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# Absolute Configuration of (+)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride

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## Abstract

(+)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline with an $[\alpha]_D^{25}$ value of +47.58° in CCl₄ (c 2.83) has been synthesized and the crystal structure of its hydrochloride, $C_{15}H_{16}N^+.Cl^-$, determined by X-ray methods. The

anomalous dispersion effect indicates that the absolute configuration is *S*.

## Comment

1-Phenyl-1,2,3,4-tetrahydroisoquinoline (PTIQ) is a basic compound for the development of new drugs. The absolute configuration of (−)-PTIQ has been assigned to be *S* (Yamato *et al.*, 1990). However, our related compound suggested that (+)-PTIQ has the *S* configuration (Nakahara *et al.*, 1997). In order to confirm the absolute configuration, an X-ray diffraction study of the title compound, (I), was undertaken.



(I)
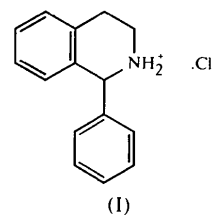
The optically resolved PTIQ we prepared had an $[\alpha]_D^{25}$ value of +47.58° in CCl₄ (c 2.83) indicating that it is the enantiomer of (−)-PTIQ (Leithe, 1929; Yamato *et al.*, 1990). Compound (I) crystallizes in the monoclinic space group $P2_1$ and the asymmetric unit contains two independent molecules, *A* and *A'*, having almost the same three-dimensional structure, with an r.m.s. deviation of 0.026 Å. They are related by a pseudo-twofold symmetry; their fractional atomic coordinates are related by the following equations: $x = -0.9995x' - 0.0117y' - 0.0389z' - 0.4600$, $y = -0.0027x' + 0.9999y' - 0.0330z' - 0.4185$, $z =$
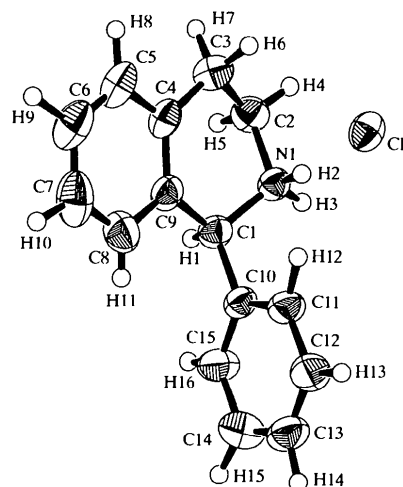


Fig. 1. *ORTEPII* drawing (Johnson, 1976) of molecule *A* of (I) with the atomic numbering. Displacement ellipsoids are shown at the 50% probability level and H atoms are shown as spheres of arbitrary size.

$0.0018x' - 0.0056y' - 1.0003z' + 1.5038$. The absolute configuration was unambiguously determined to be $S$ by two methods, an $R$-factor ratio test (Hamilton, 1964) and a comparison between $|F_o(+)| - |F_o(-)|$ and $|F_c(+)| - |F_c(-)|$. The ratio between $wR(1S) = 0.0825$ and $wR(1R) = 0.1196$ indicates the $1S$ configuration at more than the 99.9% significance level. The signs of the $|F_o(+)| - |F_o(-)|$ values for 40 selected Bijvoet mates were also consistent with those of $|F_c|$ values calculated for the $S$ enantiomer. From these results, it was concluded that the absolute configuration of (−)-PTIQ should be $R$. Fig. 1 shows the molecular structure of molecule $A$, together with the absolute configuration. The bond lengths and angles given in Table 1 are within the normal ranges and the piperidine rings exhibit twist-chair conformations similar to those found for 1-methyl-1,2,3,4-tetrahydroisoquinoline (Ohkubo et al., 1996). The interplanar angle between the least-squares planes of the benzene rings is 87.3 (2)° for molecule $A$ and 87.6 (2)° for molecule $A'$.

The crystal packing is shown in Fig. 2. In both $A$ and $A'$, the N1 atom links the two chloride ions related by a translation along the $a$ axis through the two hydrogen bonds to form an infinite chain.
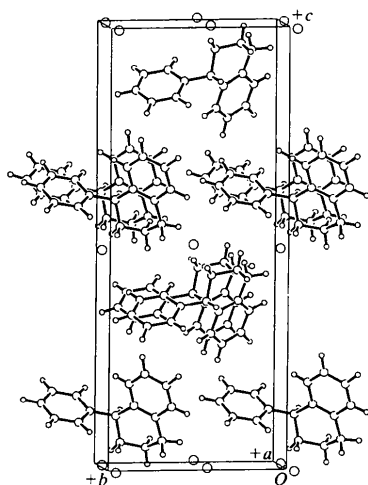


Fig. 2. Packing diagram of the crystal structure of (I).

## Experimental

(+)-PTIQ was prepared and optically resolved according to the method of Leithe (1929), and its optical rotation was measured in $CCl_4$ solution ($c$ 2.83) at 298 K using a 1 dm cell with a HORIBA polarimeter SEPA-200. Compound (I) was recrystallized from aqueous solution.

*Crystal data*

$C_{15}H_{16}N^+.Cl^-$
$M_r = 245.751$
Monoclinic
$P2_1$
$a = 5.264 (3)$ Å
$b = 10.084 (4)$ Å
$c = 24.758 (3)$ Å
$\beta = 93.02 (4)°$
$V = 1312.4 (8)$ Å$^3$
$Z = 4$
$D_x = 1.244$ Mg m$^{-3}$
$D_m$ not measured

Cu $K\alpha$ radiation
$\lambda = 1.54184$ Å
Cell parameters from 20
    reflections
$\theta = 22.5–30.0°$
$\mu = 2.37$ mm$^{-1}$
$T = 298.2$ K
Plate
$0.62 \times 0.28 \times 0.06$ mm
Colorless

*Data collection*

Rigaku AFC-7R diffractometer
$\omega–2\theta$ scans
Absorption correction:
    $\psi$ scans (North et al., 1968)
    $T_{min} = 0.571$, $T_{max} = 0.867$
5824 measured reflections
2636 independent reflections

2627 reflections with
    $I > 0$
$R_{int} = 0.047$
$\theta_{max} = 70.0°$
$h = -6 \rightarrow 6$
$k = -12 \rightarrow 12$
$l = -30 \rightarrow 30$
3 standard reflections
    every 150 reflections
    intensity decay: 3.95%

*Refinement*

Refinement on $F$
$R = 0.059$
$wR = 0.077$
$S = 1.160$
2627 reflections
307 parameters
Only coordinates of H atoms refined
$w = 1/[\sigma^2(F_o) + 0.00286|F_o|^2]$
$(\Delta/\sigma)_{max} = 0.003$
$\Delta\rho_{max} = 0.28$ e Å$^{-3}$
$\Delta\rho_{min} = -0.34$ e Å$^{-3}$

Extinction correction:
    Zachariasen (1967) type
    2 Gaussian isotropic
Extinction coefficient:
    0.03 (2)
Scattering factors from
    *International Tables for Crystallography* (Vol. C)
Absolute structure:
    determined by $R$-factor
    ratio test (Hamilton,
    1964) and the comparison
    between $|F_o(+)| - |F_o(-)|$
    and $|F_c(+)| - |F_c(-)|$

Table 1. *Selected geometric parameters (Å, °)*

| | | | |
|---|---|---|---|
| N1—C1 | 1.493 (4) | N1'—C1' | 1.502 (5) |
| N1—C2 | 1.492 (5) | N1'—C2' | 1.505 (6) |
| C1—C9 | 1.522 (5) | C1'—C9' | 1.535 (6) |
| C1—C10 | 1.506 (5) | C1'—C10' | 1.513 (6) |
| C2—C3 | 1.502 (6) | C2'—C3' | 1.498 (6) |
| C3—C4 | 1.506 (6) | C3'—C4' | 1.507 (6) |
| C4—C5 | 1.397 (6) | C4'—C5' | 1.402 (6) |
| C4—C9 | 1.396 (6) | C4'—C9' | 1.401 (6) |
| C5—C6 | 1.379 (8) | C5'—C6' | 1.381 (8) |
| C6—C7 | 1.382 (9) | C6'—C7' | 1.383 (10) |
| C7—C8 | 1.377 (8) | C7'—C8' | 1.373 (8) |
| C8—C9 | 1.399 (5) | C8'—C9' | 1.405 (6) |
| C10—C11 | 1.389 (5) | C10'—C11' | 1.394 (6) |
| C10—C15 | 1.400 (5) | C10'—C15' | 1.379 (6) |
| C11—C12 | 1.396 (6) | C11'—C12' | 1.391 (7) |
| C12—C13 | 1.375 (7) | C12'—C13' | 1.386 (8) |
| C13—C14 | 1.381 (8) | C13'—C14' | 1.363 (9) |
| C14—C15 | 1.371 (7) | C14'—C15' | 1.405 (9) |
| C1—N1—C2 | 111.6 (3) | C1'—N1'—C2' | 110.8 (3) |
| N1—C1—C9 | 109.1 (3) | N1'—C1'—C9' | 108.7 (3) |
| N1—C1—C10 | 111.0 (3) | N1'—C1'—C10' | 110.0 (3) |
| C9—C1—C10 | 114.3 (3) | C9'—C1'—C10' | 115.3 (3) |
| N1—C2—C3 | 110.0 (3) | N1'—C2'—C3' | 110.6 (3) |
| C2—C3—C4 | 112.9 (3) | C2'—C3'—C4' | 113.2 (4) |
| C3—C4—C5 | 119.0 (4) | C3'—C4'—C5' | 119.2 (4) |
| C3—C4—C9 | 121.8 (4) | C3'—C4'—C9' | 121.5 (4) |

| | | | |
|---|---|---|---|
| C5—C4—C9 | 119.1 (4) | C5'—C4'—C9' | 119.2 (4) |
| C4—C5—C6 | 121.0 (5) | C4'—C5'—C6' | 120.9 (5) |
| C5—C6—C7 | 120.1 (4) | C5'—C6'—C7' | 119.7 (5) |
| C6—C7—C8 | 119.5 (5) | C6'—C7'—C8' | 120.4 (5) |
| C7—C8—C9 | 121.3 (5) | C7'—C8'—C9' | 121.0 (5) |
| C1—C9—C4 | 121.3 (3) | C1'—C9'—C4' | 121.7 (4) |
| C1—C9—C8 | 119.7 (4) | C1'—C9'—C8' | 119.5 (4) |
| C4—C9—C8 | 118.9 (4) | C4'—C9'—C8' | 118.8 (4) |
| C1—C10—C11 | 121.8 (3) | C1'—C10'—C11' | 121.3 (4) |
| C1—C10—C15 | 120.5 (3) | C1'—C10'—C15' | 120.0 (4) |
| C11—C10—C15 | 117.7 (4) | C11'—C10'—C15' | 118.7 (5) |
| C10—C11—C12 | 121.2 (4) | C10'—C11'—C12' | 120.8 (4) |
| C11—C12—C13 | 119.4 (4) | C11'—C12'—C13' | 119.5 (5) |
| C12—C13—C14 | 120.4 (4) | C12'—C13'—C14' | 120.5 (5) |
| C13—C14—C15 | 120.0 (4) | C13'—C14'—C15' | 119.8 (5) |
| C10—C15—C14 | 121.3 (4) | C10'—C15'—C14' | 120.6 (5) |

Table 2. *Hydrogen-bonding geometry (Å, °)*

| D—H···A | D—H | H···A | D···A | D—H···A |
|---|---|---|---|---|
| N1—H2···Cl1 | 0.90 | 2.23 | 3.126 (3) | 172 |
| N1—H3···Cl1$^i$ | 1.01 | 2.09 | 3.084 (3) | 167 |
| N1'—H2'···Cl1' | 0.90 | 2.22 | 3.116 (4) | 176 |
| N1'—H3'···Cl1'$^{ii}$ | 1.11 | 1.98 | 3.074 (4) | 168 |

Symmetry codes: (i) $1 + x, y, z$; (ii) $x - 1, y, z$.

The intensity data for $hkl$ and $\bar{h}k\bar{l}$ were alternately measured every five reflections during the data collection. After structure determination, 40 reflections with large differences in $F_c$ values between the Bijvoet reflections were chosen and their intensity data were measured more precisely. The structure was solved by direct methods and all non-H atoms were refined anisotropically by full-matrix least-squares techniques. Although all H atoms were located on a difference Fourier map, their positions were not refined. Their displacement parameters were assumed to be 1.2 times $B_{eq}$ of the attached atom. For the $R$-factor ratio test, all atoms were refined again by full-matrix least-squares techniques with the reflections $hkl$ and $\bar{h}k\bar{l}$ (total of 4919 reflections). The angles of the least-squares planes were calculated using the program *LISTUP* (Takenaka, 1990) and the other structural parameters were calculated using the program *TEXSAN* (Molecular Structure Corporation, 1997).

Data collection: *Rigaku/AFC Diffractometer Control Software* (Rigaku Corporation, 1995). Cell refinement: *Rigaku/AFC Diffractometer Control Software*. Data reduction: *TEXSAN*. Program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994). Program(s) used to refine structure: *TEXSAN*. Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *TEXSAN*.

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# The Monoclinic Form of Acetaminophen at 150 K

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## Abstract

The crystal structure of the anti-inflammatory agent acetaminophen [*N*-(4-hydroxyphenyl)acetamide, $C_8H_9$-$NO_2$] has been refined using a Siemens SMART three-circle automatic diffractometer with a charge-coupled device (CCD) detector at 150 K. Monoclinic crystals of acetaminophen were grown from ethanol solution (m.p. 443–444 K). The crystal structure exhibits two kinds of hydrogen bonds [2.656 (2) Å, OH donates to O=C; 2.914 (2) Å, HO accepts from HN]. The molecules form a pleated sheet parallel to the (101) plane. The sheets are stacked along [010]. The molecules within a stack are held together by van der Waals interactions. Molecules from different sheets form 'head-to-tail'-type dimers.

## Comment

Acetaminophen, (I), is the most prominent pain-relieving drug among acetanilide derivatives. Its physical and chemical properties have been intensively studied by Grant & Chow (1991). Precise data on its crystal structure are required for controlling processes such as dissolution and sublimation, which are important