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The Chiral Selector *N*-(2′-*S*-Hydroxypropyl)-*N*,*N*′-bis(3,5-dichlorobenzoyl)-1*R*,2*R*-diaminocyclohexane†

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Abstract

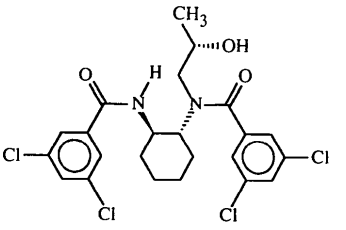
The title compound, $C_{23}H_{24}Cl_4N_2O_3$, is a chiral selector used as a stationary phase in the chromatographic separation of enantiomers. Its structure was solved by direct methods and its absolute configuration was confirmed.

Comment

Recently, much attention has been placed on the consequences of stereochemistry in biological processes. As a result, the preparation and analysis of pure enantiomers have become of increasing interest, especially in the pharmaceutical field (Ariens, 1989). The direct chromatographic separation of enantiomers represents a powerful tool for solving stereochemical problems. This technique is based on the preferential interaction of one enantiomer of a racemic compound (selectand) with a chiral discriminating agent (selector) immobilized on or adsorbed onto an inert support. Proteins, polysaccharides, cyclodextrins and synthetic polymers, as well as low molecular weight synthetic molecules, are generally used as selectors, frequently bonded to silica microparticles (Allenmark, 1991).

We have recently developed a family of chiral stationary phases (CSPs) for high-performance liquid chromatography (HPLC) applications, based on different derivatives of 1*R*,2*R*-diaminocyclohexane (DACH) (Gaparrini, Misiti & Villani, 1992). One of these CSPs, containing the *N*,*N*′-bis(3,5-dichlorobenzoyl) derivative of DACH, is particularly effective in the separation of the enantiomers of a large number of 1,2-aminoalcohols (pharmacologically active as β-blockers) in the form of oxazolidin-2-ones. It has been shown that knowledge of the recognition mechanism underlying such separations can lead to the design of improved CSPs (Pirkle, Burke & Wilson, 1989).

In this respect, we are now investigating the enantioselective interactions between a soluble model of the above CSP and the enantiomers of several racemates by a combination of physicochemical and computational techniques. Solid-state structure determination of our selector, (1), was required as a starting point for a complete conformational analysis by molecular mechanics and docking simulations with enantiomeric selectands.



(I)

The analysis of this structure does not show significant differences of bond distances and bond angles between the two molecules found in the asymmetric unit. Both have chiral N atoms quite out of plane from the corresponding cyclohexane-calculated least-squares planes. In fact, their distances from such planes are 0.75 (1), 0.002 (14), −0.33 (1) and 0.28 (1) Å for N7, N18, N107 and N118, respectively. The angle between the arylic planes is 115.6 (6) for molecule I and 128.1 (6)° for molecule II. These two molecules show slight conformational differences, mostly around one of the two N atoms. Examples of this occurrence are the torsion angles C2—N18—C19—C20 and C3—C2—N18—C19 which have values of 70 (2) and −117 (2)°, respectively, in I, while the corresponding torsion angles in II exhibit values of 97 (2) and −128 (2)°.

The two independent molecules interact with symmetry related molecules so as to form two different hydrogen bonds. The former is established by N7 with O24 of the molecule at $1-x, y-\frac{1}{2}, -z$ with a contact length of 2.92 (1) Å. The second one is due to the interaction between O22 and O122 belonging to II at $2-x, y-\frac{1}{2}, -z$ with a length of 3.00 (2) Å. Another intermolecular interaction detected in this structure determination is that involving carbonyl atoms O9, O22 and O109, and Cl

† Alternative name: (1*R*,2*R*)-2-(3,5-dichlorobenzamido)-1-{*N*-[(2*S*)-hydroxypropyl]-3,5-dichlorobenzamido}cyclohexane.

atoms Cl13, Cl16 and Cl113. The distances O9···Cl113 3.20 (1) and O109···Cl13 3.24 (2) Å involve atoms in the same asymmetric unit.

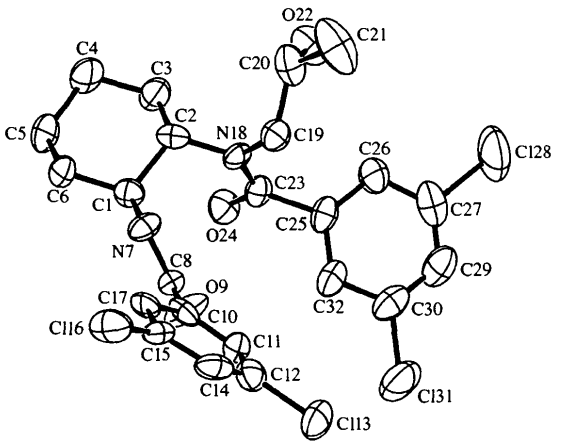


Fig. 1. The molecular structure of molecule I of (1) showing 50% probability displacements ellipsoids. Molecule II is not shown for clarity.

Experimental

To a solution of 1*R*,2*R*-diaminocyclohexane (20 mmol) in 2 ml methanol, *S*-1,2-epoxypropane (4 mmol) was added and the resulting solution kept at room temperature for 72 h; excess of diamine was removed by bulb-to-bulb distillation leaving the *N*-(2′-*S*-hydroxypropyl)-1*R*,2*R*-diaminocyclohexane compound as a colourless oil (0.48 g, 70%). To a cooled (273 K) solution of *N*-(2′-*S*-hydroxypropyl)-1*R*,2*R*-diaminocyclohexane (1.16 mmol) in 5 ml tetrahydrofuran (THF), triethylamine (2.40 mmol) and a solution of 3,5-dichlorobenzoyl chloride (2.40 mmol) in 2 ml THF were added. The solution was stirred at room temperature for 4 h, then the solvent was removed *in vacuo* and the residue partitioned between dichloromethane and 0.1 *M* aqueous HCl. The organic phase was dried (Na_2SO_4) and evaporated to give a crude material containing *N*-(2′-*S*-hydroxypropyl)-*N*,*N*′-(3,5-dichlorobenzoyl)-1*R*,2*R*-diaminocyclohexane which was purified by chromatography (LiChroprep 15–25 µm, chloroform as eluent). The yield was 90% (0.54 g). Crystals of this compound were obtained by slow evaporation from a chloroform solution kept at 273 K.

Crystal data

$C_{23}H_{24}Cl_4N_2O_3$
M_r = 518.3
Monoclinic
$P2_1$
a = 13.480 (2) Å
b = 11.459 (3) Å
c = 15.890 (3) Å
β = 90.37 (2)°
V = 2454.4 (9) Å^3
Z = 4
D_x = 1.402 Mg m^{-3}
D_m not measured
Cu $K\alpha$ radiation
λ = 1.5418 Å
Cell parameters from 16 reflections
θ = 36.12–39.53°
μ = 4.612 mm^{-1}
T = 293 (2) K
Prism
0.750 × 0.200 × 0.125 mm
Colourless

Data collection

Rigaku AFC-5*R* diffractometer
2θ–ω scans
Absorption correction: empirical *via* ψ scans (*TEXSAN*; Molecular Structure Corporation, 1989)
T_{min} = 0.79, T_{max} = 1.00
4294 measured reflections
4104 independent reflections
3208 reflections with $I > 2\sigma(I)$
R_{int} = 0.039
θ_{max} = 62.13°
h = 0 → 15
k = 0 → 13
l = −18 → 18
3 standard reflections
every 150 reflections
intensity decay: 13%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.088
$wR(F^2)$ = 0.334
S = 1.150
4045 reflections
577 parameters
H atoms not refined
$w = 1/[\sigma^2(F_o^2) + (0.0724P)^2 + 16.7639P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.620 e Å^{-3}
$\Delta\rho_{min}$ = −0.510 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0024 (5)
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute configuration: Flack (1983)
Flack parameter = 0.03 (5)

The hydroxyl H atoms were not localized and therefore not considered during refinement. The low value (7.01) of the ratio between number of reflections and number of parameters refined is mainly due to the intensity decay in collecting data. This also explains the occurrence of relatively high values of R factors. The hardware instrumental limit of the diffractometer in collecting data in the 2θ plane is 124.5°. The C27 atom is affected with a considerable disorder degree as shown by its high anisotropy and thermal displacement parameters. It was not possible to localize this atom better. An intensity decay correction was applied.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1991). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN*. Program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994). Program(s) used to refine structure: *SHELXL*93. Molecular graphics: *TEXSAN*. Software used to prepare material for publication: *TEXSAN*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1272). Services for accessing these data are described at the back of the journal.

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Two Tosylated 1,2-*O*-Isopropylidene-α-D-xylofuranoses

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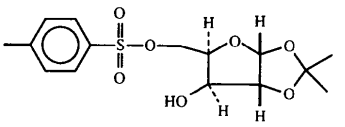
Abstract

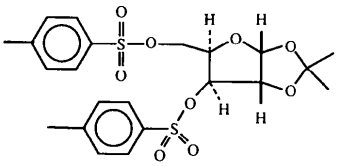
The tosyl side-chain orientation in 1,2-*O*-isopropylidene-5-*O*-*p*-tosyl-α-D-xylofuranose, $C_{15}H_{20}O_7S$, and in 1,2-*O*-isopropylidene-3,5-di-*O*-*p*-tosyl-α-D-xylofuranose, $C_{22}H_{26}O_9S_2$, is influenced by ring substitution and intermolecular hydrogen bonding.

Comment

As part of a continuing study involving novel functionally substituted carbohydrate molecules (Armishaw *et al.*, 1996), we have prepared two tosylated xylofuranoses, namely, 1,2-*O*-isopropylidene-5-*O*-*p*-tosyl-α-D-xylofuranose, (1), and 1,2-*O*-isopropylidene-3,5-di-*O*-*p*-tosyl-α-D-xylofuranose, (2).



(1)



(2)

Intermolecular –OH···O=C hydrogen bonding is present in (1) but absent in (2). In (1), O4···O1($-1+x$, y, z) is 2.868 (7), O4—H4 is 0.820 (11), H4···O1 is 2.061 (11) Å and the angle at H4 is 168 (4)°. In both carbohydrates, the groups attached to C3 and C4 are *syn* with similar O4—C3—C4—C8 torsion angles of −37.3 (6)° in (1) and −40.9 (8)° in (2). However, the orientation of the tosyl group which is common to both molecules differs, with the torsion angle S1—O5—C8—C4 having values of 95.0 (5)° in (1) and 156.3 (5)° in (2). This is due to the different substituents at C3, the only feature not common to both molecules.

The puckering parameters (Cremer & Pople, 1975) in (1) for the furanose ring are q_2 = 0.350 (5) Å and φ_2 = 294.2 (8)°, and for the isopropylidene ring, q_2 = 0.259 (5) Å and φ_2 = 265.7 (11)°. Similarly, in (2), for the furanose ring, q_2 = 0.346 (8) Å and φ_2 = 321.8 (14)°, and for the isopropylidene ring, q_2 = 0.269 (8) Å and φ_2 = 314.9 (17)°.

To date, 14 X-ray structures of tosylated carbohydrates have been reported (Allen & Kennard, 1993). Of these, the most similar compound to those reported

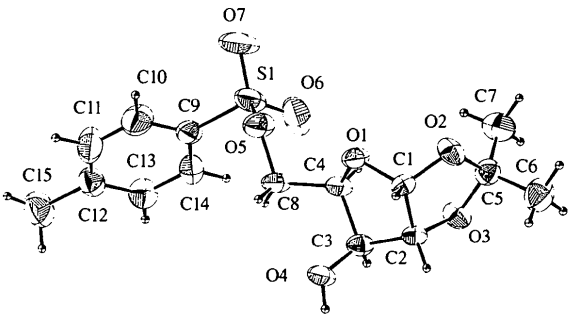


Fig. 1. The atomic arrangement in molecule (1). Displacement ellipsoids are shown at the 50% probability level.

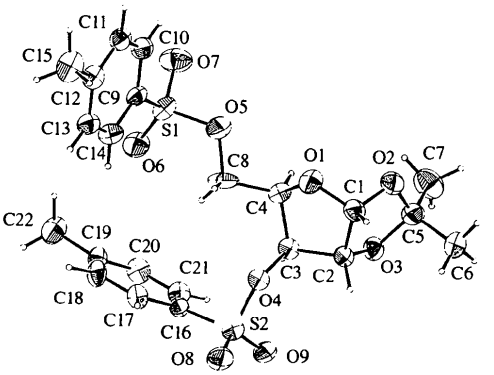


Fig. 2. The atomic arrangement in the molecule (2). Displacement ellipsoids are shown at the 50% probability level.