The Absolute Configuration of (−)-Nefopam Based on the Crystal Structure of (−)-Nefopam Hydrochloride Monohydrate

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Nefopam hydrochloride, *cf.* Fig. 1, a novel analgesic, which works by descending inhibitory pain pathways which are serotonergic, is currently used in the racemic form.[1-4] Optical resolution,[2] and subsequent metabolic[3] and pharmacological[4] studies of the nefopam enantiomers, have been carried out previously by others. The absolute configuration of the title compound has been determined by X-ray crystallographic methods according to the procedure described below.

Crystals of (−)-nefopam hydrochloride, obtained by slow evaporation (8 days) from acetone, are colourless prisms; mp 180−183 °C; $[\alpha]_D^{22}$ −119° (*c* 1; DMSO); $[\alpha]_D^{20}$ −100.4° (*c* 0.7; CH_3OH). A crystal of dimensions 0.5×0.4×0.4 mm was used for the X-ray measurements which were carried out at 20 °C on a CAD4 diffractometer using graphite monochromatized Cu$K\alpha$ radiation (λ=1.5418 Å).

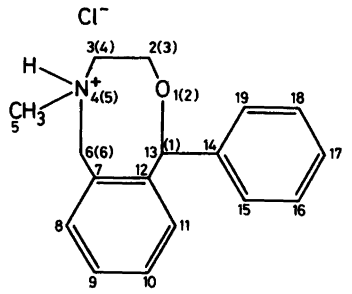

Fig. 1. Schematic drawing of the molecule showing the numbering of atoms. Numbers in parentheses refer to the systematic name.

The crystals are orthorhombic, space group $P2_12_12_1$ with cell dimensions, a=8.507(1), b=9.661(1), and c=19.781(1) Å, Z=4 and μ=21.1 cm^{-1} (Cu$K\alpha$).

The intensities of 1923 independent Friedel pairs within θ=65° were measured using $\omega-2\theta$ scan ($\Delta\omega(°)$=0.80+0.14 tan θ). 1919 of these

Table 1. Atomic coordinates for the non-hydrogen atoms.

Atom	*X*	*Y*	*Z*
Cl	0.51539(7)	0.22076(5)	0.09049(3)
O(1)	0.40196(13)	0.39823(14)	0.27237(6)
C(2)	0.42370(25)	0.51819(25)	0.23126(10)
C(3)	0.29683(22)	0.54114(18)	0.17978(8)
N(4)	0.25595(17)	0.41551(14)	0.13958(6)
C(5)	0.15303(26)	0.45474(26)	0.08174(8)
C(6)	0.18598(22)	0.29623(18)	0.18080(8)
C(7)	0.07096(18)	0.34299(18)	0.23378(8)
C(8)	−0.08961(21)	0.32740(22)	0.21833(10)
C(9)	−0.20305(22)	0.36553(23)	0.26381(12)
C(10)	−0.16116(22)	0.42348(22)	0.32492(12)
C(11)	−0.00264(23)	0.43961(20)	0.34126(9)
C(12)	0.11421(17)	0.39753(16)	0.29638(7)
C(13)	0.28153(18)	0.41079(16)	0.32275(7)
C(14)	0.32137(18)	0.30090(16)	0.37480(7)
C(15)	0.25891(20)	0.16746(18)	0.37095(8)
C(16)	0.30240(26)	0.06666(17)	0.41685(8)
C(17)	0.41051(28)	0.09802(21)	0.46735(9)
C(18)	0.47122(27)	0.22969(23)	0.47174(9)
C(19)	0.42859(24)	0.33067(20)	0.42572(8)
O(20)	−0.12005(20)	0.19211(24)	0.05396(8)

0302-4369/84 $2.50

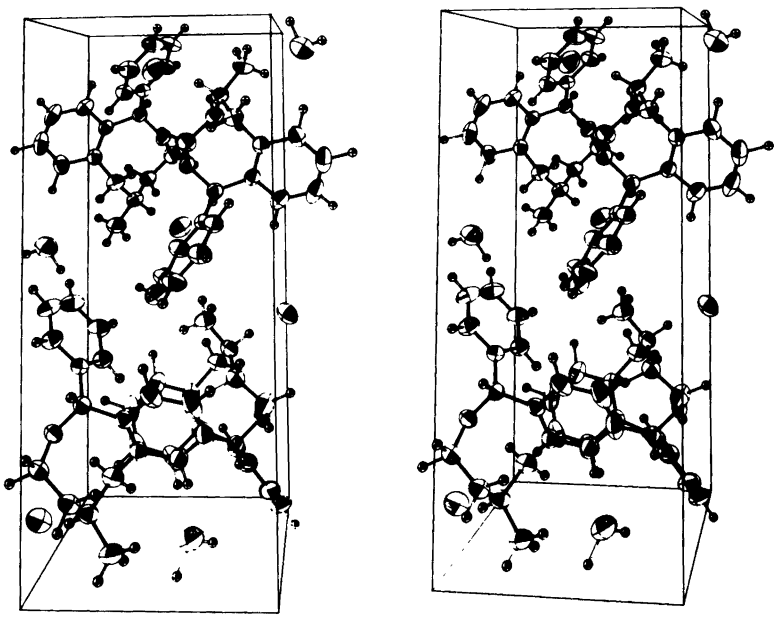

Fig. 2. Stereoscopic view of the molecule.[8]

which had $I>2\sigma(I)$ were regarded as observed. L*p*, but no absorption corrections, were applied.

The structure was solved by direct methods (MULTAN)[5] and refined by full matrix least squares methods.[6] The hydrogen positions were found from difference maps. Anisotropic temperature factors were used for Cl, O, N, and C, and isotropic for H.

Anomalous dispersion corrections for Cl were included in the last stages of the refinement. By using anomalous scattering factors for Cl with $+f''=0.702$[7] the refinement converged to an R factor of 0.052. On changing the sign of the f'' term the refinement converged to $R=0.041$.

On the basis of this result signs were changed for *y*-coordinates and temperature parameters U_{12} and U_{23}. The final list of coordinates corresponding to the correct absolute configuration of the molecule is given in Table 1.

Ratios of calculated and observed structure factors for selected Bijvoet pairs most affected from anomalous dispersion are listed in Table 2. A stereoscopic view[8] of the molecule is shown in Fig. 2. One sees from the figure that the configuration is the *R*-type. The complete systematic name of the actual epimer is therefore (1*R*)-(−)-5-Methyl-1-phenyl-1,3,4,6-tetrahydro-5*H*-benzo[*f*]-2,5-oxazocine. Bond lengths and angles are given in Table 3. There is a Cl···H−N hydrogen bond in the crystal structure where the Cl···N distance is 3.06(2) Å and the Cl···H−N angle 158(3)°. Bond lengths and angles in the molecule are normal.

Lists of structure factors, atomic coordinates for the hydrogen atoms, and temperature factors are available from Lars K. Hansen on request.

Table 2. Ratios of calculated and observed structure factors for selected Bijvoet pairs most affected from anomalous dispersion. (+) and (−) denotes (*hkl*) and ($\bar{h}\bar{k}\bar{l}$), respectively.

h	*k*	*l*	$\lvert F_c(+)\rvert/\lvert F_c(-)\rvert$	$\lvert F_o(+)\rvert/\lvert F_o(-)\rvert$
1	3	18	1.46	1.54
1	1	20	0.69	0.68
2	9	2	1.54	1.63
2	11	4	2.00	1.96
4	1	1	0.68	0.69
4	8	3	0.72	0.69
5	6	1	0.58	0.56
5	5	14	2.59	2.00
7	5	7	1.73	1.70
10	1	7	0.70	0.73

Table 3. Bond lengths and angles.

Distance	(Å)
O(1)–C(2)	1.428(3)
O(1)–C(13)	1.434(2)
C(2)–C(3)	1.500(3)
C(3)–C(4)	1.492(2)
N(4)–C(5)	1.490(2)
N(4)–C(6)	1.532(2)
C(6)–C(7)	1.503(2)
C(7)–C(8)	1.408(2)
C(7)–C(12)	1.395(2)
C(8)–C(9)	1.370(3)
C(9)–C(10)	1.379(3)
C(10)–C(11)	1.395(3)
C(11)–C(12)	1.393(2)
C(12)–C(13)	1.521(2)
C(13)–C(14)	1.517(2)
C(14)–C(15)	1.396(2)
C(14)–C(19)	1.389(2)
C(15)–C(16)	1.382(2)
C(16)–C(17)	1.391(3)
C(17)–C(18)	1.376(3)
C(18)–C(19)	1.383(3)

Angle	(°)
C(2)–O(1)–C(13)	114.8(2)
O(1)–C(2)–C(3)	114.4(2)
O(1)–C(13)–C(12)	115.0(2)
O(1)–C(13)–C(14)	104.6(2)
C(2)–C(3)–N(4)	114.2(2)
C(3)–N(4)–C(5)	109.8(2)
C(3)–N(4)–C(6)	114.8(2)
C(5)–N(4)–C(6)	111.8(2)
N(4)–C(6)–C(7)	113.4(2)
C(6)–C(7)–C(8)	116.6(2)
C(6)–C(7)–C(12)	124.1(2)
C(8)–C(7)–C(12)	119.3(2)
C(7)–C(8)–C(9)	120.8(2)
C(7)–C(12)–C(11)	119.2(2)
C(7)–C(12)–C(13)	125.7(2)
C(8)–C(9)–C(10)	120.2(2)
C(9)–C(10)–C(11)	119.9(2)
C(10)–C(11)–C(12)	120.6(2)
C(11)–C(12)–C(13)	115.1(2)
C(12)–C(13)–C(14)	112.5(2)
C(13)–C(14)–C(15)	121.6(2)
C(13)–C(14)–C(19)	119.6(2)
C(15)–C(14)–C(19)	118.7(2)
C(14)–C(15)–C(16)	120.9(2)
C(14)–C(19)–C(18)	120.2(2)
C(15)–C(16)–C(17)	119.7(2)
C(16)–C(17)–C(18)	119.7(2)
C(17)–C(18)–C(19)	120.8(2)

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