

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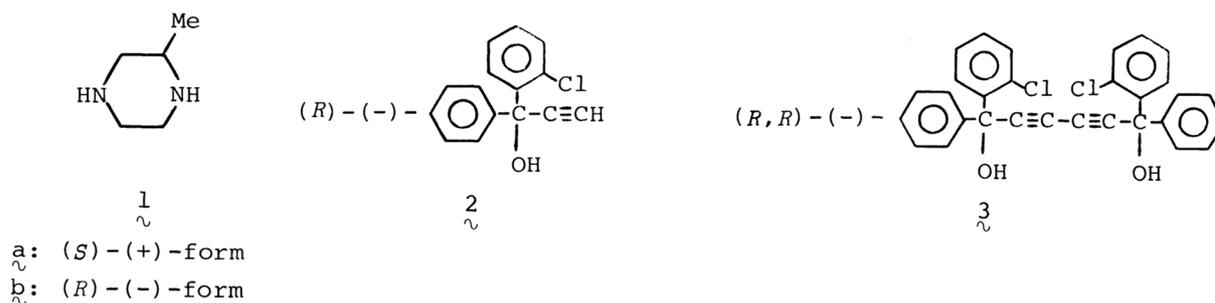
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An efficient optical resolution of 2-methylpiperazine was achieved by complex formation with the title host compounds. X-Ray crystal structure of a 1:2 complex of (*S*)-(+)-piperazine and (*R*)-(-)-1-phenyl-1-(*o*-chlorophenyl)prop-2-yn-1-ol was studied.

It is very difficult to obtain optically pure 2-methylpiperazine ( $\text{1}$ )<sup>1)</sup>. 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 ( $\text{1a}$ )<sup>1)</sup> of 44% ee and (*R*)-(-)-isomer ( $\text{1b}$ )<sup>1)</sup> of 30% ee have been obtained.

We succeeded in obtaining  $\text{1a}$  and  $\text{1b}$  in optically pure state by complexation of racemic  $\text{1}$  with optically active host compounds, (*R*)-(-)-1-phenyl-1-(*o*-chloro-2,3)-phenyl)prop-2-yn-1-ol ( $\text{2}$ )<sup>2,3)</sup> and (*R,R*)-(-)-1,6-diphenyl-1,6-di(*o*-chlorophenyl)-3,4)-hexa-2,4-diyne-1,6-diol ( $\text{3}$ )<sup>3,4)</sup>.

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



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

The optical purity of  $\underset{\sim}{1a}$  and  $\underset{\sim}{1b}$  can be determined by measuring  $^1\text{H}$  NMR spectra of their complexes with  $\underset{\sim}{2}$  and  $\underset{\sim}{3}$  in  $\text{CDCl}_3$ , because  $\underset{\sim}{2}$  and  $\underset{\sim}{3}$  work as a chiral shift reagent<sup>5)</sup>. Methyl signal of racemic  $\underset{\sim}{1}$  in the presence of two molar amounts of  $\underset{\sim}{2}$  and an equimolar amount of  $\underset{\sim}{3}$  appeared as two doublet signals centered at  $\delta$  0.77 and 0.90 and 0.77 and 0.83 ppm, respectively.

In order to know mechanism of the chiral recognition between  $\underset{\sim}{1}$  and  $\underset{\sim}{2}$  or  $\underset{\sim}{3}$ , X-ray crystal structure of a 1:2 complex ( $\underset{\sim}{4}$ ) of  $\underset{\sim}{1a}$  and  $\underset{\sim}{2}$  was studied. Crystal data of  $\text{C}_5\text{H}_{12}\text{N}_2 \cdot 2\text{C}_{15}\text{H}_{11}\text{OCl}$  ( $\underset{\sim}{4}$ ) are as follows: FW = 585.58, monoclinic, space group  $\text{P}2_1$ ,  $a = 12.688(6)$ ,  $b = 7.920(4)$ ,  $c = 15.971(3)$  Å,  $\beta = 104.82(3)^\circ$ ,  $D_c = 1.25$  g/cm<sup>3</sup>,  $\mu = 2.5$  cm<sup>-1</sup> and  $Z = 2$ .

The cell dimensions and intensities were collected on a Synthex R3 four-circle diffractometer with graphite-monochromated Mo-K $\alpha$  radiation by the  $\omega$ -scan mode within  $2\theta$  less than  $45^\circ$ . 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  $\underset{\sim}{4}$ , 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  $\underset{\sim}{4}$  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.

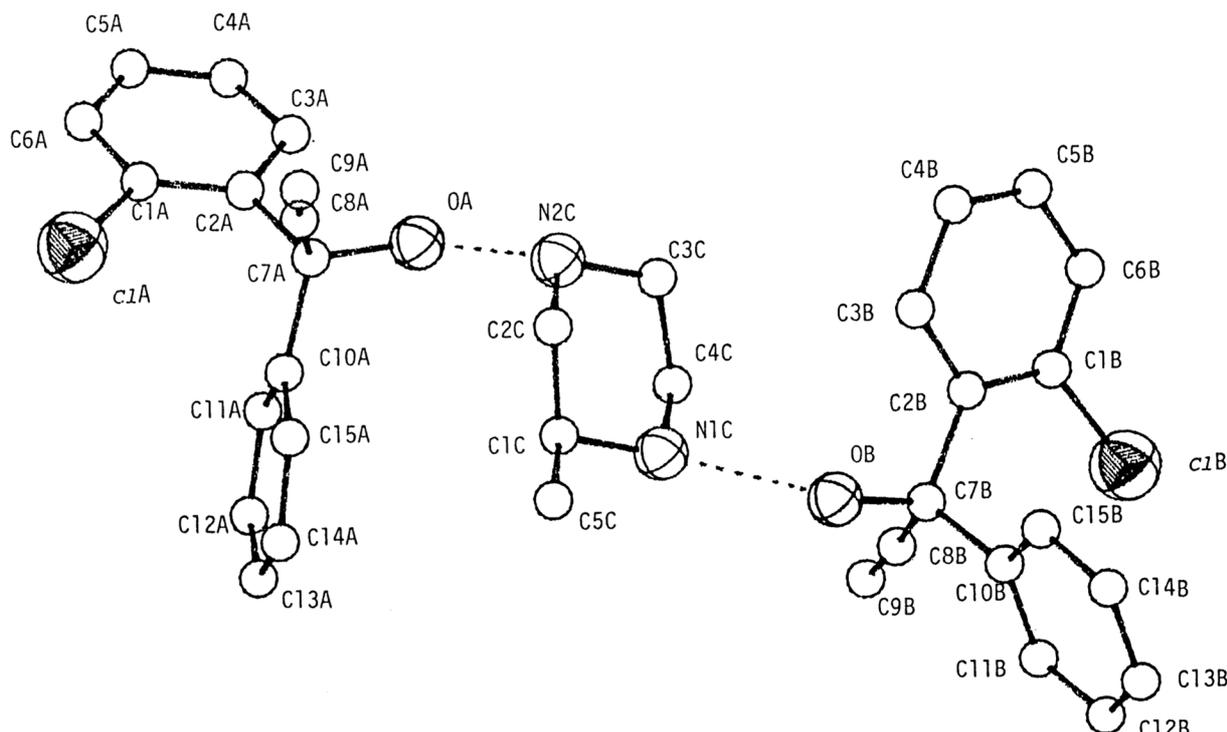


Fig. 1. Host-guest interaction of  $\mathbf{4}$  and atom labelling, with the  $\text{OH}\cdots\text{N}$  hydrogen bonds represented by broken lines. Bond lengths ( $\text{\AA}$ , standard deviations in parentheses): C1A-C(1)A 1.750(9), C1B-C(1)B 1.733(8), OA-C(7) 1.425(8), OB-C(7)B 1.436(8), N(1)C-C(1)C 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-C(9)15)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  $\mathbf{4}$ , two hydrogen bonds between OH of  $\mathbf{2}$  and N of  $\mathbf{1a}$  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  $\mathbf{2}$  of (*R*)-configuration and  $\mathbf{1}$  of (*S*)-configuration ( $\mathbf{1a}$ ) would be important to form the stable complex ( $\mathbf{4}$ ), because  $\mathbf{2}$  does not form complex with  $\mathbf{1}$  of (*R*)-configuration ( $\mathbf{1b}$ ). This is probably the same in the complex of  $\mathbf{1}$  and  $\mathbf{3}$ . Although  $\mathbf{3}$  includes  $\mathbf{1}$  of (*R*)-configuration ( $\mathbf{1b}$ ),  $\mathbf{3}$  does not include  $\mathbf{1}$  of (*S*)-configuration ( $\mathbf{1a}$ ). For the present, it is not clear why  $\mathbf{2}$  and  $\mathbf{3}$  of the same configuration include  $\mathbf{1}$  of the different configuration,  $\mathbf{1a}$  and  $\mathbf{1b}$ , respectively.

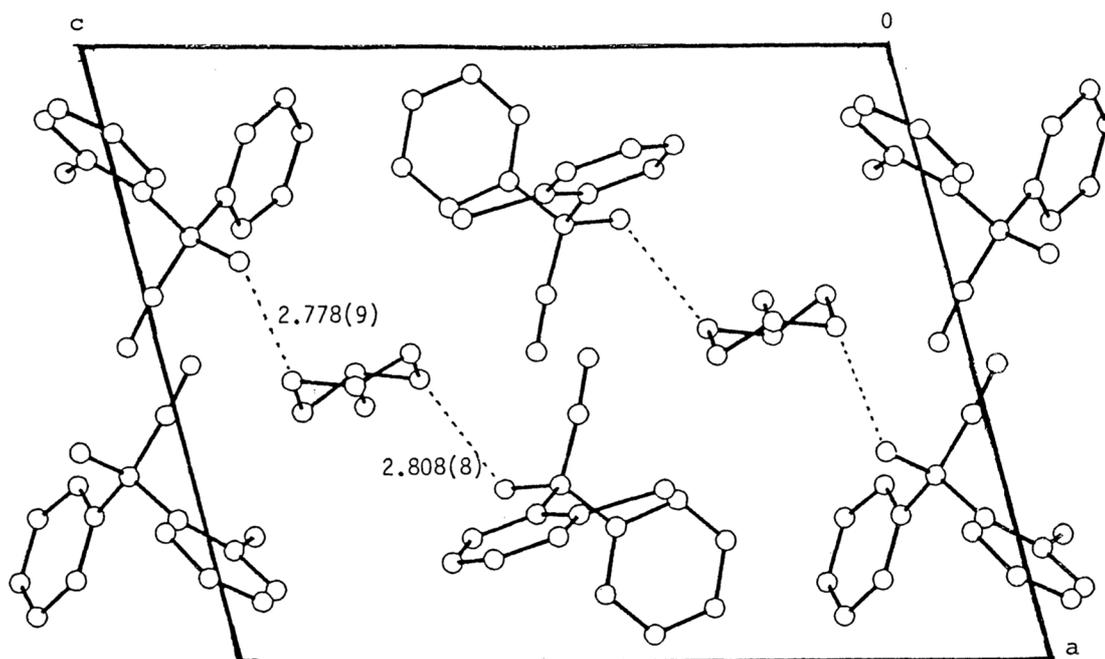


Fig. 2. The crystal structure projected along  $b$ -axis showing the hydrogen bonds (Å).

From the Figs. 1 and 2, the absolute configuration of (+)- $\lambda$  can be determined directly to be ( $S$ ), because the configuration of (-)- $\lambda$  has been determined to be ( $R$ ).<sup>2,3)</sup> This is identical with the reported ( $S$ )-configuration which has been determined by an indirect method.<sup>1)</sup>

#### References

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