Crystal and Molecular Structure of an (*S*)-(+)-Enantiomer of Modafinil, a Novel Wake-Promoting Agent

Yasuko In,*[a] Koji Tomoo,[a] Toshimasa Ishida,[a] and Yasuhiko Sakamoto[b]

[a] *Department of Physical Chemistry, Osaka University of Pharmaceutical Sciences; 4–20–1 Nasahara, Takatsuki, Osaka 569–1094, Japan: and* [b] *Research & Development Division, AZWELL, Inc.; 2–24–3 Sho, Ibaraki, Osaka 567–0806, Japan.*
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The (+)-enantiomer of modafinil [(*RS*)-2-(diphenylmethylsulfinyl)acetamide], a novel wake-promoting agent, was clarified to be *S*-configuration by X-ray crystal structure analysis. The crystal consists of two crystallographically independent conformers that are different at the torsion angles around the sulfinylacetamide moiety, and this results from the molecular packing requirement to form a two-dimensional hydrogen-bonding network *via* neighboring amide groups in the crystal. The crystal structure is characterized by the formation of alternative hydrophobic and hydrophilic layers, which are formed among the symmetry-translated assemblies of diphenylmethyl and sulfinylacetamide moieties, respectively. The spatial orientation between the diphenyl and amide groups is believed to be important for the activity of modafinil.

Key words modafinil; wake-promoting agent; absolute configuration; X-ray crystal analysis

Narcolepsy is a disorder of the central nervous system (CNS) characterized by symptoms that include excessive daytime sleepiness (EDS). Although CNS stimulants such as amphetamine and methylphenidata have been used as the traditional therapy for narcolepsy symptoms, they are unable to fully control EDS in most narcoleptic patients. On the other hand, modafinil (Fig. 1), (*RS*)-2-(diphenylmethylsulfinyl) acetamide, discovered by Laboratoire L. Lafon (Maisons Alfort, France), has gained attention for its apparent selectivity in promoting wakefulness and potential for treating narcolepsy,[1—3] and is currently being developed by Cephalon, Inc. (West Chester, PA, U.S.A.) as Provigil® for the management of EDS. Modafinil is chemically and pharmacologically distinct from CNS stimulants.[4] Thus, it is important for further development of EDS-treating agents to clarify the structural and conformational features of modafinil, because its mechanism of action is not yet known. Modafinil, which has a chiral center at the sulfur atom, has been used as a racemic compound. Concerning the structure–activity relationship of modafinil, it has been shown that (+)- and (−)-forms have the same pharmacological activity as the racemate in mice, and its major metabolite, modafinil acid (Fig. 1), does not possess any wake-promoting activity.[5] It is well known that the terminal amide group participates importantly in the biological activity, as observed in the biologically active peptides.[6] Although L. Lafon has reported the preparation of (−)-modafinil from (*RS*)-modafinil acid,[7] its absolute configuration is currently unknown. Therefore, the X-ray crystal structures of (+)- and (−)-enantiomers of modafinil were analyzed to determine their absolute configurations by X-ray diffraction. The results showed the same structural features, except for their mirror-imaged molecular conformations. Thus, we report herein on the absolute configuration, molecular conformation, and crystal packing feature of (+)-modafinil, based on its crystal structure. These insights should be useful for determining the structure–activity relationship of modafinil.

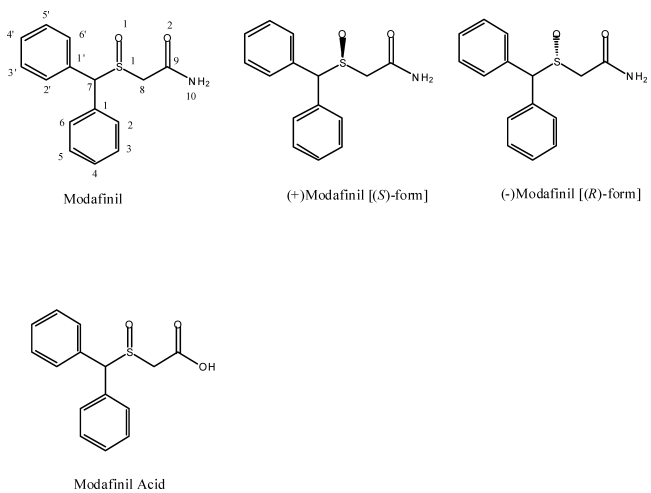

Fig. 1. Chemical Structures of Modafinil and Modafinil Acid
The atomic numbering used in this work is also shown.

Experimental

The (+)- and (−)-enantiomers of modafinil were supplied by Cephalon, Inc. Single crystals were obtained from slow evaporation of methanol or acetone solvent. These solvents afforded the transparent prism or plate crystals without containing the solvent molecule. The crystals from methanol and acetone were used for the X-ray study of the (+)- and (−)-forms, respectively.

All X-ray measurements were conducted on a Rigaku AFC-5R diffractometer with graphite-monochromated Cu$K\alpha$ radiation (λ=1.5418 Å) and a 12 kW rotating anode generator. The crystallographic data and structure refinements of (+)-modafinil are summarized in Table 1; (−)-modafinil showed essentially the same crystallographic data. Cell refinements, data collections, and reductions were performed using MSC/AFC software.[8] Unit-cell dimensions were determined by the least squares fit of 2θ angles of 25 reflections ranging from $40°<2\theta<45°$. Intensity data less than 2θ=135.3° were collected at 293 K in an ω–2θ scan mode; the backgrounds were counted for 5 s at both extremes of each reflection peak. The weak intensities ($I<2\sigma(I)$) were rescanned (up to 7 scans) to ensure good counting statistics. The observed intensities were corrected for the Lorentz and polarization effects. Absorption corrections by the ψ scan method[9] were also applied. Four standard reflections were monitored for every 100 reflection intervals throughout the data collections, showing a random variation of $<\pm1\%$ without significant trends for respective crystals.

The crystal structures were solved by the direct method using the SIR92 program.[10] For the structural refinement, the reflections with $I>2\sigma(I)$ were used, and the atomic scattering factors and terms of anomalous dispersion corrections were taken from the *International Tables for Crystallography*.[11]

* To whom correspondence should be addressed. e-mail: in@gly.oups.ac.jp

Table 1. Summary of Crystal Data, Intensity Collection, and Structure Refinement

	(*S*)-(+)-Modafinil
Crystallographic data	
Chemical formula	$C_{15}H_{15}N_1O_2S_1$
Molecular weight	273.35
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	
a, Å	5.689(3)
b, Å	26.504(4)
c, Å	9.332(3)
β, °	105.96(3)
Volume, Å^3	1352.8(8)
Z	4
F(000)	576
Crystal size, mm	0.15×0.15×0.9
Density (calculated), g·cm^{-3}	1.342
Absorption coefficient (Cu$K\alpha$), mm^{-1}	2.10
Data Collection	
Scan speed in ω, ° min^{-1}	12
Scan range in ω, °	1.523+0.3 tanθ
Index ranges	$-6 \leqq h \leqq 0$
	$0 \leqq k \leqq 31$
	$-10 \leqq l \leqq 11$
θ max, °	67.63
No. of unique data measured	2463
No. of reflections with $I > 2\sigma(I)$	2383
Structure refinement	
No. of variables refined	343
Flack χ parameter	−0.02(2)
R (*Rw*)	0.033 (0.086)
R (*Rw*) (all data)	0.036 (0.089)
Goodness-of-fit on F^2	1.091
Extinction coefficient	0.021(1)
Largest diff. peak and hole, e Å^{-3}	0.336 and −0.214
Max and mean shift/esd	0.009 and 0.001

The refinement of non-H atoms was carried out by the full-matrix least squares calculations with anisotropic thermal parameters using the program SHELXL97.[12] H atoms of amide NH_2 were located from the difference Fourier map, and the others were geometrically located, and they were treated as riding with fixed isotropic displacement parameters (*U*iso=1.2*U*eq for the associated C or N atoms). H atomic positions were not included as variables for the refinements. The function of $\Sigma w(Fo^2-Fc^2)^2$ was minimized using a weighting scheme of $w=1/[\sigma^2(Fo^2)+(0.1000P)^2]$, where $P=(Fo^2+2Fc^2)/3$. Final *R* [$=\Sigma(|Fo|-|Fc|)/\Sigma|Fo|$], *Rw* [$=(\Sigma w(|Fo|-|Fc|)^2/\Sigma w|Fo|^2)^{1/2}$] and *S* (goodness-of-fit) [$=(\Sigma w(|Fo|-|Fc|)^2/(M-N))^{1/2}$, where M=no. of reflections and N=no. of variables used for the refinement] are given in Table 1. The absolute configurations for the (*S*)-(+)- and (*R*)-(−)-enantiomers were confirmed by the Flack χ parameter[13,14] (=−0.02(2) and 0.01(2), respectively). The averaged estimated standard deviations for the bond lengths and angles of non-H atoms at the final stage were 0.006 Å and 0.3° for both enantiomers.

The final atomic coordinates, anisotropic temperature factors, bond lengths, bond angles, torsion angles of non-H atoms, and the atomic coordinates of H atoms have been deposited in the Cambridge Crystallographic Data Centre, Cambridge University Chemical Laboratory, Cambridge CB21EW, U.K. (CCDC 241713 & 241714). All numerical calculations were carried out at the Computer Center, Osaka University of Pharmaceutical Sciences.

Results and Discussion

Molecular Structure The configuration around the sulfinyl bond of (+)-modafinil was determined to be *S*-form by the Flack χ parameter. Therefore, the absolute configurations of (+)- and (−)-modafinil are described as (*S*)- and (*R*)-modafinil, respectively.[15] The crystal contains two crystallographically independent molecules (differentiated as molecules A and B) per asymmetric unit. The conformational difference of these molecules is shown in Fig. 2, and the respective torsion angles are given in Table 2. A conformational feature of modafinil could be a rigid structure of the diphenylmethyl moiety, because the torsion angles around two benzene rings take nearly the same, but reversed signed, values, indicating that the rotations around two benzene rings are severely limited within a narrow range, and thus little conformational flexibility is permitted. In contrast, the C7–S1–C8–C9–O2/N10 sequence defining the orientation of the amide group with respect to the diphenylmethyl moiety is relatively flexible, and two different conformers are different at the torsion angles around S1–C8 and C8–C9 bonds. The existence of two different conformers is primarily due to the requirement of the molecular packing in the crystal (discussed later), and no conformational preference is observed between them because their torsion angles are both in the

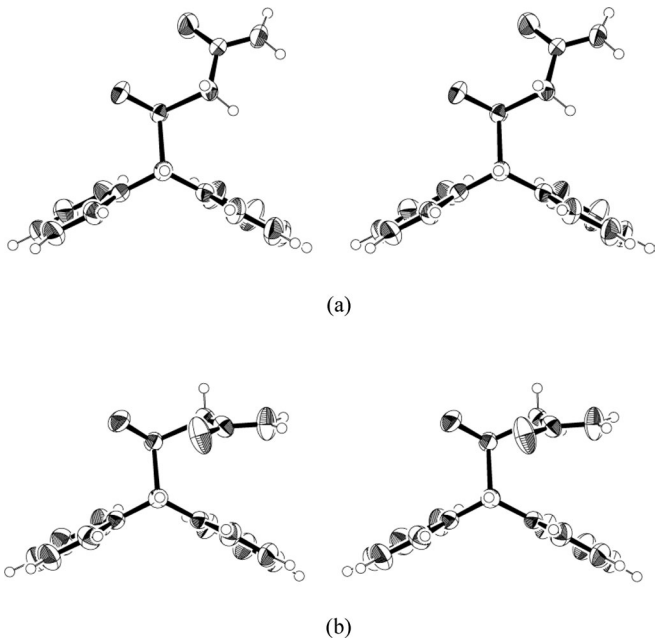

Fig. 2. Stereoscopic Views of Molecule A (a) and Molecule B (b) Observed in Crystal of (*S*)-(+)-Modafinil

Table 2. Torsion Angles (°) of (*S*)-(+)-Enantiomer[a]

	Molecule A	Molecule B
C2–C1–C7–S1	123.0 (3)	117.7 (3)
C6–C1–C7–S1	−56.1 (3)	−62.4 (3)
C2′–C1′–C7–S1	55.0 (3)	58.8 (3)
C6′–C1′–C7–S1	−123.6 (3)	−119.6 (3)
C2–C1–C7–C1′	−115.8 (4)	−120.0 (4)
C6–C1–C7–C1′	64.9 (4)	59.7 (4)
C1–C7–C1′–C2′	−68.3 (4)	−66.4 (4)
C1–C7–C1′–C6′	112.8 (4)	115.0 (4)
C1–C7–S1–C8	−61.6 (3)	−51.1 (3)
C1′–C7–S1–C8	171.5 (3)	−179.3 (3)
C1–C7–S1–O1	−172.3 (3)	−164.5 (3)
C1′–C7–S1–O1	60.8 (2)	67.2 (2)
C7–S1–C8–C9	165.1 (3)	−46.5 (3)
S1–C8–C9–O2	28.0 (4)	−23.2 (4)
S1–C8–C9–N10	−147.8 (4)	155.9 (4)

a) The estimated standard deviations are given in parentheses.

energetically stable region.

Crystal Packing and Molecular Association The crystal packing of (*S*)-(+)-modafinil is shown in Fig. 3. Respective independent molecules are face-to-face packed in the crystal lattice. The diphenylmethyl and sulfinylacetamide moieties form the discrete hydrophobic and hydrophilic layers, respectively, and are alternatively running parallel to the *a*-axis. The diphenyl moieties of molecules A and B are stabilized to each other by van der Waals contacts, in which the neighboring benzene rings of molecules A and B assemble together with an edge-to-face fashion and form the hydrophobic double layers. Interestingly, one of two benzene rings of molecule A rides just on the center of two benzene rings of molecule B with the mean H$\cdots\pi$ (plane) distance of 3.1 Å and with dihedral angles of 85° and 63° for the left and right benzenes of B (Fig. 4), respectively.

The sulfinylacetamide moieties of molecules A and B are linked together by the hydrogen bonds and short contacts *via* the amide groups and form the layer perpendicular to the *b*-axis (Table 3). The hydrogen-bonding pattern in which the amide group of molecule A participates is the same as that of molecule B. The amide NH_2 is bifurcately hydrogen-bonded to the sulfinyl and carbonyl O atoms of neighboring molecules, thus forming the two-dimensional hydrogen-bonding network along the *a*-axis. The electrostatic short contacts further stabilize the network (Fig. 5); this type of hydrogen-bonding network has been most frequently formed observed in the amide compounds.[16—18]

Structure–Activity Relationship Since it has been reported that both the (*R*)- and (*S*)-forms show the same pharmacological activity as the racemate,[5] it is reasonable to con-

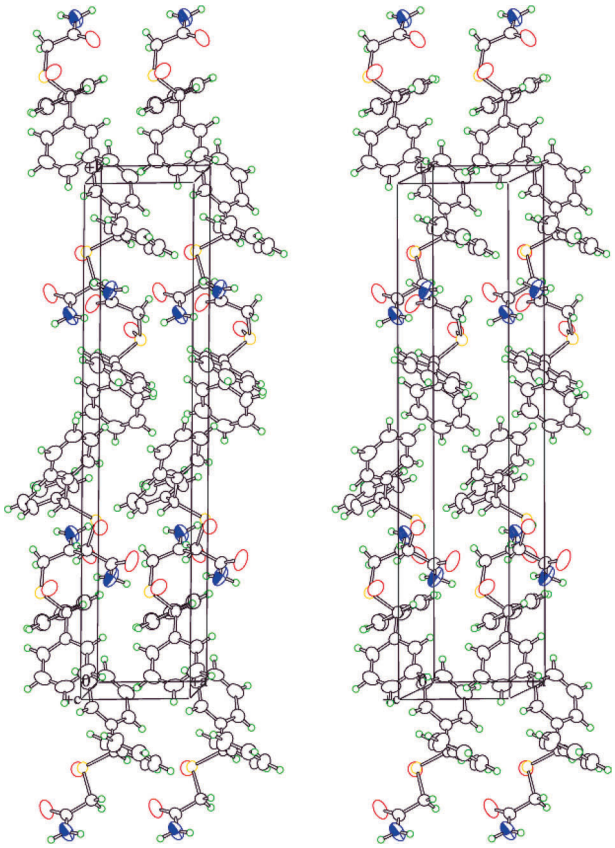

Fig. 3. Stereoscopic View of Crystal Packing of (*S*)-(+)-Modifinil Crystal, Viewed from *c*-Axis

Horizontal and vertical lines correspond to *a*- and *b*-axes, respectively. The oxygen and nitrogen atoms are depicted with red-colored circles and blue-colored ellipses, respectively.

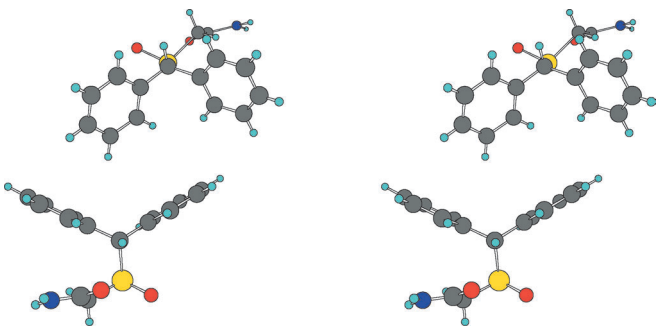

Fig. 4. Stereoscopic View of Interaction between Diphenylmethyl Moieties of Molecules A (Upper Side) and B (Lower Side), Observed in Crystal Structure

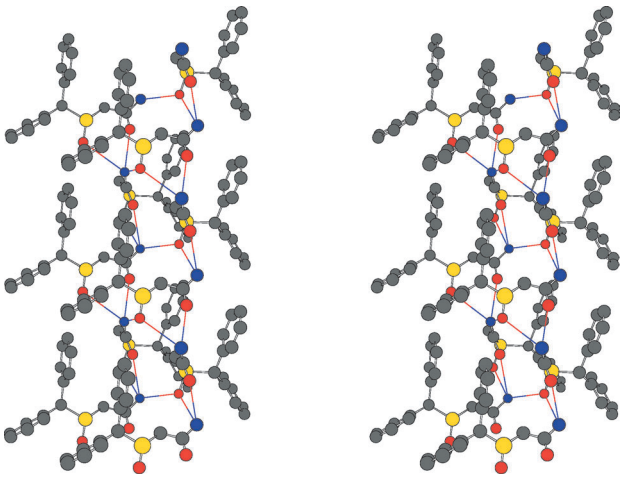

Fig. 5. Stereoscopic View of Hydrophilic Layer Running Along to *a*-Axis in Crystal Structure of (*S*)-(+)-Modafinil, Created by Interactions among Amide and Sulfinyl Groups of Neighboring Molecules

The thin lines show hydrogen bonds or short contacts.

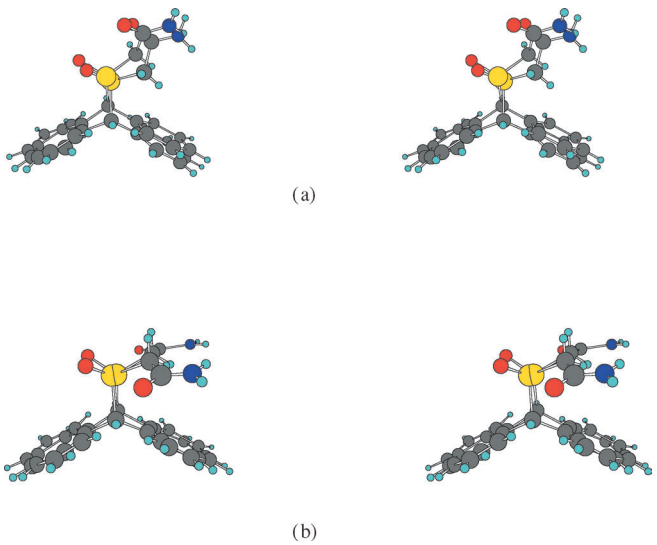

Fig. 6. Superimposed Stereoviews of (*S*)-(+)- and (*R*)-(−)-Enantiomers

(a) Molecules A, (b) Molecules B.

Table 3. Hydrogen Bonds and Short Contacts of (*S*)-(+)-Enantiomer (Less Than 3.5 Å)[a)]

Donor (D–H)	Acceptor (A)	Sym. code of A	D···A (Å)	H···A (Å)	D–H···A (°)
N(10)A[b)]	O(1)B	$-x+1, y-1/2, -z+1$	3.030 (5)	2.10	160.9 (2)
N(10)A	O(1)B	$-x, y-1/2, -z+1$	3.259 (5)	2.50	144.4 (2)
N(10)A	O(2)B	$-x, y-1/2, -z+1$	2.903 (6)	2.25	131.0 (3)
N(10)B	O(1)A	$-x, y+1/2, -z+2$	2.939 (5)	2.02	159.4 (2)
N(10)B	O(1)A	$-x+1, y+1/2, -z+2$	3.492 (5)	2.73	137.5 (2)
N(10)B	O(2)A	$-x+1, y+1/2, -z+2$	2.888 (6)	2.09	140.7 (3)

a) The estimated standard deviations (esds) for atomic distances of non-H atoms are given in parentheses. The esds for the distances and angles including H atoms are not given because of the fixed refinement of H atoms. *b*) The suffix letters, A and B, represent two crystallographically independent molecules A and B, respectively.

sider that the common structural features in the crystals of (*R*)- and (*S*)-enantiomers are importantly related with the activity of modafinil. As the structural features of modafinil, the present X-ray analyses showed the conformationally rigid diphenylmethylsulfur skeleton and the potent hydrogen-bonding ability of the amide group. The importance of the amide group has also been indicated by the inactivity of modafinil acid for the wake-promoting function.[5)] Therefore, we examined whether these groups take the same spatial situation in both enantiomers. The superimpositions of the respective conformers in both enantiomers are shown in Fig. 6. In the superimposition of molecules A, their spatial orientations between the amide group and the benzene ring of the diphenyl moiety are nearly consistent with each other in both enantiomers, whereas the molecules B orient their amide groups in a different way with respect to the benzene rings. Therefore, molecule A may be a conformation responsible for the activity; this conformation could be described as an open structure in which the sulfinyl S, amide N, and the center of benzene ring are almost aligned in a straight line.

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