The Absolute Configuration of (*R*)-(+)-Nadifloxacin

Masaru KIDO,* Daisuke NOMI, and Koji HASHIMOTO

Second Tokushima Institute of New Drug Research, Otsuka Pharmaceutical Co., Ltd., Kagasuno 463–10, Kawauchi-cho, Tokushima 771–01, Japan. Received April 20, 1994; accepted October 16, 1995

The optically active (+)-enantiomer of 5,6-difluoro-2-methyl-1,2,3,4-tetrahydroquinoline was obtained as a salt with dibenzoyl-D-tartaric acid by the optical resolution method and was determined to be *R*-configuration by X-ray analysis. Since (*R*)-(+)-5,6-difluoro-2-methyl-1,2,3,4-tetrahydroquinoline is the optically resolved synthetic intermediate of optically active (+)-enantiomer of nadifloxacin[9-fluoro-6,7-dihydro-8-(4-hydroxy-1-piperidyl)-5-methyl-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic acid, OPC-7251, 1], the absolute configuration of (+)-1 was assigned to *R*.

Key words nadifloxacin; OPC-7251; absolute configuration; dibenzoyl-D-tartaric acid, 5,6-difluoro-2-methyl-1,2,3,4-tetrahydroquinoline; X-ray analysis

Nadifloxacin (**1**)[1] is the synthetic quinolone antibacterial drug and is widely used to cure dermatological diseases. The three dimensional structure of racemic **1** has been reported.[2] The two optical isomers of **1** and ofloxacin (**2**) have different activities.[3] (−)-Isomer of **1** was 64 to 256 times more potent than the (+)-**1**, and approximately twice as active as racemic **1** against gram-positive and gram-negative bacteria. The optically active

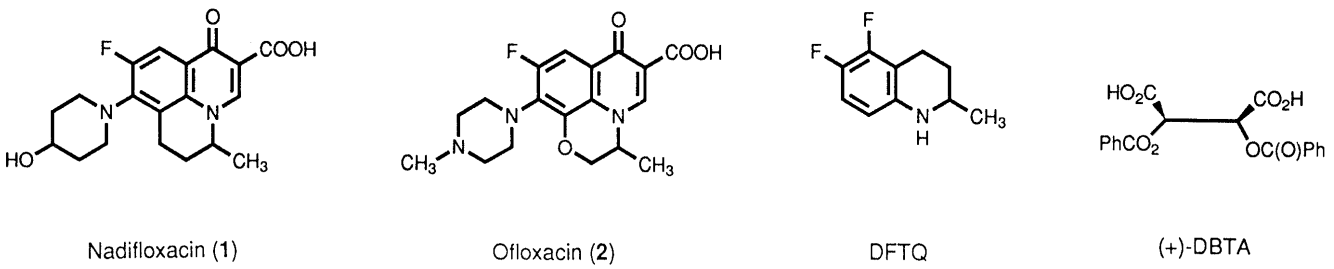

Chart 1

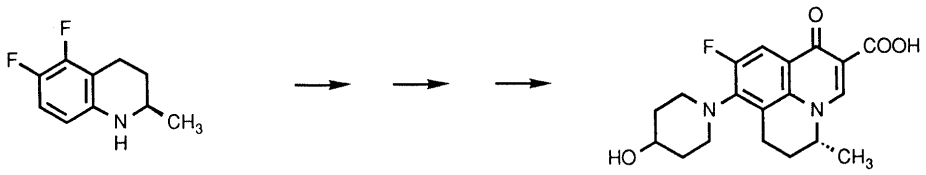

Chart 2

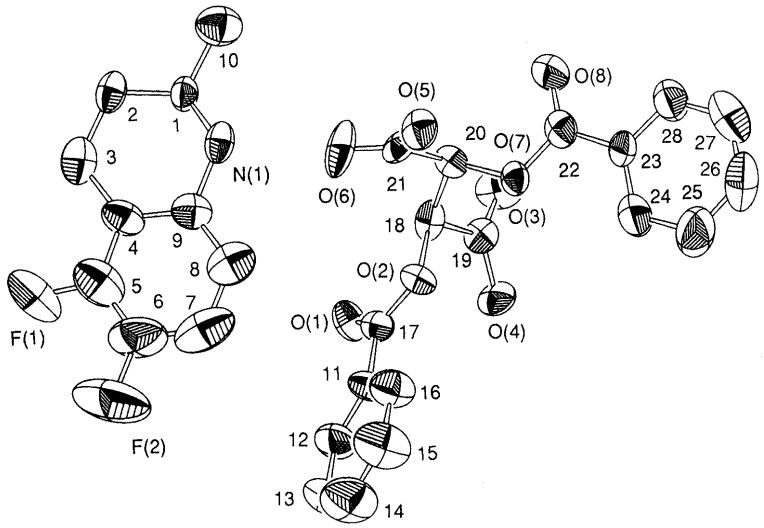

Fig. 1. ORTEP Drawing of (+)-DFTQ·(+)-DBTA Salt with the Atomic Numbering Scheme

Thermal ellipsoids are drawn at 50% probability; H atoms are not shown.

* To whom correspondence should be addressed.

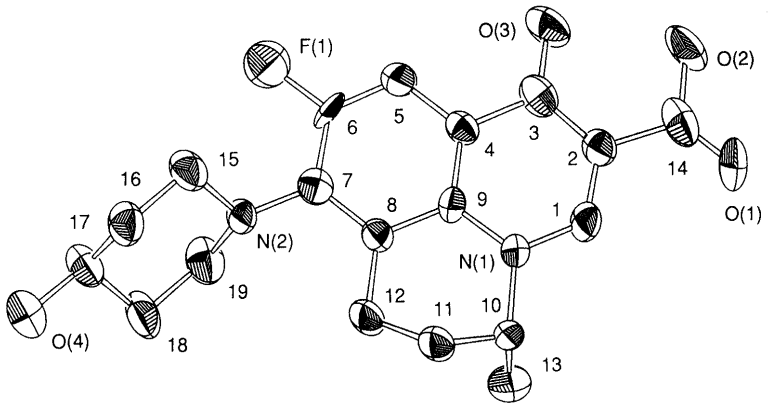

Fig. 2. ORTEP Drawing of (*R*)-(+)-**1** with Atomic Numbering Scheme for Molecule A Only

Thermal ellipsoids are drawn at 50% probability; H atoms are not shown.

Table 1. Atomic Coordinates for the Non-H Atoms of (+)-DFTQ·(+)-DBTA Salt with Their e.s.d.'s in Parentheses

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
F(1)	1.3133 (7)	0.0885 (3)	0.079 (1)	C(10)	0.951 (1)	0.2506 (5)	−0.020 (2)
F(2)	1.2206 (8)	0.0145 (3)	0.223 (1)	C(11)	0.877 (1)	0.0494 (3)	0.618 (1)
O(1)	0.9340 (5)	0.1245 (2)	0.7080 (9)	C(12)	0.960 (1)	0.0269 (4)	0.698 (2)
O(2)	0.7729 (5)	0.1176 (2)	0.5749 (8)	C(13)	0.974 (1)	−0.0201 (5)	0.679 (2)
O(3)	0.6899 (6)	0.2188 (2)	0.8045 (9)	C(14)	0.907 (2)	−0.0463 (5)	0.584 (2)
O(4)	0.7200 (6)	0.1452 (2)	0.8810 (9)	C(15)	0.822 (1)	−0.0257 (5)	0.498 (2)
O(5)	0.6539 (6)	0.1619 (2)	0.177 (1)	C(16)	0.808 (1)	0.0231 (4)	0.519 (2)
O(6)	0.8195 (7)	0.1794 (3)	0.2632 (9)	C(17)	0.8646 (9)	0.1005 (3)	0.638 (1)
O(7)	0.5751 (5)	0.1631 (2)	0.4923 (8)	C(18)	0.7570 (8)	0.1677 (3)	0.598 (1)
O(8)	0.4936 (5)	0.2324 (3)	0.441 (1)	C(19)	0.7161 (8)	0.1793 (4)	0.776 (1)
N(1)	0.9684 (7)	0.1657 (3)	0.034 (1)	C(20)	0.6785 (8)	0.1842 (3)	0.461 (1)
C(1)	1.0279 (8)	0.2122 (4)	0.030 (1)	C(21)	0.722 (1)	0.1738 (4)	0.287 (1)
C(2)	1.1249 (9)	0.2065 (5)	−0.086 (1)	C(22)	0.4875 (8)	0.1909 (4)	0.476 (1)
C(3)	1.202 (1)	0.1700 (5)	−0.021 (2)	C(23)	0.3848 (8)	0.1657 (4)	0.497 (1)
C(4)	1.146 (1)	0.1281 (4)	0.051 (2)	C(24)	0.381 (1)	0.1198 (4)	0.554 (2)
C(5)	1.204 (1)	0.0890 (5)	0.096 (2)	C(25)	0.280 (1)	0.0973 (6)	0.573 (3)
C(6)	1.158 (2)	0.0513 (5)	0.174 (2)	C(26)	0.186 (1)	0.1209 (7)	0.534 (2)
C(7)	1.050 (2)	0.0494 (6)	0.206 (2)	C(27)	0.190 (1)	0.1659 (7)	0.481 (2)
C(8)	0.986 (1)	0.0877 (5)	0.153 (2)	C(28)	0.288 (1)	0.1884 (5)	0.463 (2)
C(9)	1.035 (1)	0.1254 (4)	0.085 (1)				

compound of **1** was derived from optically active 5,6-difluoro-2-methyl-1,2,3,4-tetrahydroquinoline (DFTQ, Chart 2) which was obtained by the optical resolution method.[4] Therefore, (+)-enantiomer of DFTQ was obtained as a salt with (+)-dibenzoyl-D-tartaric acid ((+)-DBTA) and (−)-enantiomer was obtained as a salt with (−)-DBTA.

The stereochemistry of (+)-DFTQ was established by X-ray analysis, and the absolute configuration was determined by its relation to (+)-DBTA whose absolute configuration is known. As shown in Fig. 1, the result clearly indicates that (+)-DFTQ has *R*-configuration.

The (*R*)-(+)-**1** and (*S*)-(−)-**1** was derived from (*R*)-(+)-DFTQ and (*S*)-(−)-DFTQ, respectively. Each enantiomer of **1** was recrystallized, but we have not obtained a suitable crystal for X-ray analysis except for (*R*)-(+)-**1**. The crystal of (*R*)-(+)-**1** contains two crystallographically independent molecules (A and B) in an asymmetric unit. Since their molecular shapes are very similar to one another, only the ORTEP drawing of molecule A is shown in Fig. 2. Geometrical parameters of A and B molecules are similar to those of racemic **1**, respectively.

Experimental

Optical Resolution of (+)-DFTQ (±)-DFTQ and (+)-DBTA were dissolved in 70% MeOH. After cooling, the precipitates were collected by filtration. An additional recrystallization from 70% MeOH gave a salt of (+)-DFTQ and (+)-DBTA as colorless rod-shaped crystals adequate for X-ray crystallography.

X-Ray Analysis of (+)-DFTQ·(+)-DBTA Salt Crystal size, 0.3 × 0.3 × 0.5 mm. All data were obtained with a Rigaku AFC-5S automated four-circle diffractometer with graphite-monochromated MoK_α radiation. Final lattice parameters were determined from a least-squares refinement using 21 reflections. Crystal data: $C_{10}H_{11}F_2N \cdot C_{18}H_{14}O_8$, $M_r = 541.50$, orthorhombic, space group $P2_12_12_1$, $a = 12.287(9)$ Å, $b = 28.441(5)$ Å, $c = 7.873(5)$ Å, $V = 2751(3)$ Å^3, $Z = 4$, $D_x = 1.307$ g/cm^3, $F(000) = 1128$, and $\mu(\text{Mo}K_\alpha) = 0.98$ cm^{-1}. The intensities were measured using a $\omega/2\theta$ scan up to 45°. Three standard reflections were monitored every 150 measurements. The data were collected for Lorentz and polarization factors, but no absorption correction was applied. Of the 2121 independent measured reflections, 1287 reflections with $I > 1.0\ \sigma(I)$ were used for structure determination and refinement. The structure was solved by direct method using a TEXSAN crystallographic software package.[5] All the non-H atoms were found on the Fourier map. Positions of H atoms were calculated except for 3 atoms of amino and hydroxyl groups, which were obtained from difference Fourier synthesis. All the H atoms were included in the

Table 2. Atomic Coordinates for the Non-H Atoms of (*R*)-(+)-**1** with Their e.s.d.'s in Parentheses

Atom	Molecule A			Molecule B		
	x	*y*	*z*	*x*	*y*	*z*
F(1)	0.4789	0.2724	−0.4299	0.0005 (9)	0.5471 (7)	−0.7986 (7)
O(1)	0.375 (1)	0.624 (1)	0.300 (1)	0.081 (1)	0.1914 (9)	−0.022 (1)
O(2)	0.358 (1)	0.717 (1)	0.091 (1)	0.101 (1)	0.097 (1)	−0.220 (1)
O(3)	0.401 (1)	0.6101 (9)	−0.114 (1)	0.082 (1)	0.215 (1)	−0.441 (1)
O(4)	0.570 (1)	−0.301 (1)	−0.425 (1)	−0.101 (1)	1.119 (1)	−0.832 (1)
N(1)	0.461 (1)	0.2996 (9)	0.1295 (9)	0.019 (1)	0.5257 (9)	−0.2290 (9)
N(2)	0.509 (1)	0.051 (1)	−0.2704 (9)	−0.033 (1)	0.771 (1)	−0.653 (1)
C(1)	0.432 (1)	0.405 (1)	0.183 (1)	0.038 (1)	0.416 (1)	−0.165 (1)
C(2)	0.412 (1)	0.511 (1)	0.105 (1)	0.060 (1)	0.309 (1)	−0.230 (1)
C(3)	0.420 (1)	0.514 (1)	−0.038 (1)	0.062 (1)	0.310 (1)	−0.375 (1)
C(4)	0.445 (1)	0.396 (1)	−0.097 (1)	0.041 (1)	0.430 (1)	−0.447 (1)
C(5)	0.447 (1)	0.388 (1)	−0.240 (1)	0.038 (1)	0.438 (1)	−0.591 (1)
C(6)	0.469 (1)	0.277 (1)	−0.291 (1)	0.011 (1)	0.549 (1)	−0.656 (1)
C(7)	0.491 (1)	0.169 (1)	−0.212 (1)	−0.011 (1)	0.655 (1)	−0.586 (1)
C(8)	0.492 (1)	0.177 (1)	−0.069 (1)	−0.007 (1)	0.650 (1)	−0.442 (1)
C(9)	0.467 (1)	0.292 (1)	−0.011 (1)	0.019 (1)	0.535 (1)	−0.372 (1)
C(10)	0.487 (1)	0.193 (1)	0.229 (1)	−0.008 (1)	0.632 (1)	−0.145 (1)
C(11)	0.429 (1)	0.053 (1)	0.137 (1)	0.055 (1)	0.773 (1)	−0.199 (1)
C(12)	0.505 (1)	0.059 (1)	0.021 (1)	−0.021 (1)	0.766 (1)	−0.359 (1)
C(13)	0.653 (1)	0.242 (1)	0.309 (1)	−0.176 (1)	0.586 (1)	−0.154 (1)
C(14)	0.383 (1)	0.624 (1)	0.178 (1)	0.080 (1)	0.192 (1)	−0.146 (1)
C(15)	0.413 (1)	−0.016 (1)	−0.410 (1)	0.052 (1)	0.832 (1)	−0.754 (1)
C(16)	0.409 (1)	−0.168 (1)	−0.426 (1)	0.058 (1)	0.981 (1)	−0.766 (1)
C(17)	0.570 (1)	−0.163 (1)	−0.408 (1)	−0.104 (1)	0.981 (1)	−0.820 (1)
C(18)	0.667 (1)	−0.094 (1)	−0.259 (1)	−0.188 (1)	0.917 (1)	−0.714 (1)
C(19)	0.666 (1)	0.055 (1)	−0.245 (1)	−0.191 (1)	0.766 (1)	−0.697 (1)

structure factor calculation with refined isotropic temperature factors. The refinement of atomic parameters was carried out by the full matrix least-squares refinement, using anisotropic temperature factors for all the non-H atoms. The final refinement converged with $R=0.058$ and $R_w=0.051$ for 377 parameters. The minimum and maximum peaks on the final difference Fourier map were −0.23 and $0.22\,e\,\text{Å}^{-3}$. Atomic scattering factors were taken from "International Tables for X-ray Crystallography."[6] The final positional parameters of non-H atoms are given in Table 1.[7]

X-Ray Analysis of (*R*)-(+)-1 The rod-shaped crystals of (*R*)-(+)-**1** were obtained from EtOH aqueous solution. Crystal size, $0.2\times0.2\times0.4$ mm. Data collection, reduction and refinement were as described for (+)-DFTQ·(+)-DBTA salt crystal. Crystal data: $C_{19}H_{21}FN_2O_4$, $M_r=360.38$, triclinic, space group $P1$, $a=9.706(2)$ Å, $b=10.248(4)$ Å, $c=9.706(2)$ Å, $\alpha=90.34(3)°$, $\beta=105.22(2)°$, $\gamma=110.47(2)°$, $V=866.4(4)$ Å^3, $Z=2$, $D_x=1.381$ g/cm^3, $F(000)=380$, and $\mu(\text{Mo}K_\alpha)=0.98$ cm^{-1}. Of the 2287 independent measured reflections, 1639 reflections with $I>2.0\,\sigma(I)$ were used for structure determination and refinement. All the non-H atoms were found on the Fourier map. Positions of H atoms were calculated except for 4 atoms of OH groups, which were obtained from difference Fourier synthesis. All the H atoms were included in the structure factor calculation but not refined. The final refinement converged with $R=0.050$ and $R_w=0.053$ for 461 parameters. The minimum and maximum peaks on the final difference Fourier map were −0.23 and $0.28\,e\,\text{A}^{-3}$. The final positional parameters of non-H atoms are given in Table 2.[7]

References and Notes

1) Ishikawa H., Tabusa F., Miyamoto H., Kano M., Ueda H., Tamaoka H., Nakagawa K., *Chem. Pharm. Bull.*, **37**, 2103 (1989).
2) Kido M., Hashimoto K., *Chem. Pharm. Bull.*, **42**, 872 (1994).
3) *a*) Morita S., Otsubo K., Matsubara J., Ohtani T., Uchida M., *Tetrahedron: Asymmetry*, **6**, 255 (1995); *b*) Sato K., Mitsuhashi S., *Kagakuryohou No Ryoiki*, **7**, 59 (1991).
4) Hashimoto K., Fujimura T., Tominaga M., Manabe Y., Japan. Patent Tokkyo Koho Showa 63-192753 (1988) [*Chem. Abstr.*, **111**, 231449*j* (1989)].
5) Molecular Structure Corporation (1985). TEXSAN. TEXRAY Structure Analysis Package. MSC, 3200A Research Forest Drive The Woodlands, TX 77381, U.S.A.
6) Cromer D. T., Waber J. T., "International Tables for X-Ray Crystallography," Vol. IV, Kynoch Press, Birmingham, 1974, pp. 72—149.
7) The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.