anti-2-Hydroxy-2-methyl-1-tetralone oxime: X-ray and density functional theory study

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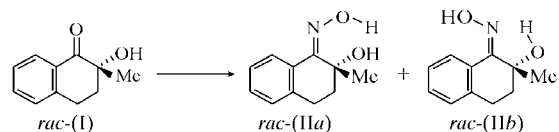
Crystals of the title racemic compound, $C_{11}H_{13}NO_2$, consist of two types of molecules (conformers); one molecule has an exocyclic OH group in an equatorial position and the other has this group in an axial position. Consequently, the hydrogen-bond schemes for the two molecules are different. The molecules with equatorial OH groups create infinite parallel chains (formed by the same enantiomer), connected by centrosymmetric dimers of molecules (of mixed enantiomers), both with axial OH groups. Possible interconversion of the conformers and the flexibility of the molecule were studied by means of different MP2 and density functional theory (DFT) methods. The optimization of the structure by the DFT method confirmed the types of the hydrogen bonds.

Comment

Recently, we have found that enantiomerically pure 2-hydroxy-2-methyl-1-tetralone, (I), can be used as a chiral auxiliary for the stereoselective synthesis and/or epimerization of α-amino acids (Solladié-Cavallo et al., 2002). We have described the synthesis of (I) in racemic or enantiomerically enriched forms elsewhere (Solladié-Cavallo et al., 2001, 2002; Pažický et al., 2006). The (R)-2-hydroxy-2-methyl-1-tetralone enantiomer was prepared by a stereoselective oxidation with chiral oxaziridines in 95% ee (Davis & Weismiller, 1990). This method is efficient but rather costly, so we decided to attempt to prepare enantiomerically pure (I) via crystallization of its oxime (II). Such an enantioseparation method was successfully applied on a similar compound; enantiomerically pure 2-hydroxypinan-3-one was obtained via crystallization of its enantiomerically enriched oxime, followed by hydrolysis (Markowicz et al., 2002).

During the synthesis of the corresponding oxime from 2-hydroxy-2-methyl-1-tetralone, (I), two racemic diastereoisomeric compounds, viz. syn-(IIa) and anti-(IIb), were formed. Compound syn-(IIa) isomerized easily to the more stable anti-(IIb). By careful crystallization of (IIb), crystals suitable for X-ray structure analysis were prepared. The X-ray experiment revealed that oxime anti-(IIb) did not form a conglomerate but preferentially crystallized as a racemic compound. Therefore, the enantioseparation of anti-(IIb) is not possible starting from its racemic mixture.

The crystal structure and theoretical investigation of the electronic structure of the title racemic compound, (IIb), are presented here.

The numbering scheme for (IIb), together with the atomic displacement ellipsoid plot, is shown in Fig. 1. Selected geometric parameters are presented in Table 1. The two molecules in the asymmetric unit differ in the conformation of the saturated six-membered ring, with a difference in the position of the exocyclic OH group. The molecules of type 1 (containing atom C11) have OH groups in axial positions, and the molecules of type 2 (containing atom C21) have OH groups in equatorial positions. From this point of view, the
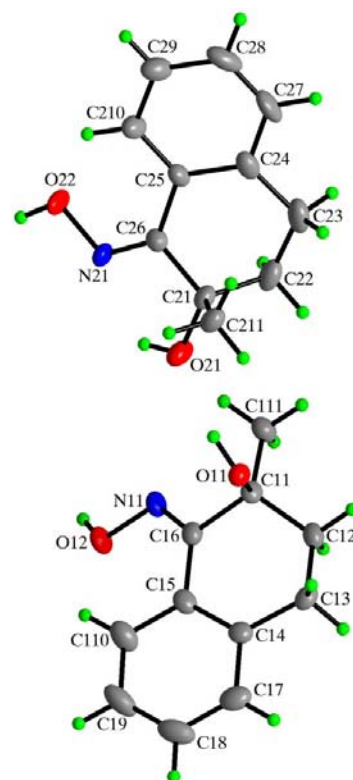

Figure 1
A perspective drawing showing the atom-numbering scheme of (IIb). Displacement ellipsoids are drawn at the 50% probability level.

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conformational flexibility of this ring is interesting. Although three atoms in the ring formally have sp^2-hybridization and further restraint is imposed by conjugation of the $=N-OH$ bond with the aromatic ring, the molecule is still quite flexible. Calculations at the MP2/6–31+G** (Pople et al., 1976; Frisch et al., 1990; Fletcher et al., 1999; Hehre et al., 1972; Clark et al., 1983) and B3LYP/6–31+G** (Becke, 1988, 1992a,b, 1993; Lee et al., 1988) levels showed that a conformational change between the OH-equatorial (OH-eq) and OH-axial (OH-ax) configurations is possible (Table 2) with an intermediate skew conformation, as seen in Figs. 2 and 3. All combinations of the standard quantum chemical methods and the basis sets used agree with the fact that the saturated ring is quite flexible and with the ordering of all three conformers discussed.

The two molecules in the asymmetric unit have different hydrogen-bonding schemes (Fig. 4). The molecules of type 2, with OH in an equatorial position, form infinite chains in the a direction. These chains are connected by centrosymmetric dimers formed by molecules of type 1. The dimers are formed in a manner similar to those of, for example, (±)-dibenzo-bicyclo[b,f][3.3.1]nona-5a,6a-diene 6,12-dioxime (Field et al., 2002; Levkin et al., 2003), (E)-17-oximino-3-hydroxy-1,3,5(10)-estratriene (Hejaz et al., 1999) and 17α-benzyl-16-hydroxyimino-3-methoxyestra-1,3,5(10)-trien-17β-ol (Stan-

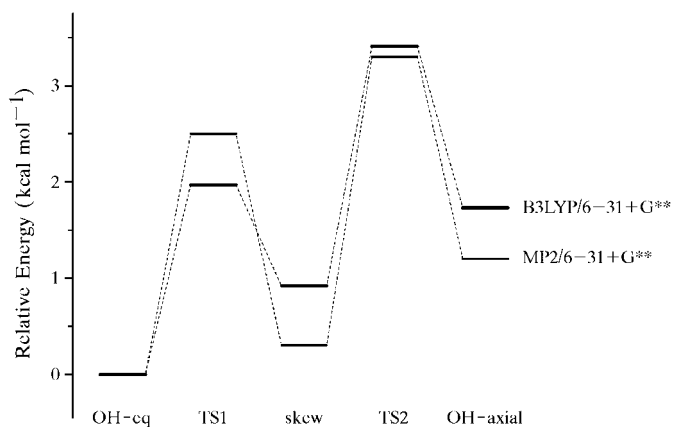**Figure 4**
The hydrogen-bonding pattern in the crystal structure of (IIb). H atoms not involved in strong hydrogen bonds have been omitted for clarity. For symmetry codes and notation of hydrogen bonds, see Table 3.

Figure 2
A schematic representation of the relative energies of the conformations of (IIb) and transition states connecting them.

Figure 3
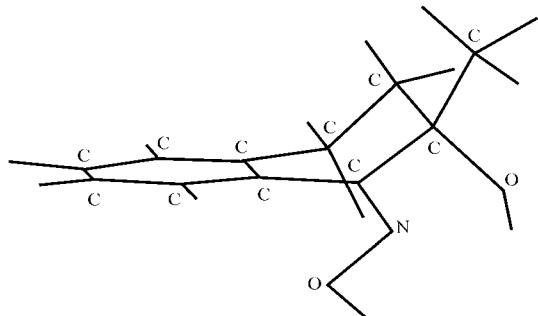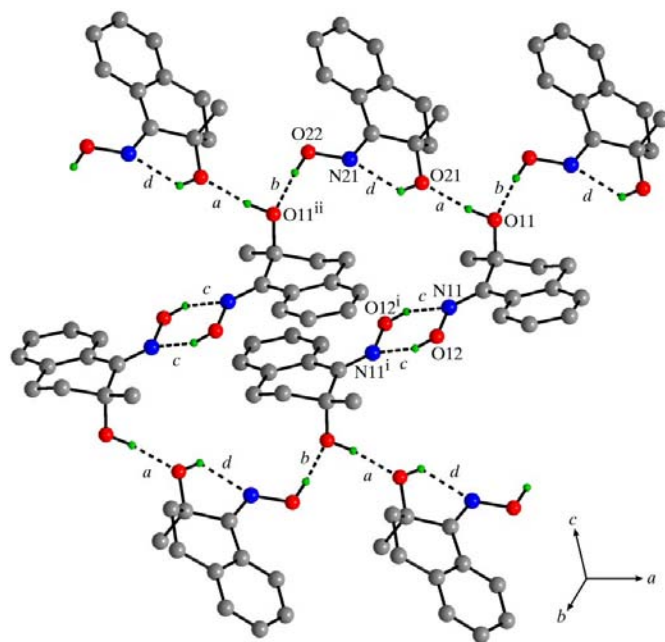A schematic representation of the skew conformation of (IIb).

ković et al., 1996). The hydrogen–bonding geometries for (IIb) are compared in Table 3. The theoretical investigation of hydrogen bonds was performed using the Vienna ab initio simulation package VASP (Kresse & Furthmüller, 1996). The calculations were based on the density functional theory (DFT) with periodic boundary conditions (Jones & Gunnarsson, 1989) using generalized gradient approximation (GGA) to the exchange-correlation functional. The optimization of the structure by the DFT method was performed mainly to improve the positions of the H atoms. The calculations confirmed the types of the hydrogen bonds found by the experiment and refined their bond lengths.

The hydrogen-bonding pattern can be described using graph-set theory (Bernstein et al., 1995; Grell et al., 1999). The first-level graph-set descriptors are dimers $D(2)$ and $D(2)$, a ring $R_2^2(6)$, and a string $S(5)$ for strong hydrogen bonds a–d, respectively, while the second-level descriptors are assigned as $C_2^2(8)$ for bonds a and b, $D_3^3(14)$ for bonds a and c, and $D_3^3(12)$ for bonds b and c. The assignment of graph-set descriptors was performed using PLUTO, as described by Motherwell et al. (1999), and the notation of the hydrogen bonds here is that given in Table 3 and Fig. 4.

Experimental

An ethanol/water solution of an equimolar ratio of (I), hydroxyl-amine hydrochloride ($NH_2OH \cdot HCl$) and sodium acetate (AcONa) was stirred for 6 d at room temperature, whereupon a mixture of diastereoisomers (IIa) and (IIb) was formed. The pure diastereo-isomer (IIb) was obtained by flash chromatography on SiO_2, followed by crystallization. To a mixture of (IIb) (36 mg, 188.3 mmol) and hexsol (5.4 ml, light fraction of petrol ether), toluene (1.2 ml) was

added. The mixture was heated to reflux. The solution obtained was left to stand in a cotton-covered flask in a small Dewar flask overnight. Straw-like crystals (32 mg, 167.3 mmol) were obtained in 88.9% yield (m.p. 387–389 K). Recrystallization was performed from a warm solution of (II*b*) (28 mg, 146.4 mmol) in hexsol (6.0 ml) and toluene (1.5 ml), standing in a cotton-covered flask in a small Dewar flask at room temperature. After 24 h, the solution was seeded with one microscope-selected crystal. In this manner, X-ray quality crystals were obtained after 48 h. The crystals were filtered off, washed with hexsol and dried in air (yield 10.9 mg, 57.0 mmol, 38.9%).

Crystal data

$C_{11}H_{13}NO_2$	$Z = 4$
$M_r = 191.22$	$D_x = 1.283$ Mg m^{-3}
Triclinic, $P\bar{1}$	Mo $K\alpha$ radiation
$a = 7.3655$ (2) Å	Cell parameters from 3464
$b = 9.6851$ (2) Å	reflections
$c = 14.4720$ (1) Å	$\theta = 2.2$–25.5°
$\alpha = 93.375$ (1)°	$\mu = 0.09$ mm^{-1}
$\beta = 99.476$ (1)°	$T = 173$ (2) K
$\gamma = 102.288$ (1)°	Plate, colourless
$V = 990.22$ (3) Å^3	$0.46 \times 0.11 \times 0.01$ mm

Data collection

Siemens SMART CCD area-detector diffractometer	3654 independent reflections
ω scans	2215 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan	$R_{int} = 0.068$
(*SADABS*; Sheldrick, 2002)	$\theta_{max} = 25.5°$
$T_{min} = 0.960$, $T_{max} = 0.999$	$h = -8 \rightarrow 8$
11309 measured reflections	$k = -11 \rightarrow 11$
	$l = -17 \rightarrow 17$

Refinement

Refinement on F^2	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2\sigma(F^2)] = 0.051$	
$wR(F^2) = 0.121$	$w = 1/[\sigma^2(F_o^2) + (0.0551P)^2]$
$S = 0.99$	where $P = (F_o^2 + 2F_c^2)/3$
3654 reflections	$(\Delta/\sigma)_{max} < 0.001$
266 parameters	$\Delta\rho_{max} = 0.18$ e Å^{-3}
	$\Delta\rho_{min} = -0.22$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O11—C11	1.448 (2)	N11—C16	1.288 (3)
O12—N11	1.403 (2)	N21—C26	1.278 (3)
O21—C21	1.436 (3)	C11—C111	1.516 (3)
O22—N21	1.392 (2)	C21—C211	1.521 (3)
O11—C11—C12—C13	57.8 (2)	O21—C21—C22—C23	179.7 (2)
C111—C11—C12—C13	177.22 (18)	C211—C21—C22—C23	−61.6 (3)
O12—N11—C16—C11	179.40 (17)	O22—N21—C26—C21	−176.56 (18)

Table 2
Zero-point energy ZPE (B3LYP/6–31G**) corrected relative energies (kcal mol^{-1}) of the three conformers and two transition states.

Method/basis	OH-eq[i]	OH-ax	Skew	TS1	TS2
(*a*)	0.0	1.93	1.02	2.12	3.58
(*b*)	0.0	2.25	1.31	2.31	3.82
(*c*)	0.0	1.73	0.92	1.97	3.41
(*d*)	0.0	1.50	0.39	2.26	3.72
(*e*)	0.0	1.21	0.30	2.52	3.31

Notes: (i) the absolute energies for the OH-eq conformer for the methods listed are −632.169233, −631.399926, −632.196664, −630.278978 and −630.321458. (*a*) B3LYP/6–31G**; (*b*) PBEPBE/6–31G**; (*c*) SP B3LYP/6–31+G**//B3LYP/6–31G**; (*d*) MP2/6–31G**; (*e*) SP MP2/6–31+G**//MP2/6–31G**.

Table 3
Hydrogen-bonding geometry (Å, °) for (II*b*) and results of DFT calculations.

Notation	D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
a	O11—H11$\cdots$O21	0.91	1.83	2.725 (2)	165
	DFT	0.90	1.53	2.429	173
b	O22—H22$\cdots$O11^{ii}	0.91	1.76	2.670 (2)	176
	DFT	1.05	1.66	2.661	157
c	O12—H12$\cdots$N11^{i}	0.89	2.01	2.801 (3)	147
	DFT	0.96	2.06	2.726	143
d	O21—H21$\cdots$N21	0.80	2.00	2.505 (2)	121
	DFT	1.07	1.63	2.287	114
	C211—H21C$\cdots$O22^{iii}	0.98	2.58	3.474 (3)	151
	DFT	1.00	2.62	3.452	149
	C110—H110$\cdots$O12	0.95	2.20	2.753 (3)	116
	DFT	1.04	2.36	2.776	102
	C210—H210$\cdots$O22	0.95	2.25	2.796 (3)	116
	DFT	1.02	2.48	2.996	114

Symmetry codes: (i) $-x, -y + 2, -z$; (ii) $x - 1, y, z$; (iii) $x + 1, y, z$;

C-bound H atoms for compound (II*b*) were constrained to an ideal geometry using an appropriate riding model and were refined isotropically with common displacement parameters for respective groups. The C—H distances were kept fixed at 0.95 Å for aromatic H atoms and at 0.99 Å for secondary H atoms. For methyl groups, the C—H distances (0.98 Å) and C—C—H angles (109.5°) were kept fixed, while the torsion angles were allowed to refine with the starting position based on the threefold averaged circular Fourier synthesis. For the hydroxy groups, the O—H distance (0.84 Å) and C—O—H angle (109.5°) were used for calculating a starting position based on the circular Fourier synthesis; both the torsion angle and the O—H distance were then allowed to refine.

Data collection: *SMART* (Siemens, 1995); cell refinement: *SAINT* (Siemens, 1995); data reduction: *SAINT* and *SADABS* (Sheldrick, 2002); program(s) used to solve structure: *SHELXTL* (Bruker, 2001); program(s) used to refine structure: *SHELXTL*; molecular graphics: *DIAMOND* (Brandenburg, 2005); software used to prepare material for publication: *SHELXTL*.

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