γ =98.22(4)°]. Both structures were solved by direct methods (SHELXS-86)[7] and refined anisotropically by large-block least-squares (SHELX-76).[8] At convergence, R=0.044 with 858 diffractometer (CAD4) data above the intesity threshold of 3σ for structure **I**, and R=0.047 with 1227 observations above the threshold of 3σ for structure **II**. The crystal structure analyses establish the absolute configuration of the included guest components.

The observed crystal structure of **I** is illustrated in Fig. 1. It consists, as in the closely related example involving phosphine oxides,[6] of continuous chains of strongly H-bonded species which are alligned along the *b*-axis of the crystal. The *N*-oxide moiety acts as a proton acceptor from, and thus bridges between, two different molecules of **5a** which are related to each other by the 2_1 screw symmetry (Fig. 1a); the corresponding OH...O distances are 2.63 and 2.65 Å. The crystalline environment of the *N*-oxide molecule is illustrated in Fig. 1b (for clarity the positions of the two neighboring *N*-oxides are shown schematically). Evidently, there is a very tight packing between the adjacent *N*-oxide molecules along the screw axis, which is reflected in a relatively short nonbonding *inter*molecular contact CH_3(27)...CH(32) of 3.36 Å. On the other hand, the nonbonding distances between the guest and the closest naphthyl groups of the host are generally equal to or larger than the corresponding sums of van der Waals radii.

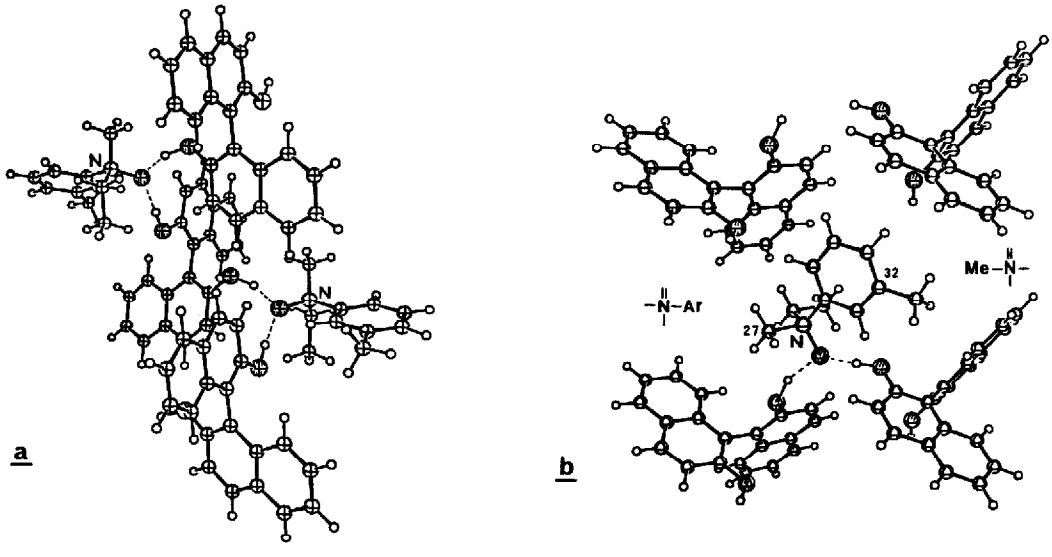


Fig. 1. Two views of the crystal structure of the 1:1 complex between host **5a** and guest (+)-**1b.**

Figure 2 illustrates the intermolecular hydrogen bonding scheme found in structure **II**. The guest molecule bridges between two adjacent host moieties related by translation along the *a*-axis of the crystal. The two OH...O bonds associated with each *N*-oxide moiety are less symmetric than in the previous example; 2.64 and 2.74 Å. This distortion is due to an unfavorable steric hindrance between the neighboring guest molecules displaced along **a**, as is

reflected in a short $CH_3(27)...CH_3(34)$ nonbonding distance of 3.70 Å (about 0.3 Å shorter than the usual van der Waals distance) between the two methyl substituents. Detailed structural interpretation of these data along with further crystallographic investigation of the other diastereomeric compounds will be carried out in relation to the selectivity results described above.

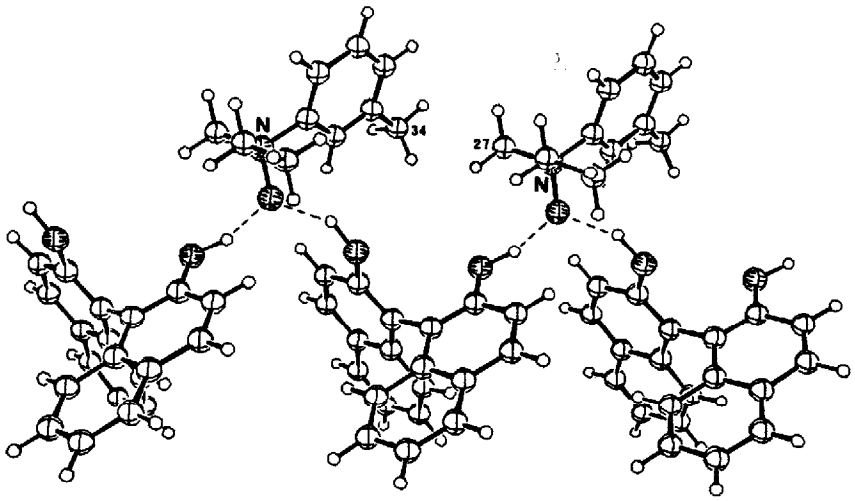


Fig. 2. Illustration of the hydrogen bonding pattern in the 1:1 complex between host **5a** and guest (-)-**1b** (the *a*-axis of the crystal is horizontal).

Finally, the chiral shift reagent **4** is also very useful in effecting an optical resolution of the piperidine *N*-oxides **2** and **3**. For example, when a solution of **2** (2.8 g, 22 mmol) and **4** (5.25 g, 11 mmol) in acetone (20 ml) was kept at room temperature for 5 h, a 1:1 complex of (-)-**2** with **4** (3.96 g) was obtained in a crystalline form. Two recrystallizations of the crude compound from an acetone-hexane mixture gave colorless needles of the pure complex (1.73 g, 64%, mp 186-188 °C). By column chromatography of the latter on silica gel, **4** (1.25 g) and (-)-**2** {0.36 g, 52%, $[\alpha]_D$ -12.5° (*c* 0.2, MeOH)} were obtained from $CHCl_3$ and MeOH fractions, respectively. Similarly, **3** was resolved to give (-)-**3** {$[\alpha]_D$ -2.5°} at 37% yield. Although the optical purity of the resolved **2** and **3** was not determined quantitatively, it is certain that diastereomers were separated completely by the complexation method. Thus, for example, racemic **2** shows in the NMR spectrum two singlet peaks of *N*-Me at δ 3.1 and 3.9 ppm and two doublet peaks of 2-Me at δ 1.3 and 1.5 ppm. On the other hand, in the corresponding spectrum of the resolved (-)-**2** only one singlet of *N*-Me (δ 3.1 ppm) and one doublet of 2-Me (δ 1.3 ppm) were indicated.

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