CHEMISTRY LETTERS, pp. 513-516, 1988.

Optical Resolution of 2-Methylpiperazine by Complex Formation with Optically Active 1-Phenyl-1-(o-chlorophenyl)prop-2-yn-1-ol and 1,6-Diphenyl-1,6-di(o-chlorophenyl)hexa-2,4-diyne-1,6-diol

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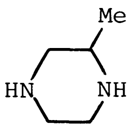
An efficient optical resolution of 2-methylpiperazine was achieved by complex formation with the title host compounds. X-Ray crystal structure of a 1:2 complex of (*S*)-(+)-piperazine and (*R*)-(-)-1-phenyl-1-(o-chlorophenyl)prop-2-yn-1-ol was studied.

It is very difficult to obtain optically pure 2-methylpiperazine (**1**).[1] Only partial resolution has been achieved hitherto, by recrystallization of the 2-methylpiperazinium (2*R*,3*R*)-di-*O*-benzoyltartarate salt from MeOH, and (*S*)-(+)-isomer (**1a**) of 44% ee and (*R*)-(-)-isomer (**1b**) of 30% ee have been obtained.[1]

We succeeded in obtaining **1a** and **1b** in optically pure state by complexation of racemic **1** with optically active host compounds, (*R*)-(-)-1-phenyl-1-(o-chlorophenyl)prop-2-yn-1-ol (**2**)[2,3] and (*R*,*R*)-(-)-1,6-diphenyl-1,6-di(o-chlorophenyl)-hexa-2,4-diyne-1,6-diol (**3**).[3,4]

When a solution of racemic **1** (100 g, 1 mol) and **2** (243 g, 1 mol) in BuOH (50 cm^3) was kept at room temperature for 12 h, a 1:2 complex of **1a** and **2** was obtained as colorless prisms, which upon three recrystallizations from BuOH gave pure crystals (60 g, 20% yield, mp 85-87 °C, $[\alpha]_D$ -109° (*c* 0.66, MeOH)). Heating of the crystals in vacuo gave **1a** of 100% ee by distillation (9.5 g, 19% yield, $[\alpha]_D$ +8.02° (*c* 0.54, MeOH)). When a solution of racemic **1** (100 g, 1 mol) and **3** (242 g, 0.5 mol) in MeOH (500 cm^3) was kept at room temperature for 12 h, a 1:1 complex of **1b** and **3** was obtained as colorless prisms, which upon three recrystallizations



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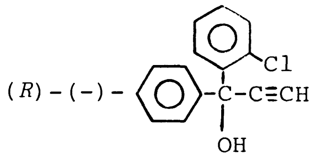
a: (*S*)-(+)-form

b: (*R*)-(-)-form



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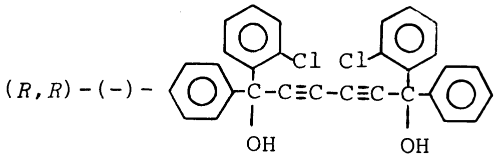

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from MeOH gave pure crystals (75 g, 26% yield, mp 86-88 °C, $[\alpha]_D$ -101° (*c* 0.22, MeOH)). Heating of the crystals in vacuo gave **1b** of 100% ee by distillation (12.5 g, 25% yield, $[\alpha]_D$ -8.02° (*c* 0.5, MeOH)). The host compounds (**2** and **3**) left after the distillation can be used again for resolution. Treatments of the filtrate left after the former and the latter experiments with **3** and **2**, respectively, gave **1b** and **1a**, respectively in the yield around 20%.

The optical purity of **1a** and **1b** can be determined by measuring ^{1}H NMR spectra of their complexes with **2** and **3** in $CDCl_3$, because **2** and **3**5) work as a chiral shift reagent. Methyl signal of racemic **1** in the presence of two molar amounts of **2** and an equimolar amount of **3** appeared as two doublet signals centered at δ 0.77 and 0.90 and 0.77 and 0.83 ppm, respectively.

In order to know mechanism of the chiral recognition between **1** and **2** or **3**, X-ray crystal structure of a 1:2 complex (**4**) of **1a** and **2** was studied. Crystal data of $C_5H_{12}N_2 \cdot 2C_{15}H_{11}OCl$ (**4**) are as follows: FW = 585.58, monoclinic, space group $P2_1$, a = 12.688(6), b = 7.920(4), c = 15.971(3) Å, β = 104.82(3)°, D_c = 1.25 g/cm^3, μ = 2.5 cm^{-1} and Z = 2.

The cell dimensions and intensities were collected on a Synthex R3 four-circle diffractometer with graphite-monochromated Mo-Kα radiation by the ω-scan mode within 2θ less than 45°. A total of 2947 independent reflections were collected, among which 2231 reflections ($I>1.96\sigma(I)$) were stored as observed. The structure was solved by the direct method using MULTAN in Syntex program. All the hydrogen atoms except seven atoms were found on difference Fourier maps. A perspective drawing of **4**, including the numbering scheme, is shown in Fig. 1. Figure 2 shows the contents of the unit cell viewed down the b-axis. Bond lengths in **4** are also shown in Fig. 1.

The refinement of atomic parameters was carried out by a block-diagonal least-squares method. Thermal parameters were refined anisotropically for all the non-hydrogen atoms and isotropically for the hydrogen atoms. The final R-value was 0.068.

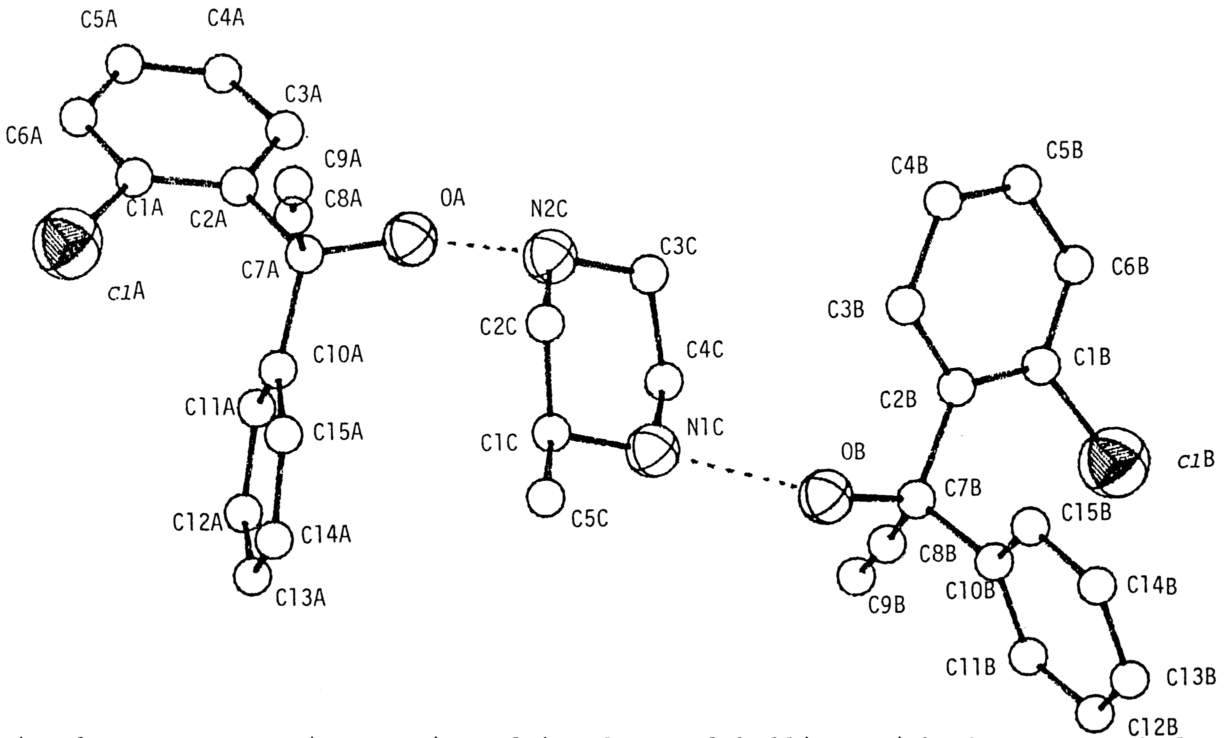

Fig. 1. Host-guest interaction of **4** and atom labelling, with the OH····N hydrogen bonds represented by broken lines. Bond lengths (Å, standard deviations in parentheses): ClA-C(1)A 1.750(9), ClB-C(1)B 1.733(8), OA-C(7) 1.425(8), OB-C(7)B 1.436(8), N(1)C-C(1)C 1.451(9), N(1)C-C(4)C 1.466(11), N(2)C-C(2)C 1.479(11), N(2)C-C(3)C 1.425(12), C(1)A-C(2)A 1.383(10), C(1)A-C(6)A 1.363(12), C(2)A-C(3)A 1.385(12), C(2)A-C(7)A 1.530(10), C(3)A-C(4)A 1.420(12), C(4)A-C(5)A 1.298(13), C(5)A-C(6)A 1.353(16), C(7)A-C(8)A 1.509(10), C(7)A-C(10)A 1.532(10), C(8)A-C(9)A 1.188(10), C(10)A-C(11)A 1.338(10), C(10)A-C915)A 1.379(11), C(11)A-C(12)A 1.393(12), C(12)A-C(13)A 1.4.6(15), C(13)A-C(14)A 1.337(13), C(14)A-C(15)A 1.384(11), C(1)B-C(2)B 1.391(11), C(1)B-C(6)B 1.386(12), C(2)B-C(3)B 1.375(10), C(2)B-C(7)B 1.561(10), C(3)B-C(4)B 1.458(14), C(4)B-C(5)B 1.328(14), C(5)B-C(6)B 1.355(12), C(7)B-C(8)B 1.436(9), C(7)B-C(10)B 1.504(9), C(8)B-C(9)B 1.161(10), C(10)B-C(11)B 1.387(9), C(10)B-C(15)B 1.358(9), C(11)B-C(12)B 1.393(11), C(12)B-C(13)B 1.376(12), C(13)B-C(14)B 1.366(11), C(14)-C(15)B 1.407(11), C(1)C-C(2)C 1.490(10), C(1)C-C(5)C 1.535(13), C(3)C-C(4)C 1.444(13).

In the crystal structure of **4**, two hydrogen bonds between OH of **2** and N of **1a** play an important role to fix the host and guest molecules close together and to recognize chirality of each other efficiently in the crystalline lattice (Figs. 1 and 2). The combination of **2** of (*R*)-configuration and **1** of (*S*)-configuration (**1a**) would be important to form the stable complex (**4**), because **2** does not form complex with **1** of (*R*)-configuration (**1b**). This is probably the same in the complex of **1** and **3**. Although **3** includes **1** of (*R*)-configuration (**1b**), **3** does not include **1** of (*S*)-configuration (**1a**). For the present, it is not clear why **2** and **3** of the same configuration include **1** of the different configuration, **1a** and **1b**, respectively.

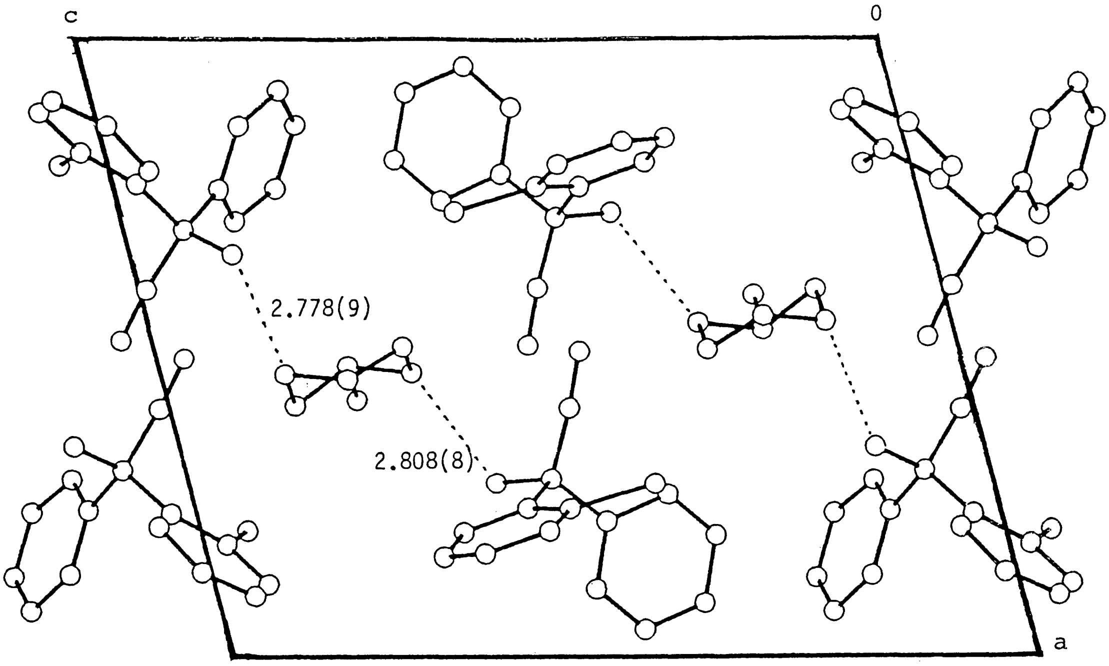

Fig. 2. The crystal structure projected along b-axis showing the hydrogen bonds (Å).

From the Figs. 1 and 2, the absolute configuration of (+)-1 can be determined directly to be (*S*), because the configuration of (-)-2 has been determined to be (*R*).[2,3] This is identical with the reported (*S*)-configuration which has been determined by an indirect method.[1]

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(Received January 5, 1988)