Crystal Structure of Ciclopirox Olamine

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The crystal structure of ciclopirox was determined. The crystal belongs to space group $I4_1/a$, and the cell dimensions are $a = 26.0133(6)$ and $c = 15.8980(8)$ Å. There are two ciclopirox molecules, of which one is neutral and the other is negatively charged, and one positively charged 2-amino ethanol molecule in an asymmetric unit. The final R -value is 0.068.

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Ciclopirox (6-cyclohexyl-1-hydroxy-4-methyl-2(1*H*)-pyridinone) is a broad-spectrum, antifungal agent that inhibits the growth of pathogenic dermatophytes, yeasts, and *Malassezia furfur*. The drug is used to treat fungal infections of the skin or nails. Ciclopirox acts by chelating of polyvalent cations, resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cells. X-ray analysis of ciclopirox was undertaken to disclose the inherent conformation to understand the chelating action of the molecule. The chemical structure is shown in Fig. 1.

The ciclopirox olamine is the 2-aminoethanol salt of ciclopirox. The compound was purchased from Sigma Co., Ltd. Suitable single crystals were obtained from a methanol-acetonitrile solution. In the original compound the molar ratio between ciclopirox and 2-aminoethanol is 1:1. In the obtained single crystals, however, the corresponding ratio was 2:1. A colorless prism crystal having approximate dimensions of $0.40 \times 0.40 \times 0.15$ mm was mounted on a glass fiber. The crystal and experimental data are shown in Table 1.

The structure was solved by direct methods and refined by full matrix least-squares methods with anisotropic temperature factors for non-H atoms. All H atoms were refined using a riding model except that of the hydroxyl group. A hydroxyl group hydrogen atom was found from the difference Fourier map. The atomic parameters for non-H atoms are listed in Table 2.

There are two molecules of ciclopirox and one molecule of 2-aminoethanol in an asymmetric unit. An ORTEP III³ drawing of the molecules together with the atomic numbering is shown

Fig. 1 Chemical structure

in Fig. 2. Selected bond distances and angles are shown in Table 3. The bond distances and angles are within the expected ranges. The cyclohexane rings of ciclopirox take chair conformation. The pyridinone rings are almost planar. The torsion angles of C106-N101-C102-C103, C102-N101-C106-C105 and O101-N101-C106-C105 in molecule I are $-3.0(4)$, $1.0(4)$ and $176.6(2)^\circ$, respectively. They are significantly different from the corresponding values of $-8.8(4)$, $6.7(4)$ and $-176.3(2)^\circ$, respectively, in molecule II. The relative orientations of cyclohexane rings with respect to the pyridinone rings are different in the crystallographically independent ciclopirox molecules. Although the torsion angle of N101-C106-C108-C109 in molecule I is $-76.8(3)^\circ$, the corresponding angle in molecule II is $82.4(3)^\circ$. There is a relatively short intermolecular hydrogen bond between the hydroxyl groups of crystallographically independent ciclopirox molecules ($O101 \cdots O201 = 2.474(3)$ Å). The hydrogen atom is refined to be located in between the two oxygen atoms, with O101-H and O201-H distances being $1.19(5)$ and $1.29(5)$ Å, respectively, and O101-H-O201 angle of $173(4)^\circ$. The N-O bond in molecule I is, however, significantly longer than the

Table 1 Crystal and experimental data

Formula: $C_{12}H_{17}NO_2 \cdot C_{12}H_{16}NO_2 \cdot C_2H_8NO$
Formula weight = 475.63
Crystal system: tetragonal
Space group: $I4_1/a$ $Z = 16$
$a = 26.0133(6)$ Å
$c = 15.8980(8)$ Å
$V = 10758.0(6)$ Å ³
$D_x = 1.175$ g/cm ³
No. observations ($I > 2.30\sigma(I)$) = 3341
$\theta_{\max} = 67.76^\circ$ with Cu K_α
R ($I > 2.30\sigma(I)$) = 0.068
$(\Delta/\sigma)_{\max} = 0.000$
$(\Delta\rho)_{\max} = 0.45$ e/Å ³
$(\Delta\rho)_{\min} = -0.39$ e/Å ³
Measurement: Rigaku RAXIS-RAPID
Program system: CrystalStructure 3.5.1 ¹
Structure determination: SIR92 ²
Refinement: full-matrix

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Table 2 Atomic coordinates and equivalent isotropic thermal parameters (B_{eq})

Atom	x	y	z	B_{eq}
molecule I of ciclopirox				
O101	0.09022(7)	-0.08376(8)	0.8439(1)	4.27(5)
O102	0.09541(8)	-0.0477(1)	0.9976(1)	5.76(6)
N101	0.04657(9)	-0.08433(9)	0.8943(1)	3.70(6)
C102	0.0519(1)	-0.0654(1)	0.9754(2)	4.24(8)
C103	0.0072(1)	-0.0675(1)	1.0257(2)	4.39(8)
C104	-0.0381(1)	-0.0884(1)	0.9980(2)	4.04(8)
C105	-0.0396(1)	-0.1089(1)	0.9161(2)	4.08(8)
C106	0.0022(1)	-0.1063(1)	0.8635(2)	3.70(7)
C107	-0.0858(1)	-0.0897(1)	1.0511(2)	5.6(1)
C108	0.0021(1)	-0.1239(1)	0.7728(2)	4.19(8)
C109	-0.0036(1)	-0.0774(1)	0.7140(2)	4.87(9)
C110	-0.0019(2)	-0.0929(1)	0.6216(2)	6.9(1)
C111	-0.0421(2)	-0.1324(2)	0.6018(3)	8.3(1)
C112	-0.0373(2)	-0.1790(2)	0.6590(3)	8.3(1)
C113	-0.0398(2)	-0.1635(1)	0.7526(2)	6.5(1)
molecule II of ciclopirox				
O201	0.11305(7)	0.00397(8)	0.7969(1)	3.79(5)
O202	0.19714(8)	-0.04152(8)	0.7385(1)	4.23(5)
N201	0.12092(9)	0.00035(8)	0.7116(1)	3.28(6)
C202	0.1645(1)	-0.0258(1)	0.6847(2)	3.49(7)
C203	0.1685(1)	-0.0329(1)	0.5968(2)	3.87(8)
C204	0.1343(1)	-0.0121(1)	0.5415(2)	4.14(8)
C205	0.0936(1)	0.0180(1)	0.5738(2)	4.37(8)
C206	0.0867(1)	0.0246(1)	0.6583(2)	3.59(7)
C207	0.1395(1)	-0.0201(1)	0.4475(2)	5.9(1)
C208	0.0481(1)	0.0604(1)	0.6978(2)	3.94(8)
C209	0.0739(1)	0.1128(1)	0.7120(2)	4.87(9)
C210	0.0371(1)	0.1529(1)	0.7492(2)	6.3(1)
C211	-0.0116(2)	0.1579(1)	0.6970(3)	6.6(1)
C212	-0.0372(1)	0.1061(2)	0.6887(3)	7.1(1)
2-aminoethanol				
O304	-0.1643(1)	0.0434(1)	0.8758(2)	8.09(9)
N301	-0.20318(9)	-0.06001(9)	0.8322(1)	4.04(6)
C302	-0.1554(2)	-0.0342(2)	0.8004(3)	7.7(1)
C303	-0.1545(2)	0.0194(2)	0.7999(3)	10.4(2)

$$B_{eq} = 8/3\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$$

corresponding one in molecule II. The N-O bond length in molecule I conforms to that of a single bond reported in the literature.⁴ Therefore the hydroxyl group in molecule II is dissociated and the resultant negative charge neutralizes the positive charge of the ammonium group in 2-aminoethanol.

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Fig. 2 Molecular structure of ciclopirox along with the labeling atoms. Thermal ellipsoids of non-H atoms are drawn at the 50% probability level

Table 3 Selected bond lengths (Å) and angles (°)

molecule I of ciclopirox		molecule II of ciclopirox	
O(101)---N(101)	1.390(3)	O(201)---N(201)	1.374(3)
O(102)---C(102)	1.271(4)	O(202)---C(202)	1.272(4)
N(101)---C(102)	1.387(4)	N(201)---C(202)	1.391(4)
N(101)---C(106)	1.379(4)	N(201)---C(206)	1.382(4)
O(101)---N(101)---C(102)	116.8(2)	O(201)---N(201)---C(202)	117.3(2)
O(101)---N(101)---C(106)	118.9(2)	O(201)---N(201)---C(206)	118.6(2)
C(102)---N(101)---C(106)	124.2(2)	C(202)---N(201)---C(206)	124.1(2)
O(102)---C(102)---N(101)	118.4(3)	O(202)---C(202)---N(201)	119.6(3)
O(102)---C(102)---C(103)	126.1(3)	O(202)---C(202)---C(203)	125.1(3)
N(101)---C(102)---C(103)	115.4(3)	N(201)---C(202)---C(203)	115.3(3)
N(101)---C(106)---C(105)	117.8(3)	N(201)---C(206)---C(205)	117.5(3)
N(101)---C(106)---C(108)	117.8(3)	N(201)---C(206)---C(208)	117.1(3)
2-aminoethanol			
N(301)---C(302)	1.500(5)	O(304)---C(303)	1.382(6)
N(301)---C(302)---C(303)	117.6(4)	O(304)---C(303)---C(302)	116.2(4)

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